SELECTED CHAPTERS OF PHARMACOLOGY
PREFACE

This book was written to provide students, researchers and educators with a user-friendly tool for keeping pace with rapidly evolving drug discovery initiatives. The primary content is based on the pharmacotherapy of various diseases, which has been an enormously rewarding and fascinating adventure. In addition, the content is also based on my research and teaching experience during the 3 decades prior to this writing in Hungary, England, France, and United States of America, which has been an enormously rewarding and fascinating adventure. Use of pharmacological agents to prevent or mitigate disease is an ancient skill maintained during the entire history of all human societies in various forms. Hunter-gatherer communities each developed culturally unique uses for plant, mineral and animal resources locally available to populations in need that evolved into sophisticated and increasingly efficacious medical traditions that persist to this day. The progressive integration of medical traditions into written record allowed evolution of progressively powerful pharmacology based increasingly on analysis of clinically valid precedent. As understanding of the molecular-biological basis of diseases, drug design has become progressively driven by consideration of how specific biochemical interactions may be modulated to achieve therapeutic endpoints. Of particular interest in this respect, is identification of compounds capable of modifying critical ligand-receptor interactions, enzyme activities and other events in cellular signaling pathways that lead to enhancement or inhibition of major symptoms of various diseases. Most descriptions of drug mechanisms given in this book focus on how small-molecule drugs affect specific molecular targets to alter well-defined aspects of cellular physiology in ways that in most cases are expected to result in improved prognosis of selected disorders. In this respect, the book reflects “orthodoxy” of strategic thinking in the pharmaceutical industry, which favors single site-acting “magic bullet” compounds that may be highly effective in some treatment venues, but are highly toxic, often costly and provide
only transitory remediation to serious chronic illness. A particularly exciting subject area covered in this book is a description of novel treatment strategies that prevent or mitigate serious diseases, particularly those with underlying inflammatory etiology, by strengthening natural host immunoregulatory mechanisms, rather than intervening in activity of host homeostasis. It is an honor and a pleasure to participate in the medical revolution, of which this book is a vanguard.


Prof. Dr. Arpad Tosaki
Chairman, Department of Pharmacology
Faculty of Pharmacy, Health Science Center
University of Debrecen
Debrecen, Hungary
CONTENTS

CENTRAL NERVOUS SYSTEM 7

General anesthesia 7

Intravenous anesthesia 9

Anesthetics for inhalation 11

Local anesthetics 13

Hypnotics and sedatives 17

(A) Benzodiazepines 17

(B) Barbiturates 19

(C) Miscellaneous sedative-hypnotics 19

Depression and anxiety disorders, drugs 19

Psychosis and mania 22

Epilepsies 24

Mechanisms of seizures and antiepileptic drugs 25

(a) hydantoins 26

(b) barbiturates 26

(c) iminostilbenes 27

(d) succinimides 27

(e) valproic acid 27

(f) benzodiazepines 27

(g) other antiseizure drugs 28

Degenerative disorders 28

PD Diseases (paralysis agitans or shaking palsy) 29

Alzheimer’s disease (AD) 32

Huntington disease (HD) 32

Amyotrophic lateral sclerosis (ALS) 33

Opioids 34

Effects of opioids 34

Morphine and opioid agonists 35

Opioid agonist/antagonists 37

Antitussive agents 38

CARDIOVASCULAR SYSTEM 40

1) Therapy of myocardial ischemia 40

(a) Nitrovasodilators 41

(b) Beta-adrenergic receptor blockers 43

(c) Calcium channel blockers 43

(d) Antiplatelet, antiintegrin, and antithrombotic agents 43
combined with statins

2). Treatment of congestive heart failure

3). Antiarrhythmic drugs

4). Treatment of hypertension including the rennin-angiotensin system

5). Vasopressin and others affecting renal function

6). Diuretics

7). Therapy of hypercholesterolemia and dyslipidemia

8). Blood, pharmacology
   (I) Hematopoietic growth factors
   (II) Drugs effective against anemias
   (III) Vitamin B12 and folic acid for the treatment of megaloblastic anemias

CANCERS AND ANTINEOPLASTIC DRUGS
   A). Alkylating agents
   B). Antimetabolites
   C). Natural extracts and products, and antibiotics
   D). Miscellaneous agents
   E). Hormones and Hormone-like agents

GASTROINTESTINAL TRACTS
   (i) The stomach
      a). Inhibitors of the proton pump (K+ -H+ pump)
      b). H2 receptor antagonists
      c). Antacids, ascid suppressants and cytoprotectants
   (ii) The bowel motility, laxatives, antinauseant, and antiemetic agents, billary and pancreatic diseases
      Bowel motility
      Laxatives
      Antinauseant and antiemetic agents
      Billary and pancreatic diseases
   (iii) Treatment of inflammatory bowel disease

ASTHMA AND PULMONARY PHARMACOLOGY
   a). Beta adrenergic agonists (beta sympathomimetics)
   b). Methylxanthine (e.g., theophylline)
   c). Muscarin receptor antagonists
   d). Corticosteroids
   (e). Other asthma and COPD mediator antagonists
   (f). Immunomodulators
(g). Other future developments in asthma therapy 120
(h). Therapy of pulmonary arterial hypertension 121

ENDOCRINOLOGY, HORMONES, AND HORMONE ANTAGONISTS 123
The hypothalamic-pituitary endocrine system 123
Somatotrophic hormones: growth hormone (GH) and prolactin (PR) 124
Glycoprotein hormones: TSH and gonadotropins 127
Oxytocin and vasopressin (posterior pituitary hormones) 129
Thyroid and antithyroid drugs 130

ESTROGENS AND PROGESTINS 137
Estrogens 137
Progestins (gestogens, progestogens) 140
  Anitprogestins and progesteron receptor modulators 141
  Contraceptives 141
  Testosterone and other androgenes 142
  Antiandrogens 143
ACTH (adrenocorticotropic hormone) and adrenal steroids 144
  Inhibitors of the biosynthesis of adrenocortical steroids 146
CENTRAL NERVOUS SYSTEM

General anesthesia

General anesthesia depresses the central nervous system (CNS) at a sufficient degree to permit the performance of various surgeries and other noxious or unpleasant procedures. General anesthesia has low therapeutic indices, and therefore, it requires great care in application. Although, general anesthetics produce a very similar anesthetic state, they are relatively dissimilar in their adverse effects in various organs. To choose specific drugs and routes of administrations to produce general anesthesia is based on their chemical and pharmacological properties and on the adverse effects of various structures, in the context of suggested diagnostic and surgical procedures with considerations of the patient’s age, conditions, and medications. Anesthesia usually is not carried out with a simple agent, thus, anesthesiologists apply various combinations of sedatives, neuromuscular blocking agents, and local anesthetics, as the actual clinical situation requires. The development of general anesthesia and the application of anesthetics started in 1846 in the United States.

The first used anesthetic was (i) ‘ether anesthesia’ achieving a revolution worldwide in surgery and medical care. Currently ether is not used in medical care, but it was the ‘ideal’ pioneer anesthetic which was relatively nontoxic to cells and organs. Furthermore, ether does not compromise, in therapeutic doses, respiration and circulation. However, ether is not used any longer in medical care, because it forms toxic peroxides in the presence of oxygen and light, and ether is explosive.

Chloroform (ii) followed ether, introduced by a Scottish doctor, J. Simpson, in 1847, as the next anesthetic used worldwide as a nonexplosive anesthetic. The chloroform molecule contains halogens (Cl), therefore it has hepatotoxic and cardiovascular depressive effects.

Nitrous oxide (N\textsubscript{2}O) was the third (iii) and ‘light’ anesthetic introduced in medical care started in 1868. N\textsubscript{2}O cannot alone induce ‘deep’ anesthesia allowing brain, cardiac or abdominal surgery, however, it was used for painless tooth extraction.

About sixty years later, in 1929, (iv) cyclopropane was discovered and used for the next 30 years. This molecule was explosive and flammable. Therefore, British scientists developed a new chemical structure, (v) halothane, which is nonflammable and possessing anesthetic properties. Halothane was introduced in surgery as a general anesthetic agent in 1956, and since then it has been widely used for general anesthesia.

Principles of anesthesia:

a). Minimizing the harmful effects of the procedure (techniques) and agents.
b). Stabilize and sustain the homeostasis during surgery related to blood loss, metabolic shifts and coagulation.
c). Improve postoperative recovery and treat surgery-induced stress responses.

Anesthesia and hemodynamics:

Anesthesia results in a reduction in the systemic arterial blood pressure. The cause of blood pressure reduction is vasodilation, cardiac depression or both, a diminution of baroreceptor control and a generalized reduction in central sympathetic tone. The reduction in blood pressure is enhanced by volume depletion or myocardial dysfunction. Those anesthetics which have hypotensive properties under physiological conditions should be used with caution in trauma victims.

Anesthesia and respiration:

Oxygen supply is essential during anesthesia, therefore, ventilation must be assisted and controlled. The gag reflex is disappeared, and lower esophageal sphincter tone is reduced.
Endotracheal intubation is necessary in order to avoid and mitigate respiration-related deaths in general anesthesia. Muscle relaxation is also an important factor, and neuromuscular blockers are commonly used to produce relaxation.

Hypothermia:
Because the reduced metabolic rate during anesthesia body temperature is dropped. Thus, thermoregulatory vasoconstriction is activated to defend heat loss. Metabolic rate and oxygen conception decrease by about 30 % leading to a reduced heat generation. The fall in body temperature could lead cardiac complications and impaired coagulation. Thus, the prevention of hypothermia could be done by controlling body temperature and introduction of warm-air covers and heat exchangers.

Nausea and vomiting:
Anesthetics stimulate the chemoreceptor trigger zone and the brain stem vomiting center increasing tissue serotonin (5-HT), histamine, acetylcholine, and dopamine concentrations. The 5-HT receptor antagonists, especially 5-HT\textsubscript{3} receptor antagonists (e.g., ondansetron) are very effective in suppressing of anesthetic-induced nausea and vomiting.

Other emergency and postoperative needs:
The stimulation of sympathetic nervous system by anesthetics results in (i) ventricular tachycardia and (ii) hypertension leading to (iii) ischemia and (iv) pain. All of these symptoms are significantly reduced when opioids are applied in general surgery. Morphine is frequently used by intravenously. Obstruction of airways (v) could also occur because anesthetics palliate reflexes. The suppression of respiration associated with opioids is a problem in patients who have still residual anesthetics in tissues and bodies.

Mechanism(s) and strength of general anesthesia:
General anesthesia may be defined as a global and reversible depression of central nervous system (CNS). Another way to define general anesthesia can be summarized by the effects of “components” of anesthesia. The components of anesthesia include (i) amnesia, (ii) immobility, (iii) reduction of autonomic responses to stimulation, (iv) analgesia, and (v) unconsciousness. The surgery generally requires an immobilized subject (patient) who does not have an extended autonomic response to carry out surgery, and who has amnesia during the procedure. The potency of anesthetics is measured and expressed in MAC (minimum alveolar concentration). The MAC value shows the minimum alveolar concentration of an anesthetic that prevents movement in response to surgical stimulation in 50% of subjects. The strengths of MAC could be monitored by (1) the end-tidal anesthetic concentration using MS (mass spectrometry) or IR (infra red) spectroscopy. The measurement of MAC (2) directly correlates with the free concentration of anesthetics at its action site in the CNS. It is (3) simple to acheive the end point (immobilization) of that showing the clinical aim.

The potency of intravenous anesthetics is more difficult to measure (almost impossible) because there is not an available technique to continuously determine blood or plasma anesthetic concentration, and because of the free concentration of anesthetic at its action site cannot be measured. The potency of intravenous anesthetics can be defined as the free plasma concentration producing the loss of responses to surgical incision in 50% of subjects.

Action mechanisms of general anesthetics:
General anesthetics act by a common mechanism, based on the perturbation of physical properties of cell membranes. The anesthetic potency of inhaled agents correlates with its solubility in oil. This mechanism is suggested by Meyer and Overton implicating the lipid bilayer component of cell membranes as the likely target of gaseous anesthetics. This
hypothesis supports the role of specific protein binding sites for gaseous anesthetics. Thus, general anesthetics interrupt the function of nervous system by inhibition of electrical activity in the cerebral cortex, brainstem (e.g., thalamus and hippocampus), spinal cord, and sensory neurons. General anesthetics hyperpolarize neurons by reducing synaptic communication and excitability of postsynaptic neurons. Both intravenous and inhalational anesthetics have substantial effects on synaptic transmission, transmitter release, and less effect on action potential generation or propagation. The inhibition of Ca\(^{2+}\) release is also responsible for the effects of anesthetics, because Ca\(^{2+}\) is responsible for the release of neurotransmitters (e.g., norepinephrine). The ligand-gated ion channels, including halogenated inhalation and intravenous agents, are important targets for the molecular action of anesthetics. Chloride channels gated by the inhibition of GABA\(_A\) receptors are sensitive to concentrations of anesthetics. General anesthetics increase the sensitivity of GABA\(_A\) receptors to GABA; thus, nervous system activity and neurotransmission are depressed. The action mechanism of anesthetics on GABA\(_A\) receptors is mediated by binding of anesthetics to specific sites on GABA\(_A\) receptor proteins.

Other ligand-gated ion channels, e.g., glycine receptors, and neuronal nicotin and acetylcholine receptors, structurally are closely related to GABA\(_A\) receptors. Glycine receptors mediate the responses of anesthetics to noxious stimuli inhibiting neurotransmission in the spinal cord and brainstem. Some anesthetics also inhibit neuronal nicotinic-acetylcholine receptors, and could generate analgesia and/or amnesia.

General anesthetics that don’t have effects on GABA\(_A\) and glycine receptors are ketamine, nitrous oxide (N\(_2\)O), cyclopropane, and xenon. These anesthetics inhibit different types of ligand-gated ion channels and N-methyl-D-aspartate (NMDA) receptors. NMDA receptors are glutamate-gated cation channels that are relatively selective for Ca\(^{2+}\). Nitrous oxide and cyclopropane are selective inhibitors of NMDA-regulated currents, and these agents produce unconsciousness via NMDA receptors.

Halogenated anesthetics activate, Ca\(^{2+}\) channels alone with various K\(^+\) channels known as two-pore domain channels. The two-pore domain channels responsible for the resting membrane potential of neurons and the molecular locus of hyperpolarized neurons.

**Intravenous anesthesia**

(barbiturates, propofol, etomidate, ketamine)

Parenteral anesthetics are the most frequently used drugs for the induction of anesthesia in humans. Lipophilic properties of parenteral anesthetics are related to relatively quick penetration in the brain and spinal cord, resulting rapid onset and short duration of anesthesia after a single bolus dose. Parenteral agents are substituted aromatic or heterocyclic structures. Hydrophobicity is a critical factor related to their pharmacokinetics. These drugs ultimately accumulate in fatty tissues. After a single intravenous injection, these anesthetics enter the highly perfused and lipophilic brain and spinal cord tissues where, within a single circulation time, they produce anesthesia. The anesthetics then distribute between brain, spinal cord and less perfused tissues such as muscle and adipose tissues. Then anesthetics redistribute between the central nervous system and other tissues. The elderly usually require a lower anesthetic dose because their metabolic system is slower.

**Barbiturates:**
The derivatives of barbituric acid are sodium thiopental, thiamylal, and methohexital used for intravenous anesthesia. Thiobarbiturates are stable in solution for 5-6 days, while methohexital is stable for 6 weeks. Doses of thiopental at 3 to 5 mg/kg produce
unconsciousness in 60 sec with a peak effect in 1 to 2 min with duration of anesthesia between 5 min to 10 min. If benzodiazepines, opiates, or α₂ adrenergic agonists are used as premedication, the doses of thiopental are reduced by 30 to 40% because of their additive hypnotic effect. The anesthetic effect of thiamylal is equipotent to thiopental. However, methohexital is a 3-fold more potent anesthetic than thiopental. Intravenous anesthetics can produce muscle tremor, hypertonus, and hiccups. Limiting anesthetic duration after a single dose of an intravenous anesthetic is dependent on the redistribution and hydrophobic property of the drug between the brain and other tissues. After multiple doses of barbiturates, the duration of action varies regarding their clearances. Methohexital has a rapid clearance, thus, it accumulates less during the application of multiple doses or infusion. Prolonged infusions or large doses of thiopental and thiamylal produce unconsciousness lasting several days.

Side effects of barbiturates:
  a). Barbiturates reduce cerebral metabolic rates and oxygen consumption. As a result of cerebral oxygen consumption, intracranial pressure and cerebral blood flow are reduced.
  b). Barbiturates produce a significant reduction in blood pressure. The reduction in blood pressure is due to vasodilation, venodilation, and a direct decrease in myocardial contractility. However, heart rate is increased as a compensatory response to reduced blood pressure.
  c). Barbiturates reduce ventilation and respiratory rate leading to apnea. Anaphylactoid reactions could rarely occur. Barbiturates have little effects on bronchomotor tone and can be safely used in asthmatic patients.

Propofol:
This drug is most frequently used parenteral anesthetic agent in the world. A typical dose of propofol is between 1.5 mg/kg to 2.5 mg/kg in healthy adults. For short anesthesia lower doses of propofol can be repeated in every 5 minutes. Onset and duration of propofol anesthesia are similar to barbiturates. However, the recovery after multiple doses of propofol is much faster in comparisons with barbiturate anesthetics. Propofol is metabolized by the liver to less active metabolites. Side effects of propofol are similar to those of barbiturates on nervous and cardiovascular systems than that produced by barbiturates. Propofol provokes bronchospasm less frequently than barbiturates. Furthermore, propofol has significant antiemetic action which is useful in order to prevent nausea, vomiting and respiration of components of gastric content.

Etomidate:
This molecule is a substituted imidazole structure, and poorly soluble in water. Etomidate has a rapid onset and short duration of action. Side effects of the drug are similar to those of barbiturates on cardiovascular, respiratory, and central nervous systems. Etomidate slightly increases heart rate, induces nausea and vomiting. Etomidate interferes with adrenal biosynthetic enzymes required for production of steroid hormones.

Ketamine:
Ketamine is a derivative of arylcyclohexylamine ring structure. The molecule is useful for anesthetizing patients at risk for hypotension and bronchospasm. Ketamin is mainly used intravenously, but intramuscular, oral, and rectal applications are also possible. The duration of ketamine-induced anesthesia is longer than those of barbiturates. The highest dose of ketamine for anesthesia is 8 to 10 mg/kg. Ketamin does not produce the general and classic anesthetic state, but the subjects are anesthetic and unresponsive to painful stimuli. Ketamin has indirect sympathomimetic activity, increases cerebral blood flow, and intracranial pressure.
Therefore, ketamine is contraindicated for patients with elevated intracranial pressure or cerebral ischemia. Ketamine increases blood pressure, heart rate, and cardiac output. While ketamine is not an arrhythmogenic agent, the drug increases cardiac oxygen consumption. As a consequence, ketamine is not an ideal anesthetic agent for patients at risk for myocardial ischemia. Ketamine is a potent bronchodilator due to its sympathomimetic activity, therefore, ketamine particularly useful for anesthesia in patients at high risk for bronchospasm. Thus, ketamine is the best suited for patients suffered from asthma, and children undergoing short, and painful surgical procedures.

Anesthetics for inhalation

Volatile liquids and gases can be used for inhalation anesthesia. The most commonly used inhalational anesthetics are halothane, enflurane, isoflurane, desflurane, sevoflurane, and nitrous oxide ($N_2O$). The therapeutic indices that range from 2 to 4 (LD 50 / ED 50 ) making these drugs are very dangerous for clinical use. An inhaled agent, ideally, produces a fast induction of anesthesia, and a rapid recovery after the surgical procedure.

Pharmacokinetics of inhalation anesthetics: Inhalational anesthetics distribute between tissues and blood, thus, equilibrium is achieved when the partial pressure of anesthetic gas is equal in blood and tissue. It is important to note that the partial pressure of an anesthetic may be equal in all tissues, but the concentration of anesthetic in each tissue will be different. Blood-gas, blood-brain, and blood-fat partition coefficients are different for various inhalational agents. Equilibrium is achieved when the partial pressure of an inspired anesthetic is equal to the partial pressure of gas in alveolars. This is the point at which there is no additional uptake of anesthetic from alveoli into blood. Anesthetics that are not very soluble in blood or other tissues, equilibrium is achieved quickly. Consequently, if a gas anesthetic is more soluble in a tissue such as fat, equilibrium could take many hours to reach. Anesthesia is carried out when the partial pressure of anesthetic in brain is equal to or higher than MAC (mean alveolar concentration). Elimination of inhalational agents depends on their solubility and blood perfusion of tissues, and their lipid solubility.

Halothane: Halothane is a bromo-chloro-fluoro molecular structure with light sensitivity. Therefore, bottles have to be packed in amber bottles. Mixtures of halothane with oxygen or air are not flammable and explosive. The major metabolites of halothane are trifluoroacetic acid, bromide, and chlorine can be detected in urine. The drug was introduced in 1956 as the first modern and low cost inhalation anesthetic in clinical use. Its working concentration is about 1%. Halothane has no serious side effects, therefore, it can be safely used in children. Halothane possesses side effects on: (i) Cardiovascular system. Thus, the drug dose-dependently reduces arterial blood pressure leading to a reduced cardiac output. Reduced heart rate is originated from a direct depressive effect of halothane on the sinus node. Halothane-induced hypotension is related to a reduction of heart rate. Halothane inhibits hypoxic vasoconstriction and increases the perfusion of poorly ventilated region of the lung. (ii) Respiratory system: A decreased alveolar ventilation results in an elevation in CO$_2$ concentration. Halothane is a potential bronchodilator, therefore, its use is beneficial in patients suffer from status asthmaticus. (iii) Nervous system: Halothane can induce brain edema and intracranial pressure. For this reason, halothane is contraindicated in patients having elevated intracranial pressure. (iv) Halothan causes relaxation of skeletal muscle. Therefore, halothane potentiates the action of muscle relaxants. Halothane could trigger hyperthermia, leading to severe muscle contraction. This syndrome is frequently fatal.
Isoflurane, eflurane, desflurane and sevoflurane: Isoflurane and enflurane are commonly used inhalational anesthetics. These drugs are useful for the maintenance of anesthesia during surgery. Desflurane and sevoflurane are anesthetics for induction of anesthesia, in outpatient surgery, because of their rapid onset of action and quick recovery. Isoflurane and enflurane anesthesia can be achieved within 10 min with inhaled concentrations of 3% to 4%, and maintained for concentrations of 1% to 2%. Desflurane-induced inhalational anesthesia can be maintained with concentrations of 6% to 8%, and the maintenance of sevoflurane anesthesia can be achieved by 2% to 4%. All four inhalational anesthetics (isoflurane, eflurane, desflurane and sevoflurane) produce a reduction in arterial blood pressure, a concentration-dependent increase in respiratory rate and intracranial pressure, and a reduced cerebral metabolic O2 consumption, and skeletal muscle relaxation.

Nitrous oxide (N2O): N2O is insoluble in blood and several tissues, however is very soluble in the brain tissue. N2O is almost completely eliminated by the lung, and is not biotransformed by enzymatic action in human tissues. N2O is a weak anesthetic agent and produces weak analgesia at a concentration of 20%. However, N2O is able to induce sedation in concentrations between 40% and 80%. N2O must not be used at concentrations above 80%. N2O is usually used in combinations with other inhalational or intravenous anesthetics. Side effects of nitrous oxide is weak, but its combinations with other anesthetics result in an increased heart rate, blood pressure, cardiac output, and respiratory rate. N2O also increases cerebral blood flow and intracranial pressure. However, N2O does not relax skeletal muscle.

Anesthetic adjuncts: General anesthesia is done in combination with anesthetic adjuncts in order to reduce the side effects of an anesthetic. These adjuncts are (i) benzodiazepines, (ii) analgesics, and (iii) neuromuscular blocking agents.

(i). Benzodiazepines: Benzodiazepines are more commonly used for sedation rather than general anesthesia. As adjuncts, benzodiazepines are used for anxiolysis, amnesia, and sedation prior to induction of surgical anesthesia, or for sedation during various procedures not requiring general anesthesia. Midazolam, diazepam, and lorazepam are frequently used as anesthetic benzodiazepine adjuncts. Midazolam has the pharmacokinetic advantage, particularly over diazepam and lorazepam, of being more rapid in onset and duration of anesthesia. Sedative doses (0.01 mg/kg to 0.07 mg/kg) of intravenous midazolam reach a peak within two min and provide sedation for 30 min. Midazolam is more suitable for infusion than other benzodiazepines, although its duration of effect does not significantly increase with the prolonged time of infusion. Benzodiazepines are very effective anticonvulsants, therefore, these drugs are also used for the treatment of status epilepticus. Benzoiazepines slightly decrease blood pressure and respiratory drive.

It is important to note that alpha 2 adrenergic agonist, dexmedetomidine (imidazole structure), is useful for short term sedation in adults. The Federal Drug Administration (FDA) has approved the use of dexmedetomidine, as anesthetic adjunct, since 1999. Dexmedetomidine is highly selective for α2 adrenergic receptor stimulation, and the activation of α2A adrenergic receptors by dexmedetomidine produces both sedation and analgesia, but does not provide general anesthesia. The side effects of dexmedetoidine are hypotension and bradycardia. Nausea and dry mouth also are common side effects of this drug.

(ii) Analgesics: Analgesics are together administered with general anesthetics to minimize hemodynamic changes and side effects. Nonsteroid antiinflammatory drugs (COX inhibitors) or acetaminophen could provide adequate analgesia for minor surgical procedures. However, opioids are the primary analgesics used before the induction of general anesthetics for
surgery. Thus, fentanyl, sufentanil, alfentanil, remifentanil, meperidine, and morphine are the major parenteral opioids used before surgical procedures. The analgesic activity of these opioids is produced by agonist (stimulation of μ-opioid receptor) activity at μ-opioid receptors. The choice of application of a perioperative opioid is based primarily on the duration of action, side effects, and the condition of patients. For instance, remifentanil has an ultrashort duration, while fentanyl, alfentanil, and sufentanil have similar intermediate durations of action. Subsequent doses either by bolus or infusion are determined by the surgical stimulus and the patient’s hemodynamic response. Spastic activity of the Oddi sphincter is increased by all opioids, although morphine appears to be more potent in this regard. Opioids are often administered intrathecally and epidurally for the reduction of acute and chronic pain.

(iii). Neuromuscular blocking agents: Depolarizing and nondepolarizing muscle relaxants are given during the induction of anesthesia to relax muscles of jaw, neck, and airway to facilitate laryngoscopy and endotracheal incubation. Neuromuscular blocking agents are used to provide additional insurance for immobility. The action of nondepolarizing muscle relaxants can be antagonized with an acetylcholinesterase inhibitor such as neostigmine or edrophonium. However, succinylcholine has serious side effects (e.g., myalgia, bradycardia, and hyperkalemia) including malignant hyperthermia in certain individuals.

Local anesthetics

Local anesthetic agents reversibly bind to a specific receptor site in the pore of Na-channels in nerves and block ion transport through Na-channel pore. Thus, local anesthetic agents in contact with nerve trunks cause both sensory and motor paralysis in the innervated area. The effects of local anesthetics are reversible with a complete recovery of nerve function and no evidence of damage exists to nerve fibers.

Cocaine, an ester of benzoic acid, was the first local anesthetic for use of local anesthesia in ophthalmic surgery in the late 19th century. Cocaine is found in the leaves of the coca shrub (Erythroxylon coca). The structure of local anesthetics contains hydrophilic and hydrophobic moieties that are dissociated by an intermediate ester or amid group. Molecular size of local anesthetics determines their dissociation from their receptor sites. Today, the most widely local anesthetics are lidocaine, bupivacaine, and tetracaine.

Action mechanisms for local anesthetics are localized at the cell membrane to prevent the generation and the conduction of nerve impulses. The sodium channels consist of alpha and beta subunits and various segments and domains. Thus, these agents block conduction by reducing or preventing the transient increase in the permeability of excitable membranes to Na+. This action of anesthetics is due to their direct interaction with voltage-gated Na+ channels, thus, as a consequence, the action potential declines and impulse conduction slows. After the opening of Na+ channels, the channels are inactivated within a few milliseconds due to closure of an inactivation gate. As a final result, local anesthetics block the unmyelinated C fibers and myelinated Aδ fibers. The resting nerve is much less sensitive to a local anesthetic than one that is repetitively stimulated. The frequency dependent block of ion channels is most important for an atiarrhythmic drug. In additional, local anesthetics can also block K+ channels, but this action requires higher concentrations of local anesthetics.

The duration of local anesthetic agents is depending on the time of contact with nerve fibers. Thus, the combination of local anesthetics with vasoconstrictors e.g., epinephrine (adrenaline) prolong the effect of local anesthetics at the site of action. Vasoconstrictor agents
could be absorbed systematically causing untoward reactions (e.g., hypoxic damage, tissue edema, necrosis after local anesthesia).

Undesired effects of local anesthetics: Systemic absorption of anesthetics can cause central nervous system stimulation such as restlessness, tremor, and clonic convulsions. Central stimulation may be followed by depression and respiratory failure. Benzodiazepines are the agents of choice for the prevention and arrest convulsions. Systematic absorption of local anesthetics, at high doses, acts on the myocardium by decreasing electrical excitability, conduction, and contraction force, and ventricular fibrillation. Local anesthetics relax vascular and bronchial smooth muscle. Local anesthetics also inhibit the transmission in the neuromuscular junction. These effects are originated from the blocking of ion channels of the acetylcholine receptor. Some individuals are hypersensitive to anesthetics. Reactions lead to dermatitis and asthmatic attacks.

Metabolism: (i) Ester type (e.g., tetracaine) local anesthetics are mainly hydrolyzed and inactivated by a plasma esterase, which is the plasma cholinesterase. The liver is also involved in hydrolysis of local anesthetics. (ii) The amid-like anesthetic agents are degraded by cytochrome P 450 enzymes (CYPs). The use of amid-like local anesthetics is contraindicated in patients suffered from hepatic diseases.

Cocaine: Cocaine occurs in the leaves of the coca shrub. The actions of cocaine are blockade of nerve impulses, and local vasoconstriction, and inhibition of local norepinephrine and dopamine reuptake in the central and peripheral nervous systems. Cocaine hydrochloride is used in 1%, 4%, and 10% solution for topical application especially in ophthalmology.

Lidocaine: Lidocaine induces an intense, more faster, and more extensive anesthesia than procaine, another amide type local anesthetic. Lidocaine is absorbed from mucosa, respiratory tract, and the skin using as a transdermal patch (LIDODERM). Side effects of lidocaine include dizziness, tinnitus, CNS seizures, coma, and respiratory depression. Lidocaine is also used as an antiarrhythmic agent. In this case parenteral (i.v.) injection of lidocaine has to be used.

Bupivacaine: Bupivacaine’s (MARCAINE) structure is similar to that of lidocaine. Levobupivacaine (CHIROCAINE) is the s-enantiomer of bupivacaine. Both agents are able to produce a prolonged local anesthesia. Bupivacaine is more cardiotoxic than equi effective doses of lidocaine, therefore, very careful attention has to be paid on patients having cardiac diseases. The anesthetic block by bupivacaine is cumulative and more than would be substantially predicted.

Other local anesthetics suitable injection:

a). Amid type local anesthetics: articaine (SEPTOCAINE), etidocaine (DURANEST), mepivacaine (CARBOCAINE), prilocaine (CITANEST), ropivacaine (NAROPIN), procaine (NOVOCAIN).

b). Ester type local anesthetics: chloroprocaine (NESACAINE), tetracaine (PONTOCAINE). Tetracaine is mainly used for local surface and spinal anaesthesia. Tetracaine is more slowly metabolized than other ester local anaesthetics, therefore, its systemic toxicity is extremely high.

Local anesthetics used for mucous membranes and skin: These molecules are effective in symptomatic relief of anal and genital, acute and chronic dermatoses. These anesthetic agents
are dibucaine (NUPERCAINAL), dyclonine (DYCLONE), and pramoxine (ANUSOL). The application of these agents has to be avoid in eyes because they are too irritating structures. However, many local anesthetics are restricted for ophthalmological use because they are too irritating. The two anesthetic agents are most frequently used in ophthalmology are praparacaine (ALCAINE) and tetracaine (PENTOCAINE). These local anesthetics are administered dropwise, and an additional drop can be used to reach satisfactory conditions.

**Clinical use of local anesthetics:**

(i). Topical anesthesia: Direct application of aqueous solutions of salts can be used for anesthesia of mucous membranes of the nose, mouth, throat, esophagus, and genitourinary tract. For topical anesthesia tetracaine, lidocaine, and cocaine are mainly used. Sometimes a vasoconstrictor (e.g., phenylephrine, epinephrine) is used in combination with a local anesthetic to prolong the local anesthetic action. Local anesthetic agents are rapidly absorbed into the circulation after topical application on mucous membranes and denuded skin. Thus, after topical anesthesia the risk of systemic toxic reactions is quite at a high level.

(ii). Infiltration anesthesia: Infiltration anesthesia is based on the injection of anesthetics into various tissues without taking any consideration the network of cutaneous nerves. Infiltration anesthesia can be focused on the skin, and deeper structures like infiltration of intraabdominal organs. The application of epinephrine with combination of anesthetics can double the duration of anesthesia, and also reduces the peak concentrations of anesthetics in blood. The application of epinephrine can cause gangrene at the site of injection, therefore, epinephrine must not be injected into tissues supplied by end-arteries such as fingers, toes, ears, nose, and penis. The most frequently used infiltration anesthetics are lidocaine (0.5% and 1.0 %), procaine (0.5% and 1.0 %), and bupivacaine (0.125% and 0.25%).

(iii) Field block anesthesia: This kind of anesthesia is induced by subcutaneous injection of local anesthetic agents to anesthetize the region distal to the injection. This anesthesia can be done in scalp, anterior abdominal wall, and lower extremities.

(iv). Nerve block anesthesia: Anesthetics are injected into peripheral nerves or nerve plexuses producing a greater area of anesthesia leading to skeletal muscle relaxation. Blocking the brachial plexus is particularly useful for procedures on the upper extremities and shoulders. Blocking the cervical plexus is appropriate for neck surgery. The local anesthetics are injected around the nerves or plexuses, and never into the nerves, because it induces nerve damages. Thus, the anesthetics must diffuse from the site of injection into the nerve, where they act. Local anesthetics could be divided in three different groups; (a) short duration of action (e.g., procaine, for 25 to 45 min), (b) intermediate duration of action (e.g., lidocaine and mepivacaine, for 70 to 120 min), and (c) long duration of action (e.g., bupivacaine, ropivacaine, and tetracaine, for 450 min).

(v). Intravenous regional anesthesia: These agents anesthetize the nerve trunks and endings. Local anesthetics are used for blocking nerve trunks and endings. This technique is consisted of with an elastic (Esmarch) bandage with proximally located tourniquet which is inflated to 150 mmHg (above the systolic blood pressure). The bandage is removed and the anesthetic is injected into a previously cannulated vein. This technique is used for anesthesia of limb and arm, and it starts within 5 to 10 min. Lidocaine and procaine are usually used for intravenous regional anesthesia.

(vi). Spinal anesthesia: The anesthetic is injected into the cerebrospinal fluid (CSF). The spinal cord is terminated above the second lumbar vertebra. This is the place for the injection: the thecal sac in the sacrum, because the lumbar and sacral roots are bathed in CSF. Lidocaine, tetracaine, and bupivacaine are usually used for spinal anesthesia. Sympathetic and parasympathetic nerves are blocked, and vasodilation is more dominated on the venous than on the arterial side of circulation. Epinephrine (200 microgram) often is applied in spinal
anesthesia to increase the duration or intensity of nerve blocks. Neurological deficits are very rare during spinal anesthesia. After the administration of local anesthetics, it is diluted rapidly and quickly reached non-toxic concentrations. Sometimes headache is occurred as a side effect after spinal anesthesia. Spinal anesthesia is used for the surgery of lower abdomen, lower extremities, and the perineum.

(vii). Epidural anesthesia: The injection is administered into the epidural space. Continuous infusion or repeated bolus injections can be used. The site of action is on the spinal nerve roots. High concentrations of anesthetics are used, if sympathetic, somatic sensory, and somatic motor blockade are required. Local anesthetics cross the placenta, enter the fatal circulation, and may cause general depression of the neonate. Bupivacaine, lidocaine and chloroprocaine are mainly used for epidural anesthesia. Small quantities of opioids also can be used in epidural anesthesia together with local anesthetics. Spinally administered opioids (e.g., morphine) alone do not provide satisfactory anesthesia for surgical procedures.
Hypnotics and sedatives

Many drugs have the capacity to depress the physiological function of the central nervous system (CNS) when calming and drowsiness (sedation) is produced. Sedative-hypnotic agents depress the CNS in a dose-dependent manner, inducing sedation, sleep, unconsciousness, surgical anesthesia, coma, and finally fatal depression of respiration and circulation. A sedative agent decreases activity, moderates excitement, and calms, whereas a hypnotic drug produces drowsiness and facilitates the sleep. Sedation is also a side effect of many drugs which are not CNS depressant (e.g., neuroleptics and antihistamines), but such agents can intensify the effects of various CNS depressants. However, these molecules cannot produce surgical anesthesia in the absence of a real inhalational or intravenous anesthetic.

About 200 years ago bromide was the first agent to be introduced as a sedative-hypnotic agent. At the beginning of the 20th century, chloral hydrate, paraldehyde, urethane came in the use before the application of barbital in 1903, and phenobarbital in 1912. Barbiturates were the dominant sedative-hypnotics until 1950s. In the 1960s, benzodiazepines were introduced as sedative-hypnotic agents, and became as the most popular sedative-hypnotics.

The hypnotics and sedatives can be divided as (A) benzodiazepines, (B) barbiturates, and (C) agents having diverse chemical structures.

(A) Benzodiazepines

Benzodiazepines have the capacity to promote the binding of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) to the GABA-A subtype of GABA receptors which are ligand-gated chloride channels increasing the Cl⁻ currents through these channels into the cell. The effects of benzodiazepines result from their actions on the CNS. These effects are sedation, hypnosis, decreased anxiety, muscle relaxation, anterograde amnesia, and anticonvulsant activity. The two effects of benzodiazepines result from peripheral actions are (i) coronary vasodilatation and (ii) neuromuscular blockade. The latter can be seen only after the application of high doses benzodiazepines. An overdose of benzodiazepines can be antagonized with flumazenil.

Benzodiazepines affect:
- the CNS: They do not produce the same degree of neuronal depression as do barbiturates and volatile anesthetics. The increase in the dose of benzodiazepines results in sedation progress to hypnosis and then to stupor. Attempts are made to separate the anxiolytic actions of benzodiazepines from their sedative-hypnotic effects, a dissociation between these properties still is problematic. Benzodiazepines exert most of their effects by interacting with neurotransmitter receptors activated directly by GABA. Benzodiazepine agents act at GABA_A, but not GABA_B receptors by binding directly to a specific site that is distinct from that of GABA binding. Benzodiazepine agonist agents at the binding site increase, and antagonists decrease the Cl⁻ current in the cell. Flumazenil, as an antagonist, reverses the effects of benzodiazepines. The GABA_A receptor consists of 16 different subunits including α, β, γ, δ, ε, π, and θ ones.
- the respiration: In hypnotic doses of benzodiazepines have no effect on respiration in healthy subjects. At higher doses, which are used for preanesthetic medication, these drugs moderately depress alveolar ventilation and cause respiratory acidosis. Benzodiazepines could cause apnea during anesthesia or when given together with opioids. In humans, with obstructive sleep apnea (OSA), hypnotic doses of benzodiazepines can decrease smooth muscle tone in the upper airway. Additionally, the drugs can promote the appearance of apnea episodes during REM sleep in patient recovering from myocardial infarction.
- the cardiovascular system and gastrointestinal tract: The effects of benzodiazepines, in therapeutic doses, on the cardiovascular system is negligible in normal subjects. In preanesthetic (higher) doses, the drugs decrease blood pressure and increase heart rate. In large doses, oxygen assimilation and cerebral blood flow are considerably reduced. Benzodiazepines protect against stress-induced ulcers, and decrease gastric secretion in patients.

Pharmacokinetics of benzodiazepines: The drugs absorb completely and bind to GABA receptors. Benzodiazepines, based on elimination half-lives in the body, can be divided in four groups: (i) ultra-short acting agents (half-lives are less than 3 hours), (ii) short-acting agent (half-lives are 5 to 6 hours: chlorazepate, flurazepam, midazolam, triazolam), (iii) intermediate-acting agents (half-lives are between 7 and 24 hours: chlordiazepoxide, estazolam, alprazolam, temazepam, oxazepam, lorazepam), and (iv) long acting agents (half-lives are more than 24 hours: diazepam, quazepam, demoxepam, nordazepam). The drugs are metabolized by cytochrome P-450 enzymes. Various drugs including erythromycin, clarithromycin, ritonavir, intraconazole, ketoconazole, nefazodone, grapefruit juice inhibit P-450 enzymes, therefore the metabolism of benzodiazepines is slow. The ideal benzodiazepines, as hypnotic, may have a rapid onset of action, and a sufficiently sustained action in sleep throughout the night, and no residual action in the next morning.

Therapeutic uses: The drugs are used for (a) anxiety disorders, (b) management of alcohol withdrawal, (c) anesthetic premedication, (d) skeletal muscle relaxation, (e) insomnia (sleep problem), and (f) seizure disorders including status epilepticus.

Untoward effects of benzodiazepines are lightheadedness, motor incoordination, increased reaction time, lassitude, and anterograde amnesia. These effects impair driving and other psychomotor skills if combined with ethanol. Other side effects are weakness, headache, blurred vision, vomiting, chest pain, and joint pain. Benzodiazepines can cause paradoxical effects by increasing nightmares, anxiety, irritability, sweating, euphoria, and hallucination. Paranoia, depression, and suicidal ideation may also occur. Chronically applied benzodiazepines possess a risk for the development of dependence and abuse but these effects are not as intensive as it is in the application of opioids. Withdrawal symptoms can also occur.

Novel benzodiazepine agonists: The molecular structures of these agonists completely differ from those of benzodiazepines, however the action site is the GABA<sub>A</sub> receptor alpha-1 subunit. These drugs are zolpidone, zolpidem (AMBIEN, imidazopyridine structure), zaleplon (SONATA, a pyrazolopyrimidine structure), and indiplon. These drugs have sustained hypnotic efficacy without occurrence of rebound insomnia. Current investigations show that zaleplon (the only molecule in this group) has no more side effects than placebo. This group of hypnotics has very little effect on sleep in normal subjects, however the therapeutic effect of these drugs are expressed in patients with insomnia. These drugs do not produce severe respiratory depression, at higher doses, as the classic benzodiazepines do.

A benzodiazepine receptor antagonist: flumazenil.
Flumazenil (ROMAZICON) is an imidazobenzodiazepine structure which is a specific benzodiazepine receptor antagonist and binding to the GABA<sub>A</sub> receptor. Flumazenil (1 mg as a bonus injection) can be administered intravenously, half-life is about one hour, and the elimination is going through the liver. A single injection in a dose of 1 mg of flumazenil is able to abolish the effects of benzodiazepines within 2 minutes. If it is necessary, the dose of flumazenil can be repeated after 15-20 minutes.
(B) Barbiturates

Barbiturates were used extensively as sedative-hypnotic agents. Since 1980s, the barbiturates have been extensively replaced, with some exceptions, by much safer benzodiazepine agents.

Effects of barbiturates: Barbiturates reversibly depress the activity of excitable tissues including CNS and cardiovascular system. Barbiturates act at GABA, and GABA-related chloride channels. Chloride channels are opened leading to hyperpolarization of cell membranes and blocking the impulse conductance. Barbiturates also depress voltage-activated calcium currents. At higher concentrations of barbiturates also reduce K+ conductance. The drugs increase the total sleep time, and some tolerance can be developed. Functional and pharmacokinetic tolerance to barbiturates can occur over a period to months. The effect of tolerance on mood, sedation, and hypnosis occurs more readily and is greater than tolerance to the anticonvulsant effect. Barbiturates depress respiration and the cardiovascular system as well. The drugs decrease tone of gastrointestinal musculatures and rhythm contractions. Barbiturates enhance the activity of P-450 enzymes, thus the metabolisms of a number of drugs are increased.

Absorption, fate, and excretion of barbiturates: Oral doses are absorbed rapidly and completely. The intravenous route is reserved for the management of general anesthesia (thiopental and methohexital) and status epilepticus (phenobarbital). With the exception of lipid soluble aprobarbital and phenobarbital, the complete metabolism of barbiturates is in the liver and renal extraction. Repeated administration shortens the half life of barbiturates that are metabolized as a result of the induction of microsomal enzyme systems.

Therapeutic uses of barbiturates: Phenobarbital and butobarbital are still available as sedative agents. Phenobarbital is used most frequently as an anticonvulsant. Ultra short acting agents such as thiopental and methohexital are employed as intravenous anesthetics. Anesthetic doses of barbiturates attenuate cerebral edema resulting from surgery or head injury. Amobarbital is used for narcotherapy in psychiatry.

Untoward effects: Drowsiness, impair performance of driving, vomiting, and diarrhea are sometimes observed. In some individuals, barbiturates produce excitement rather than depression. Allergic reactions occur, especially in patients with asthma, urticaria, and angioedema. The combination of barbiturates with other CNS depressants causes severe depression. Barbiturates enhance porphyrin synthesis, therefore, they are absolutely contraindicated in patients with porphyria. Rapid intravenous injection of barbiturates cause cardiovascular collapse.

( C ) Miscellaneous sedative-hypnotics

Paraldehyde is used for the treatment of withdrawal reactions including delirium tremens, and other psychiatric states characterized by excitement. Chloral hydrate has been employed for sedation in children. Meprobamate is used for sedation and against anxiety. The abuse is also occurred by this drug. Etomidate (AMIDATE) is used as a sedative-hypnotic agent, and combination with fentanyl for general anesthesia. Clomethiazol is used as a sedative, anticonvulsant, and muscle relaxant agent. Furthermore, this drug is used for ethanol withdrawal.

Depression and anxiety disorders, drugs

The introduction of psychotropic drugs originates in conjunction with the synthesis and degradation of monoamine neurotransmitters including catecholamines and serotonin (5-
Antipsychotic, mood-stabilizing, and antidepressant drugs are used to treat various severe mental disorders. The leading hypothesis is that antidepressants increase the biological activity of neurotransmitters in the CNS, and antiadrenergic molecules could induce depression. Thus, a deficiency in monoamine transmission can cause depression in CNS activity, whereas an excess may result in mania. In addition, antipsychotic-antimanic agents are able to antagonize the dopamine-induced neurotransmission in the forebrain, promoting an overactivity of dopamine in the limbic system and cerebral cortex in schizophrenia and mania. Antipsychotic, antianxiety, antimanic, and antidepressant agents have substantial effects on cortical, limbic, hypothalamic, and brainstem functions that are of basic importance in the regulation of autonomic mechanisms. The basic clinical manifestations of depressions are depressions on the mood, thinking, loss of concentrations of learning and work. The depressive disorders include panic-agoraphobia, severe phobias, generalized anxiety, posttraumatic stress, and obsessive-compulsive disorders. Secondary changes in mood are also associated with psychotic disorders. Mood and anxiety disorders are the most common mental illnesses, affecting about 15% of the population at some time in their lives. The clinical depression has to be distinguished from normal sadness, disappointment, and demoralization associated with medical disorders. The depression includes insomnia or hypersomnia, overeating or anorexia, disruption of regular circadian rhythms, changes in endocrine functions, and suicidal behaviour. Patients suffer from depression usually well respond to antidepressant therapy, however, in severe or resistant ceases electroconvulsive therapy can be used for life saving in acutely suicidal patients.

Antidepressants: These drugs have an action on the metabolism of monoamine neurotransmitters. The routes to influence the metabolisms are the following:

- Inhibition of monoamine oxidase (MAO): In the middle of the XXth century, isoniazid and iproniazide (as antituberculosis agents) were recognized as MAO inhibitors and were also used to treat depression. Later tranylcypromine, as a nonselective MAO inhibitor (blocking MAO-A and MAO-B enzymes), was used for the therapy of depression. Other MAO inhibitors are phenelzine, isocarboxazid, tranylcypromine (nonselective MAO inhibitors), and selegiline (a specific MAO-B inhibitor). Selegiline as a MAO-B inhibitor is used for Parkinson’s disease and as antidepressant as well. MAO-A is expressed in noradrenergic neurons, while MAO-B is expressed in serotonergic and histaminergic neurons. Selegiline has no (or very little) effect on MAO-A in the gut allowing liberalization of the tyramine-restricted diet that is necessary to avoid fatal hypertensive crises. MAO inhibition develops immediately and maintains for a few days.

- Tricylic antidepressants, and inhibitors of selective serotonin reuptake (SSRIs): Imipramine, amitriptyline, clomipramine, and doxepin block the neuronal uptake of serotonin and norepinephrine. These drugs have antihistamine, sedative, analgesic, and antiparkinson effects. In the 1970s, it was realized that chlorpheniramine, diphenhydramine, fluoxetine, and fluvoxamine inhibited both the serotonin and norepinephrine transports. Citalopram, fluoxetine, norfluoxetine, sertraline, and paroxetine are selective inhibitors of serotonin reuptake. While, amoxapine, maprotiline, nortriptyline, atomoxetine, and reboxetine, are relative inhibitors of norepinephrine transport (reuptake).

Properties of tricyclic antidepressants: The advantage of these tricyclic norepinephrine-active antidepressants is that these agents do not block dopamine transport. Most tricyclic antidepressants have moderate affinity for alpha-1 receptors. Because of the direct alpha-1 blockade, blood pressure is initially decreased. SSRIs block the neuronal transport of serotonin immediately and chronically. Increased synaptic availability of 5-HT stimulates postsynaptic 5-HT-receptors including 5-HT-3 (nausea, vomiting and impaired orgasm), 5-HT-2C (agitation and restlessness), 5-HT-1 (suppressing the function of serotonin
neurons), and 5-HT-2A (responsible directly to antidepressive effects) receptors. The stimulation of 5-HT-2A receptors is also related to the cAMP-related activation.

Other drugs affecting monoamine neurotransmission: The inhibition of dopamine uptake is also related to the antipsychotic effect. Thus, bupropion and tranylcypromine have dopamine reuptake inhibitor effect. Tranylcypromine possesses also MAO inhibitor effect. Nefazodone and trazodone have prominent direct antagonistic effect at 5-HT-2A receptors that are contributing to antidepressant and anxiolytic activity. Both nefazodone and trazodone inhibit presynaptic 5-HT-1 autoreceptors to enhance neuronal release of serotonin. Atypical antidepressants, mirtazapine and mianserin have postsynaptic serotonin antagonistic effects at 5-HT-2A, 5-HT-2C, and 5-HT-3 receptors. Mirtazapine is also a potent histamine receptor-1 antagonist and is relatively sedating.

Absorption, distribution, and metabolism of antidepressants: They are well absorbed from the gastrointestinal tract therefore, these agents are orally administered. Antidepressants are lipophilic and bind to plasma proteins and accumulate in cardiac and brain tissues. Antidepressants are oxidized by hepatic microsomal enzymes followed by conjunction with glucuronic acid and leave the body via the urine. The metabolism of antidepressants is related to the activity of hepatic cytochrome P450 enzymes. Most MAO inhibitors are long acting, because the recovery from their effects requires the synthesis of new enzyme over a period of 1 week.

Tolerance and adverse effects of antidepressants: Tolerance to the sedative effects of tricyclic antidepressants is associated with the inhibition of serotonin reuptake. The development of tolerance can be manifested after 1 or 2 years of application. Physical dependence on the tricyclic antidepressants is muscle aches, sleep disturbance, gastrointestinal symptoms, vomiting, nightmares, agitation, psychosis, and convulsions. Emergence of agitated and manic reactions has been observed after abrupt discontinuation of tricyclic antidepressants.

Adverse effects of antidepressants: these effects include metallic taste, constipation, dizziness, palpitation, cardiac arrhythmias, blurred vision, urinary retention, fatigue, variable risk of confusion and delirium, sedation, weight gain, edema, tremor, sexual dysfunction, hyperreflexia, hallucinations (MAO inhibitors), fever, and convulsions, and suddenly switching from depression to hypomanic excitement. Children are very vulnerable to the cardiotoxic effect of tricyclic antidepressants. Suicidal risk is also increased in some juveniles treated with antidepressants.

Toxic effects and interactions: The overdose of MAO inhibitor antidepressants is potentially life-threatening. Deaths have been known to occur with acute doses of antidepressants between 1.5 and 2 grams. Antidepressants that have strong antimuscarinic potency induce an atropine-like syndrome of mydriasis, dry skin and mucosae, urinary retention, and severe cardiac arrhythmias including QT prolongation and expanded QRS complex.

Drug interaction may occur with the binding of antidepressants to plasma albumin, which can be reduced by competition with phenytoin, aspirin, scopolamine, and phenothiazines. Barbiturates and other anticonvulsant agents as well as smoking increase the hepatic metabolism of antidepressants by inducing cytochrome P-450 enzymes. The inhibitors of selective serotonin reuptake (SSRIs) include the potentiation of agents metabolized by cytochrome P-450 enzymes e.g., beta receptor antagonists, caffeine, benzodiazepines, and antipsychotics. Antidepressants potentiate the effect of alcohol and other sedatives. To avoid
drug toxicity and occurrence of serotonin syndrome, duration of effects have to be considered when switching between the various antidepressants.

Therapeutic uses of antidepressants: The drugs are used as antidepressants, hyperactivity disorders in children and adults, anxiety disorders including panic disorder with agoraphobia, social phobias, disturbed sleep, mood disorders, and chronic pain disorders such as diabetic and other peripheral neuropathic syndromes. SSRIs are of choice for the treatment of obsessive preoccupations, impulse dyscontrol, compulsive gambling, and body dysmorphic disorder.

**Psychosis and mania**

Psychosis includes schizophrenia, the manic phase of bipolar (manic depressive) illness, acute idiopathic psychotic illness, reasoning, hallucination (abnormal sensation) and severe manic agitation. Psychosis are the most severe psychiatric disorders including impairment of behaviour, inability to think coherently, the misjudgement of reality. Psychotic features can be also seen in major mood disorders, and severe melancholic depression. Antipsychotic agents are also useful to electroconvulsive therapy (ECT) in depression with psychotic features, and psychosis associated with delirium or dementia.

Antipsychotic agents are (i) phenothiazines (chlorpromazine: THORAZINE; mesoridazine: SERENTIL; thioridazine: MELLARIL; fluphenazine: PROLIXIN; perphenazine: TRILAFON; trifluoperazine: STELAZINE), (ii) thioxanthenes (promethazine, diethazine), (iii) benzepines (loxapine: LOXITANE; clozapine: CLOZARIL; olanzapine: ZYPREXA), (iv) butyrophenones (haloperidol: HALDOL), (v) diphenylbutylpiperidines (fluspirilene, penfluridol, pimozide: ORAP), (vi) indolones (molindone: MOBAN; oxypertine), and (vii) other heterocyclic compounds (risperidone: RISPERDAL; ziprasidone: GEODON).

The neuroleptic agents have evidence of antagonism of D2-dopamine receptor activity with a substantial risk of adverse extrapyramidal effects and increased release of prolactin. Atypical antipsychotic is the term to agents that are associated with relatively low risks of extrapyramidal effects. Atypical antipsychotic agents are aripiprazole, clozapine, quetiapine, ziprasidone, and low doses of olanzapine and resperidone.

Antipsychotic effects (including tricyclic antipsychotics) were observed using the extract of Rauwolfia plant, and this was the reserpine. Phenothiazines were synthesized in 1890s, and then promethazine was found to have antihistaminic and sedative effects. The first antipsychotic agent to treat mental illness was chlorpromazine in 1951, and then new generations of antipsychotics were developed. These new antipsychotic drugs have complex effects including antiserotonergic (5-HT-2A), antidopaminergic (D2-like), antiadrenergic (alpha-1), antihistaminic (H1) activity, and sedative effects.

Antipsychotic agents have extrapyramidal effects. These are rigidity and bradykinesia, which mimic catatonia, can be induced by large doses of potent neuroleptics (antipsychotic drugs). These symptoms can be suspended by anti-parkinson drugs. Antipsychotic drug effects derived from their ability to antagonize the action of dopamine as a neurotransmitter in basal ganglia, limbic portions of the forebrain, and in the cerebral cortex. Antagonism of dopamine-mediated synaptic neurotransmission is a basic action of antipsychotic agents on D2 receptors. Butyrophenone antipsychotics are relatively selective antagonists of D2 receptors, but they possess D3 and D4 receptor affinity.

Absorption, distribution, and excretion of antipsychotics: The absorption is unpredictable after oral administration, therefore these drugs usually are administered
intramuscularly. The drugs are highly lipophilic, protein-bound and accumulate in the brain, lung and other tissues with a rich blood supply. The elimination half-lives are 20 to 40 hours in the plasma. Metabolites of some antipsychotics are detected in the urine after several months of the application of the last dose. The half-life of some antipsychotic agents is about 10 days when administered via intramuscular injection. These drugs are metabolized by hepatic P450 enzymes by glucuronidation and sulfation. The metabolites of antipsychotic drugs are biologically inactive. The antipsychotic drugs are not addicting.

Toxic reactions and adverse effects of antipsychotics: These drugs have a high therapeutic index and safety profile. A very common adverse effect is Parkinson’s disease, an extrapiramidal effect. Adverse effects are on the cardiovascular, endocrine, and central and autonomic nervous systems. Symptoms include seizures, facial grimacing, agranulocytosis, palpitations, nasal stuffiness, dry mouth, worsening of glaucoma, hypotension, and cardiomyopathy. Akathasia can develop. This refers to strong subjective feelings of anxious discomfort and a compelling need to be in constant movement. Tardive dyskinesia is a late appearing neurological syndrome, and it occurs and more frequent in older patients. Weight gain can occur and this is a risk factor for the developing of type-2 diabetes.

Interaction with other drugs: Antipsychotic agents can strongly potentiate the effects of sedatives and analgesics. The drugs increase the respiratory depression produced by opioids. The antimuscarinic action of antipsychotics can induce tachycardia and increase the central effects of other anticholinergic drugs. Phenytoine (an antiepileptic and antiarrhythmic drug) induces P450 enzymes and enhances the metabolism of anticoagulants and contraceptives.

Drug treatment of psychosis:
1). Short term treatment: The target symptoms of short term treatment for which antipsychotic drugs are beneficial include hostility, hallucinations, acute delusions, insomnia, agitation, negativism, and anorexia. In addition, the drugs are also effective against memory and orientation disorders. However, individuals may respond better with one drug than another one. Drug selection for short-term treatment depends on the tolerability of side effects, minimizing extrapyramidal symptoms, the need for sedation, history of cardiovascular disease or stroke, and the threat for hypotension. Usually 2 or 3 weeks are required for the development of a beneficial effect of antipsychotic therapy.

2). Long term treatment: Atypical (no Parkinson side effects) antipsychotic drugs are used for long term treatment. In this case, a single injection can be done in every 2nd or 4th week. Modern atypical agents are not established for psychosis with delirium and dementia. In the latter case haloperidol can be effective. Most antipsychotics are rapidly effective for long term treatment of mania with the combination of lithium. Low doses of modern atypical agents are preferred to avoid interference with daytime activities in work and school. In long term treatment, the potential risk of stroke in elderly patients should be also considered.

Treatment of mania: Lithium carbonate, sharing some characteristics with those of sodium and potassium, was the first and introduced for the treatment of mania in 1949. The salt is effective against the development of mania and the prevention of recurrent attacks of bipolar manic-depressive illness. Lithium is assayed in various biological fluids and brain by magnetic resonance spectroscopy. Lithium is not a sedative, depressant, or euphoriant agent. The exact mechanism of lithium as an antimanic agent is unknown.

Pharmacological properties of lithium: An important characteristic of lithium that it has a relatively little gradient of distribution across cell membranes. Lithium can replace sodium in supporting a single action potential in the nerve. Lithium inhibits the
depolarization-provoked and calcium-dependent release of norepinephrine and dopamine from nerve endings. Lithium treatment leads to consistent decrease in functioning of protein kinases in the brain, and this effect can change the release of monoamine neurotransmitters.

Absorption, distribution, and excretion of lithium: Concentrations considered to be effective and acceptably safe are between 0.6 and 1.2 mEq per litre for the treatment of acutely manic or hypomanic patients. Lithium is completely absorbed from gastrointestinal tract, and is distributed in the extracellular fluid and various tissues. After distribution, the concentration of lithium is about 50% compared to the plasma. The elimination half-life of lithium is 24 hours, and eliminated in the urine. Potential drug interaction can occur with nonsteroidal anti-inflammatory agents and angiotensin converting enzyme inhibitors.

Toxic reactions and side effects of lithium: These are vomiting, diarrhea, ataxia, tremor, coma, and convulsions. Additionally, in mild intoxication, mental confusion, hyper reflexia, cardiac arrhythmias, hypotension, albuminuria, weight gain, and tremor are sometimes observed. In patients treated with lithium, thyroid uptake of iodine is increased, and thyroid stimulating hormone (TSH) secretion is moderately elevated. Lithium has an action on carbohydrate metabolism causing an increase in skeletal muscle glycogen by depletion of glycogen from the liver. There is no specific antidote for lithium intoxication.

Therapeutic uses of lithium: Lithium is suitable for the treatment of mania and bipolar disorders. The combination of lithium treatment with antipsychotics, anticonvulsants, and sodium valproate can be done with high efficacy. The treatment can be continued for months to restore the normal condition. Discontinuation of maintenance treatment of lithium carries a high risk of suicidal behaviour over several months. The risk can be moderated by slowing the gradual removal and supply of lithium when it is medically feasible. In summary, mania and bipolar disorders can be treated with lithium and antipsychotic agents. Antipsychotic drugs block D2 receptors, and have interactions with 5-HT-2A, 5-HT-2C, and H1 receptors.

Epilepsies

The term of epilepsy refers to an illness of brain function characterized by the periodic and unpredictable occurrence of central nervous system related seizures. Epileptic seizures cause transient impairment of consciousness for a certain period of time throughout the life interfering with the abilities of education and employment. The pharmacological agents, in clinical use, action mechanisms of antiepileptic agents are divided in three groups. 1). The promotion of the inactivated state of voltage-activated sodium channels. 2). The enhanced GABA-mediated synaptic inhibition. 3). Limited activation of voltage-mediated Ca-channels. The treatment of epilepsies can be preventive or symptomatic.

Seizures are originated from the cortex, and not from other structures of CNS such as thalamus, brainstem, and cerebellum. Epileptic seizures can be classified as (A) partial seizures beginning focally in a cortical site, and (B) generalized seizures involving both the left and right hemispheres.

The partial seizures (A) can be further classified as (i) simple partial seizure, (ii) complex partial seizure, and (iii) partial with secondarily generalized tonic-clonic seizure. The manifestation of (i) simple partial seizure is determined by the region of cortex activated by the developed seizure. This seizure is lasting approximately about 30 to 60 seconds. The key feature of this seizure is that consciousness is preserved. The (ii) complex partial seizure involves unconsciousness lasting 1 minutes to 2 minutes in association with purposeless movements including lip smacking and hand wringing. The patients suffer (iii) from partial with secondarily generalized tonic-clonic seizure show simple or complex partial seizures evolve into tonic-clonic seizures with loss of consciousness, and sustained tonic contraction
of muscles throughout the body following by periods of relaxation lasting 1 to 2 minutes or even longer periods.

Generalized seizures (B) can be also classified as (i) absence seizures, which is abrupt onset of impaired consciousness with starting and cessation of ongoing activities lasting about 30 seconds. (ii) Myoclonic seizure which include a very brief (1 to 2 seconds), shocklike contraction of muscles what may be restricted to part of one extremity or generalized. (iii) Tonic-clonic seizure: patients suffering from this syndrome show tonic-clonic seizures with loss of consciousness, and sustained tonic contraction of muscles throughout the body following by periods of relaxation, but this seizure is not preceded by a partial seizure.

In addition to the above classification of seizures, additional classification specifies epileptic syndromes, referring to a cluster of symptoms occurring frequently together, include various seizures, etiology, age of onset, and many other factors. All together more than 40 distinct epileptic syndromes have been described and categorized into partial and generalized groups of epilepsies. Partial epilepsies may consist of a partial seizure, and account for about 60% of all types of epilepsies. The etiology is originated from some part of the cortex, tumor, developmental malformation, due to stroke or trauma damages. Generalized epilepsies are characterized by more of generalized seizures and accounted for about 40% of epilepsies. The etiology is usually genetic of origin. The most common generalized epilepsy is the juvenile myoclonic epilepsy, and the age of onset is in the early teens.

Mechanisms of seizures and antiepileptic drugs

1). Partial epilepsy is a generalized convulsion resulted when normal brain tissue is invaded by a seizure activity initiated in the abnormal focus. By the application of EEG in the first half of the 20th century permitted the continuous recording of electrical activity of the scalp, and later it was demonstrated that epilepsies are disorders of neuronal excitability related to sodium, potassium and calcium ion contents. It was demonstrated that neurons undergo depolarization and fire action potentials at high frequencies. The pattern of neuronal firing is characteristic of the development of seizure. Inhibition of the high-frequency firing is mediated by reducing the ability of sodium channels to recover from inactivation. Upon recovery from inactivation, sodium channels are able to generate another action potential. Thus, reducing the rate of recovery of sodium channels from inactivation could limit the fire of neurons at high frequencies.

2). Additional mechanisms. It was suggested that GABA-related synaptic inhibition may reduce neuronal excitability and increase the threshold of seizure. Activation of GABA-A receptor blocks the postsynaptic neuron by increasing the inflow of chloride ions which tends to hyperpolarize the neuron. Thus, in the hyperpolarized state, the neuron cannot be stimulated.

Generalized epilepsies, and absence seizures: Opposite to partial seizures that are arisen from a well localized region of the cortex, generalized-onset seizures arise from reciprocal firing of thalamus, cortex, and neocortex. Studies of absence seizures by EEG are shown that generalized spike-and-wave discharges occurs at a frequency of 3 Hz. It was also shown that spikes are associated with the firing of action potentials followed by slow wave with prolonged inhibition. Low frequency rhythms give a chance to develop reciprocal excitatory synaptic connections between neocortex and thalamus, and the 3-Hz spike-and-wave discharges are related to voltage-regulated Ca current.
Genetics of epilepsies: Genetic causes of epilepsies are attributed to juvenile myoclonic epilepsy and childhood absence epilepsy which are probably due to inheritance of two or more genes. Most patients with epilepsy are neurologically normal, thus, the elucidating the mutant genes underlying familial epilepsy. All together 11 genes have been identified which can play an important role in epileptic syndromes. All of the mutant genes encode ion channels that are gated by voltage and ligands. These ion channels are sodium and potassium channels, and channels gated by GABA and acetylcholine. For instance, generalized epilepsy is caused by a point mutation in the beta subunit of voltage gated sodium channel (SCN1B).

Antiepileptics, history: The first drug used specifically as an antiepileptic, in the late 19th century, was bromide followed by phenobarbital. Phenobarbital has a beneficial effect for most epilepsy, but has no effect on absence seizures. The next agent was phenytoin which suppressed seizures without sedative effect. The chemical structure of most antiepileptic drugs was related to phenobarbital before 1965. The antiepileptic molecules, developed between 1965 and 1990, involved benzodiazepines, iminostilbenes, and valproic acid structures. After 1990, new structures of antiepileptics such as phenyltrimazane (lamotrigine), cyclic analog of GABA (gabapentin), sulfamate-substituted monosaccharide (topiramate), nipecotic acid derivative (tiagabine), and pyrrolidine derivative (levetiracetam) were developed.

Therapeutic aspects: The ideal antiepileptic is able to suppress all kind of seizures without adverse effects. Clinicians who treat patients must select the most appropriate antiepileptics. Thus the treatment of patients is very individual. To minimize toxicity, a single drug is preferred for use in a particular patient. If the development of seizures is not controlled by a single epileptic drug, another drug can be applied with combination. Sometimes multiple drug therapy can be used if two or more types of seizures occur.

The classification of antiepileptics: (a) hydantoins, (b) barbiturates, (c) iminostilbenes, (d) succinimides, (e) valproic acid, (f) benzodiazepines, and (g) other antiseizure drugs.

(a) Hydantoins: Phenytoin (DILANTIN) and ethotoin (PEGANONE) are effective in all types of epilepsies, but not in absence seizure. Phenytoin was synthesized in 1908, having no sedative effect, and was used against seizures starting from 1938. Thus, phenytoin has antiseizure activity without causing depression in the CNS. Its effect is mediated by slowing of the rate of recovery of voltage activated sodium channels from inactivation.

Pharmacokinetic, toxicity, and uses: Usually a single dose application produces the required effect. The plasma half-life varies between 12 and 24 hours, and metabolized by cytochrome P-450 enzymes. Coadministration with warfarin (anticoagulant) can lead to bleeding disorders. Furthermore, coadministration of phenytoin with contraceptives leads to unplanned pregnancy. Toxic effects of phenytoin are arrhythmias, hypotension, cerebellar atrophy, behavioural changes, osteomalacia, megaloblastic anemia, leukopenia, hyperglycemia, inhibition of release of ADH, and gingival hyperplasia. Phenytoin is the more widely used antiepileptic, is effective in all epilepsies, but not in absence seizure.

(b) Barbiturates: Phenobarbital (LUMINAL) is inexpensive and very effective drug, and having maximal antiseizure action among all barbiturates. Phenobarbital is a GABA-A agonist, and limits sustained repetitive firings. Oral absorption is complete but slow, and 60% is bound to plasma proteins, metabolized by cytochrome P-450 enzymes in the liver causing enzyme induction. Tolerance is developed after chronic application, and Phenobarbital
produces hyperactivity in children, and confusion in elderly. Phenobarbital is an effective agent for generalized tonic-clonic and partial seizures. Mephobarbital (MEBARAL) is another barbiturate which is used for the treatment of epileptic seizures.

(c) Iminositilbenes: Carbamazepine (TEGRETOL, CARBATROL) was initially used for the treatment of trigeminal neuralgia. Currently these drugs are used primarily for the treatment of partial and tonic-clonic epilepsies. Oxcarbazepine (TRILEPTAL) has the same effects as those of Carbamazepine, but has less potential to induce P-450 enzyme activity in the liver. Carbamazepine is chemically related to tricyclic antidepressants. Both drugs limits the repetitive firing of action potentials which relates to the recovery of sodium channels from inactivation. At therapeutic doses these drugs do not affect GABA or glutamate activities. Carbamazepine is slowly absorbed after oral application, but distributed rapidly into all tissues, and excreted in the urine as glucuronides. Intoxication of carbamazepine and oxcarbamazepine may result in stupor, coma, convulsion, depression, mild leukopenia, and aplastic anemia. Both drugs are beneficial for the treatment of generalized tonic-clonic and complex seizures. Carbamazepine is now still the primary molecule for treatment of trigeminal and glossopharyngeal neuralgias. Carbamazepine is suitable for the treatment of bipolar affective disorders.

(d) Succinimides: Ethosuximide (ZARONTIN) is the primary drug for the treatment of absence seizure. Methsuximide (CELONTIN) has phenyl substituents and is more effective against maximal electroshock seizures. These drugs reduce low threshold Ca currents in thalamic neurons. Succinimides do not inhibit GABA responses at clinical doses. Absorption of both drugs is complete from the gastrointestinal tract, and 25% of ethosuximide is excreted unchanged form via the urine. Side effects are vomiting, anorexia, euphoria, headache, Parkinsonlike syndromes, agitation, anxiety, and skin reactions. Succinimides are effective against absence seizures, but not tonic-clonic seizures.

(e) Valproic acid (DEPAKENE): Valporate inhibits tonic and clonic seizures. Valproic acid mediates the prolonged recovery of voltage-activated Na channels from inactivation, and reduces the low threshold calcium current. The drug is completely absorbed after oral administration, it binds to plasma proteins. The majority (95%) of valproic acid undergoes hepatic metabolism via beta-oxidation. Its half-life is about 15 hours. Common side effects of the drug include gastrointestinal symptoms, sedation, ataxia, and tremor. Valproate is effective against the development of absence, myoclonic, partial, and tonic-clonic epilepsies.

(f) Benzodiazepines: This group of drugs is primarily employed clinically sedative-antianxiety drugs. However, the structures below are used for the treatment of various epileptic seizures: clonazepam (KLONOPIN), clorazepate (TRANXENE-SD), diazepam (VALIUM, DIASTAT), lorazepam (ATIVAN). These benzodiazepines are effective for the treatment of status epilepticus. Benzodiazepines mediate the effect of GABA at GABA-A receptors. These drugs are well absorbed after oral administration, and the extent of binding of benzodiazepines to plasma proteins is almost 100%, and their half-lives are about 30 hours. Side effects are muscular incordination, ataxia, hypotonia, anorexia. Cardiovascular and respiratory depression could occur after intravenous administration. Benzodiazepines are very effective against status epilepticus in injected forms.
(g) Other antiseizure drugs:
- Gabapentin (NEURONTIN) was designed as a GABA agonist, but its exact action mechanism is unknown. It may promote nonvesicular release of GABA, and it inhibits tonic seizures.
- Lamotrigine (LAMICTAL): its effect is related to the function of sodium channels, and this explains its protective effect against secondarily generalized tonic-clonic seizures.
- Levetiracetam (KEPPRA) inhibits partial and secondarily generalized tonic-clonic seizures. The action mechanism of levetiracetam is unknown. No interaction with sodium, calcium or GABA was reported.
- Tiagabine (GABITRIL) inhibits GABA transporters, thereby reduces GABA-reuptake into neurons. The drug is quickly absorbed after oral administration, and is used in refractory partial seizures.
- Topiramate (TOPAMAX): This drug reduces voltage-gated sodium currents and hyperpolarizing potassium current, and inhibits glutamate receptors. Topiramate is used in partial and primarily generalized epilepsy, and refractory partial epilepsy. The drug is well tolerated by patients.
- Zonisamide (ZONEGRAN) inhibits T-type calcium currents and the repetitive firing of spinal cord neurons affecting the voltage-gated sodium channels. The drug can be used in refractory partial seizure.

General principles for the therapy of epilepsies: The initiation of the treatment is necessary after the appearance of clonic-tonic seizures. It has to be started in the case who has a family history of epilepsy. Furthermore, antiepileptic therapy must be used in status epilepticus. Initially monotherapy must be used. If monotherapy is insufficient, drug combination is necessary. If an antiepileptic drug is initiated, the duration of treatment is at least two years. In many cases the treatment has to be continued during the entire life. Absence seizures can be treated by ethosuximide and valporate. Valproic acid is the drug of choice for the treatment of juvenile myoclonic epilepsy with tonic-clonic and absence seizures. Status epilepticus is a neurological emergency. The electrical seizure activity has to be blocked immediately, and drug must be administered by intravenous route. Thus, diazepam followed by phenytoin can be applied.

Degenerative disorders

Neurodegenerative diseases are characterized by progressive and irreversible loss of neurons from defined regions of the CNS. The three well known neurodegenerative disorders are the Parkinson’s disease (PD), Huntington’s disease (HD), and Alzheimer’s disease (AD). PA and HD are the loss of neurons from basal ganglia resulting in abnormalities in controlling of movements. AD is the loss of hippocampal and cortical neurons leads to the significant reduced function of memory, cognitive ability, and amyotrophic lateral sclerosis (ALS), where the reduction of muscular function results from the degeneration of spinal, bulbar, and cortical motor neurons. All three disorders (PD, HD, and AD) are very frequent in appearance, and represent a substantial medical and societal problem. These three disorders are primarily diseases of later life. PD is developed in more than 1% of individuals over the age of 65, and AD is above 10%. HD is genetically determined autosomal disorder is about 0.01%, and families are carrying this gene.

The therapy of neurodegenerative diseases is mostly limited to symptomatic treatments that do not alter the course of the underlying disease. Symptomatic treatment of PD, where the neurochemical deficit induced by the disease is well defined, is relatively
successful. Currently available treatments for AD, HD, and ALS are much more limited in success and effectiveness. PD is extensive destruction of dopaminergic neurons in the substantia nigra, whereas neurons in other areas of the brain are unaffected. Neuronal injury in AD is severe in the hippocampus, cortex, and neocortex. The mutant gene responsible for HD disorder is expressed throughout the entire brain, and most prominent in the neostriatum. There is a loss of spinal motor neurons and cortical neurons in ALS. The development of all degenerative neuronal diseases can be explained by the production of toxic free radicals as by-products of changed cellular metabolisms.

It has also long been suspected that genetics plays an important role in the etiology of neurodegenerative diseases. In HD, the molecular nature of genetic defect has been well characterized. In PD, AD, and ALS, are sporadic, but families of these diseases have been identified. It has been recognized that in the development of PD, the most important genes and their proteins are alpha-synuclein (an abundant synaptic protein), parkin, (a ubiquitin hydrolase), UCHL1 (ubiquitin-mediated degradation protein), and DJ-1 (a protein responses to stress). In AD, mutations in the genes coding the amyloid precursor proteins (APP) are involved in the inherited forms of the disease. Mutations in cooper-zinc superoxide dismutase (SOD1) may account for the development of ALS.

Causes of neurodegenerative diseases: (i) Infectious agents, toxins, and acquired brain injury have a role in the etiology of neurodegenerative diseases. Traumatic brain injury may be one of the most important factors for the development of neurodegenerative diseases as an environmental trigger. (ii) Some of the widely used agricultural pesticides (e.g., rotenone) have been shown to induce Parkinson-like disease. (iii) Glutamate is an excitatory neurotransmitter, and it is believed that glutamate mediates most excitatory synaptic transmission, thus it is required for normal brain functions. However, the excessive amounts of glutamate could lead to “excitotoxic” cell deaths. The destruction of neurons is mediated by glutamate receptors (N-methyl-D-aspartate, NMDA). The function of NMDA receptors is also related to Ca2+ entry and Mg2+ content in the neuron. Changes in energy metabolism and aging (iv) also responsible for the development of neurodegenerative disease. Patients with PD exhibit several defects in energy metabolism that are even bigger than expected from the age, and it is probably related to the reduced function in the mitochondrial electron-transport chain. Oxidative stress (v), which is related to the production of oxygen free radicals, can lead to the development of neurodegenerative diseases via the DNA damage (fragmentation) and peroxidation of membrane lipids. Oxidative stress changes the metabolism of dopamine which leads to PD.

PD Diseases (paralysis agitans or shaking palsy)

Parkinson disease is consisting of four various symptoms. These are (a) bradykinesia (slowness of movement), (b) muscular rigidity, (c) resting tremor which abates during voluntary movement, and (d) impairment of postural balance leading to disturbances of gait and falling. The pathological cause of PD is the loss of pigmented dopaminergic neurons in the substantia nigra, providing dopaminergic innervation to the striatum, with the appearance of intracellular inclusions known as “Lewy bodies”. Without pharmacological interventions, PD progress over 8 to 12 years leading to an akinetic state in which people are incapable of carrying themselves, and deaths frequently originated from complications of immobility, and as a consequence from aspiration pneumonia, and pulmonary embolism. It is important to emphasize that several illnesses can also produce PD such as intoxications and dopamine receptor antagonists. Thus, antipsychotics and antiemetics can cause PD-like disease.
Dopamine is a catecholamine and transmitter synthesized from phenylalanine through tyrosine as the Figure 1 shows below. After releasing, dopamine binds to dopamine receptors which can be classified as D1 and D2 receptors. D1 receptors (D1 and D5) stimulate the synthesis of cAMP, while D2 receptors (D2, D3, and D4) inhibit cAMP synthesis and suppress Ca\(^{2+}\) currents and activate receptor-operated K\(^{+}\) currents. At the moment, five different dopamine receptors are known, and all of them are G protein-coupled receptors (GPCRs). Under physiological conditions, the dopaminergic and cholinergic systems are functioning and balanced. In addition, many of the pathways involve not only one but several neurotransmitters. Thus, GABA (inhibitory transmitter) also has a functional significance via the glutamate (excitatory transmitter) receptor system in the development, controlling, and pharmacological therapy of PD.

![Figure 1. Synthesis of epinephrine](image)

Pharmacological treatments of PD involve (a) levodopa, (b) dopamine-receptor agonists, (c) catechol-o-methyltransferase (COMT) inhibitors, (d) selective MAO-B inhibitors, (e) muscarinic receptor antagonists, (f) amantadine, and (g) neuroprotective agents.

(a) Levodopa (L-DOPA, LARODOPA) is a metabolic precursor of dopamine, and is the major effective drug in the treatment of PD. Levodopa is able to penetrate from the blood through the blood-brain barrier into the neurons, although dopamine cannot. In the brain, levodopa is converted to dopamine by decarboxylation in the presynaptic terminals of dopaminergic neurons. After the release of dopamine from the presynaptic neurons, it is (i) transported back (reuptake) into dopaminergic terminals, and then (ii) metabolized by MAO and COMT, or (iii) is bound to dopamine receptors. Levodopa is generally co-administered with a peripherally acting inhibitor of L-amino decarboxylase such as carbidopa (SINEMET CR) or benserazide. Inhibition of the peripheral L-amino decarboxylase increases the concentration of levodopa in the blood, and remains unmetabolized and available to cross blood-brain barrier. Levodopa has a dramatic improvement on all symptoms of PD including tremor, rigidity, and bradykinesia.
Levodopa’s side effects are nausea, hallucinations, and confusions. Antipsychotics such as phenothiazines are effective against levodopa-induced psychosis, but can cause worsening of PD through the action of D2 receptors. If atypical antipsychotic agents are used, the antipsychotic-induced PD can be avoided. Decarboxylation of levodopa in blood, after oral administration, and formation of dopamine can activate D1 receptors producing orthostatic hypotension and cardiac arrhythmias. Co-administration of levodopa with non-specific MAO inhibitors (phenelzine, tranylcypromine) significantly accentuates the actions of levodopa, and precipitates life-threatening hypertensive crisis and hyperpyrexia.

(b) Dopamine receptor agonists (bromocriptine: PARLODEL; pergolide: PERMAX; ropinirole: REQUIP; pramipexole: MIRPEX), an alternative treatment to levodopa, are direct agonists of dopamine receptors. The duration of effects of all four dopamine receptor agonist is much longer (12 to 24 hours) than that of levodopa. The new generation (ropinirole and pramipexole) of dopamine agonists is well tolerated by patients, has long duration of action, and has no oxidative-related stress leading to free radical production and cell death.

(c) COMT inhibitors (tolcapone: TASMAR; entacapone: COMTAN) block the function of catechol-o-methyltransferase leading to the accumulation of catecholamines including dopamine. Daily administration of COMT inhibitors acts by both central and peripheral inhibition of COMT. Adverse effects of COMT inhibitors are nausea, orthostatic hypotension, confusion, hallucinations, and hepatotoxicity reflecting in an increase in serum alanine aminotransferase and aspartate transaminase activities.

(d) Selective MAO inhibitors: Two isoenzymes exist MAO-A and MAO-B. MAO-A is in the gut, and MAO-B is the predominant form and responsible for the oxidative metabolism of dopamine in the brain. Selegiline (ELDEPRYL) is a selective inhibitor of MAO-B. Because selegiline does not influence the function of MAO-A in the intestine, therefore, tyramine originated from cheeses and red wines cannot cause hypertensive crisis. It also has been proposed that the ability of selegiline to diminish the metabolism of dopamine can confer neuroprotection. During the metabolism of selegiline to amphetamine and methamphetamine can cause anxiety, insomnia, stupor, agitation, hyperreflexia, and hyperpyrexia. The dose of selegiline is maximum 10 mg/day.

(e) Muscarinic receptor antagonists antagonize the effect of acetylcholine reducing the symptoms of cholinergic stimulation and PD. Muscarinic receptor antagonists are trihexyphenidyl (ARTANE), benztrpine (COGENTIN), diphenhydramine (BENADRYL). All of these agents have antiparkinson activity, and diphenhydramine also blocks H1 receptors. Side effects are sedation, mental confusion, constipation, urinary retention, and blurred vision. These drugs can be avoided in patients suffered from glaucoma.

(f) Amantadine (SYMMETREL) is an antiviral drug having antiparkinson activity if the drug is used for prophylaxis. The action mechanism of amantadine is not known, however it is suggested that the drug blocks NMDA glutamate receptors. The effect of amantadine on PD is relatively modest in comparison with other antiparkinson agents. Moderate dizziness, lethargy, sleep disturbance, and vomiting have been observed after the application of amantadine.

(g) Neuroprotective agents in PD. It is desirable to identify the treatment that modifies the progressive degeneration of PD rather than attenuate the symptoms. Clinical studies show that the activation of presynaptic D2 autoreceptors reduce endogenous dopamine production
and thereby diminish oxidative stress and free radical production. In additional, drugs which are able to augment cellular energy metabolism such as coenzyme Q10, a cofactor required for mitochondrial electron-transport chain, can protect the neurons against PD development and reduce the progression of the disease.

Alzheimer’s disease (AD)

AD is producing an impairment of cognitive abilities which is gradual in onset but relentless in its progression. The lost of short-term memory is generally the first clinical symptom, but the retrieval of distant memory is well preserved into the course of the disorder. As AD is progressed, more cognitive abilities are damaged such as calculation, exercise visuospatial skills, and the use of common objects and tools. Death is generally originated from a complication of immobility including pneumonia and pulmonary embolism after 8-15 years of onset. AD is characterized by the atrophy of the cortex, and the loss of cortical and subcortical neurons. In AD, senile plaques are detected in the cortex that are spherical accumulation of beta-amyloid and other proteins. The aggregates of beta-amyloid is a characterized feature of AD.

During the progress of AD, senile plaques and neurofibrillary tangles are increased and mostly located in the hippocampus, whereas the visual and motor cortices are relatively spared. The loss of various transmitters in the cortex indicates the loss of neurons such as subcortical cholinergic neurons particularly in the basal forebrain, which provide cholinergic innervation to the cortex. Thus, the deficiency of acetylcholine could induce a confusional state and dementia indicating that AD is a “cholinergic deficiency syndrome”. However, AD is far more complex including the deficit of multiple neurotransmitters such as serotonin, glutamate, and various neuropeptides.

Treatment of AD includes the attempt to increase the cholinergic function of the brain. Such an intervention is the inhibition of acetylcholinesterase (AChE) by physostigmine, a reversible acting AChE inhibitor. The half-life of physostigmine is very short, therefore other new AChE inhibitors were introduced in the treatment of AD. These relatively new agents are tacrine (COGNEX), donepezil (ARICEPT), rivastigmine (EXCEلون), and galantamine (RAZADYNE). Side effects of AChE inhibitors are generally nausea, diarrhea, vomiting and insomnia.

Another possibility for the treatment of AD is the application of NMDA glutamate receptor antagonists. Memantine (NAMENDA) blocks NMDA receptors in patients suffered from moderate and severe AD. The drug reduces “excitotoxicity” (cell death caused by excitation). The side effects of memantine are headache and dizziness that are mild and reversible.

Hungtinton disease (HD)

HD is an inherited disorder with motor incordination and cognitive decline in the midlife. Symptoms are manifested in brief, jerk-like extreme movements of trunk, face, and neck (chorea), and personality changes. Motor incordination, rapid eye movements, bradykinesia, and dystonia are early symptoms of HD. As HD progresses, dysarthria, dysphagia, and severe impaired balance develop. Cognitive symptoms are manifested in slowness, decreased ability to organize complex tasks, irritability, and depression. Later (after 15 to 30 years) paranoia, total disability, and death because of immobility can be developed.

HD is characterized by the loss of neurons starting first in the striatum, and then proceeding anteriorly from mediodorsal to ventrolateral. HD is related to the loss of GABA concentrations while somatostatin and dopamine levels are relatively normal in the brain. In
some clinical cases, rigidity rather than chorea is the predominant symptom, and this is very common in juvenile ages. The disease is inherited equally from the mother and the father, but the symptoms developed before the age of 20 inherit mostly from the father. The inherited defect in HD originated from a polymorphic trinucleotide (CAG)n repetition. Repeated length of CAG, in HD, is between 40 and 110. The mutation of HD is connected to the gene designated as IT15.

The treatment of HD is symptomatic. No medication slows the progression of HD. Treatment is needed for patients who are depressed, irritable, anxious, paranoid, or psychotic. Thus, patients suffer from HD can be treated with antidepressant and antipsychotic agents including fluoxetine, and carbamazepine. Movements can be treated by dopamine depleting agents such as tetrabenazine. Individuals who develop myoclonus and seizures in HD, they can be treated with anticonvulsant agents.

Amyotrophic lateral sclerosis (ALS)

ALS is a disease of motor neurons of the ventral horn of spinal cord and the cortical neurons which provide their afferent input. There is a substantial loss of spinal and brainstem motor neurons which project to striated muscles. Additionally, ALS is related to the loss of large pyramidal motor neurons in the layer V of the motor cortex. The features of ALS are progressive weakness, spasticity, dysphagia, respiratory compromise, muscle atrophy and fasciculations. The progression of ALS leads to death because of respiratory compromise and pneumonia after 3 to 4 years.

ALS is the mutation in the gene of SOD1 and its protein. In many cases of ALS the abnormalities are not related to the mutation of SOD1, and the motor neuron loss is not well know, but it can be related to autoimmunity, free radical toxicity, and viral infection. There is an evidence that glutamate reuptake can be abnormal in ALS leading to accumulation of glutamate and excitotoxicity. Spasticity is a clinical symptom of ALS. Spasticity is an increase in muscle tone characterized by a resistance to passive displacement of the limb at a joint followed by a sudden relaxation.

Treatment of ALS can be done by riluzole (RILUTEK) only. Riluzol inhibits glutamate release and blocks postsynaptic NMDA and glutamate receptors. In addition, riluzol inhibits voltage-dependent sodium channels. The drug increases the elevation of serum transaminases producing hepatic injury. The symptomatic treatment of spasticity can be done by baclofen (LIORESAL), a GABA-B receptor agonist. The muscle spasticity can be also treated by tizanidine (ZANFLEX), an alpha-2 receptor agonist. Tizanidine is also used for the treatment of spasticity in multiple sclerosis.

Summary of neurodegenerative diseases: PD involves loss of dopaminergic neurons in the substantia nigra. The most effective therapy of PD is levodopa. AD is associated with accumulation of beta-amiloid protein leading to progressive loss of memory and cognition. The most effective therapy of AD is the inhibition of acetylcholinesterase by cholinesterase inhibitors. HD is caused by the mutation of protein huntingtin. At the present, there is no effective treatment for HD. ALS is a degenerative disorder of spinal motor neurons leading to muscle paralysis. The treatment of ALS can be done by riluzoloe which inhibits glutamate release.
Opioids

Opioids such as morphine exert their analgesic effects by mimicking the effects of endogenous opioid peptides e.g., endorphins, dynorphins, and enkephalins, which are synthesized in the central nervous system. The endogenous opioids system is very complex and subtle. The term of opioid refers to all structures related to opium originated from opium poppy, Papaver somniferum. Opiates include morphine, codeine, thebaine, and other semi or synthetic derivatives. The term of opioids is used in legal contexts to refer to a variety of substances with abuse or addictive potential.

Opium contains 42 alkaloids, but only a few of them are in medical use. First, in 1806, Sertturner discovered and isolated the morphine from opium. Then, the next alkaloid of opium was the codeine discovered by Robiquet in 1832, followed by the discovery of papaverine and isolated by Merck in 1848. The research for new opioid agonists resulted in the synthesis of new opioid antagonists (e.g., naloxone, nalorphine) and other molecular structures with mixed antagonist-agonist effects. The receptor-binding examinations and cloning of receptors confirmed the existence of mu (μ, MOP), delta (δ, DOP), kappa (κ, KOP), and nociceptin/orphanin (N/OFQ) opioid receptors. All four receptor families are G protein-coupled receptors (GPCRs). The last receptor family (N/OFQ) was cloned in 1994. All major opioid receptors have a unique anatomical distribution in the central nervous system and periphery. Clinically applied opioids are relatively selective for μ receptors, showing a similarity to the structure of morphine. Some opioid structures, especially mixed antagonist/agonist molecules interact with more than one receptor class, leading to an agonist interaction with one receptor and an antagonist relationship with others.

Action mechanisms of opioids: The opioid receptors in neuronal settings inhibit: (i) adenylyl cyclase activity, (ii) activation of receptor-linked K+ currents: and (iii) suppression of voltage gated Ca2+ currents. Thus, the hyperpolarization of membrane potential in neuronal cells by K+ current activation and blocking of Ca2+ entry by suppression of Ca2+ currents are major mechanisms for explaining the blockade of neurotransmitter release and pain transmission in various neurons. In addition, opioids activate of MAP kinases and the phospholipase C (PLC)-mediated cascade, leading to the formation of inositol triphosphate and diacylglycerol, and as a final result, the suppression of the action potential in neurons.

The term of tolerance refers to a reduction in effectiveness of opioids with their repeated administrations. Transient application of opioids leads to acute tolerance, whereas sustained administration results in the development of classic, so called chronic tolerance. The mechanism of tolerance involves receptor desensitization resulting in phosphorilation of μ and δ receptors by PKC (protein kinase C), PKA (protein kinase A), and β adrenergic receptor kinase (βARK). In addition, the development of chronic tolerance is related to a decrease in cAMP levels.

Effects of opioids

Morphine and its derivatives, and other clinically used opioid agonists exert their effects through μ receptors in various tissues. Their effects include analgesia, gastrointestinal, respiratory, neuroendocrine, mood, and behaviour functions. In additional, these agents possess euphoric, dysphoric, psychotomimetic, addictive, and miotic effects. Opioids also influence hypothalamus-mediated heat-regulatory mechanisms. Body temperature falls slightly with opioid use. Morphine also acts in the hypothalamus to inhibit the release of corticotropin releasing hormone (CRH) and gonadotropin releasing hormone (GRH) leading to decreasing circulating concentrations of luteinizing hormone (LH), ACTH, follicle stimulating hormone (FSH), and β endorphins. The reduction in the concentrations of
pituitary trophic hormones, the testosterone and cortison concentrations are reduced in plasma. The main indication of morphine and its derivatives is the relief of pain, and the stimulation of μ and κ receptors are responsible for the relief of pain.

**Myosis**: morphine and its natural and synthetic derivatives cause constriction of pupils by a stimulating action on parasympathetic nerve inervating pupils. Myosis is marked, and pinpoint pupils are a major characteristic symptom. However, toxic doses of opioids result in marked mydriasis, particularly if asphyxia develops. Therapeutic doses of morphine reduce intraocular pressure in normal and glaucomatous eyes.

**Respiration**: opioids depress respiration due to a direct effect on the respiratory center in the brain. In human subjects, deaths caused by opioid overdose result from respiratory arrest. Thus, the rate of respiration (four breaths per minute) and its minute volume, tidal exchange, and periodic breathing are significantly reduced in opioid treated humane subjects. The combination of opioids with anesthetics, alcohol, and sedative-hypnotic agents result in a greater risk of respiratory failure.

**Cough, nauseant, and emetic effects**: opioids depress the cough reflex on the cough center in the medulla. Morphine and other opioids cause nausea and vomiting by direct stimulation of the chemoreceptor trigger zone in the area postrema of the medulla. Nausea and vomiting occur in 50 % and 20 %, respectively, in patients treated with morphine.

**Convulsions**: opioid-like agents in addition to their depressive action, excite hippocampal pyramidal neurons as a result of inhibition of the release of GABA by interneurons. Convulsions develop if the opioid doses are higher than therapeutic concentrations. Naloxon, an opioid antagonist, is able to prevent convulsions due to opioid overdose. Anticonvulsant agents are not effective in suppression of opioid-induced convulsions.

**Cardiovascular effects**: opioids produce peripheral vasodilation, reduced peripheral resistance, orthostatic hypotension, reduction in left ventricular developed pressure, and fainting. Morphine releases histamine which results in hypotension. Morphine is given in acute myocardial infarction and decreases preload, inotropy and chronotropy; and relieves pain. Other morphine-like opioids such as fentanyl and sufentanil less likely cause hemodynamic instability because they do not stimulate histamine release.

**Gastrointestinal effects**: μ opioid agonists reduce the secretion of hydrochloric acid in the stomach, decrease gastric motility. Morphine decreases biliary, pancreatic, and intestinal secretions. Opioids constrict the sphincter of Oddi within 15 min after administration in the bile duct. This constriction persists for 2 to 3 hours. Therefore, spasmolytic agents must be coadministered with opioids.

**Ureter, urinary bladder effects**: opioid doses increase the tone and amplitude of contractions of smooth muscles in the ureter. Opioids increase the tone of the external sphincter and the volume of the bladder.

**Morphine and opioid agonists**

All opioid drugs induce tolerance, meaning that drugs lose their effectiveness, or an increased dose is required to produce the same physiological response. The term of dependence means that homeostasis of a subject (organism) is changed, and it causes a disturbance in homeostasis, if the drug intake or administration is abruptly terminated. Tolerance and dependence are physiological responses developed in all patients and not predictors of addictions. Cancer related pain requires long term treatment with high doses of morphine-like agents, leading to the development of tolerance and dependence.

The synthesis of morphine is complicated, therefore, morphine is obtained from opium or extracted from poppy straw (Papaver somniferum). The milky juice of poppy is dried and
powdered to produce opium. Opium contains 42 alkaloids but only a few of them (morphine, codeine, thebaine, papaverine, and noscapine) are used for therapy. Chemical structures of alkaloids used for therapy include (i) phenanthrene structure (morphine, codeine, and thebaine) and (ii) isoquinoline structure (papaverine and noscapine). The isoquinoline structure (papaverine) induces smooth muscle relaxant effects. Many synthetic or semisynthetic derivatives of opioids are made by modification of the structure of morphine or thebaine. Thus, the structures of thebaine, codeine, oxycodone, etorphine, diacetylmorphine (heroin), apomorphine, hydromorphone, levorphanol, and hydrocodone are made by simple modification of the structure of morphine. The modifications in the chains and rings attached to the nitrogen atom lead to morphine antagonist agents such as nalorephine, naloxone, and naltrexone. The triad of (i) depressed respiration, (ii) pinpoint pupils, and (iii) coma indicates opioid poisoning.

**Metabolism:** morphine and morphine-like agents bind to plasma proteins in blood. The major pathway for the metabolism of opioids is conjugation with glucuronic acid in the liver. The morphine-glucuronids retain opioid effects and cross the blood-brain barrier causing analgesic effects, are filtered by the kidney and are excreted in urine. 90% of the total excretion of morphine takes place during the first day following administration of the drug.

**Codeine:** this alkaloid is about 60% as effective as an analgesic and respiratory agent. Codeine analogs including methadone (DOLOPHINE), levorphanol and oxycodone (ROXICODONE) are also used orally and parenterally. The half-life of codeine in plasma is about 4 hours. The first pass metabolism of these agents is less in the liver. The metabolites of codeine are conjugated with glucuronic acid and O-demethylated to morphine and excreted in urine. The major therapeutic application of codeine is the prevention of coughing in various diseases. Tolerance and dependence can be developed to codeine after long term application.

**Tramadol (ULTRAM):** Tramadol is a synthetic codeine analog showing a low affinity to µ-opioid receptors. Its analgesic effect is produced by inhibition of norepinephrine and serotonin. Tramadol reduces acute pain, however, in the treatment of chronic pain tramadol is less effective. Respiratory depression induced by the drug is almost negligible compared to meperidine. Its analgesic effect begins about in 30 min following administration, peaks 3 hours and lasts about 6 hours. Side effects of tramadol are sedation, vomiting, nausea, dry mouth, dizziness, and headache. The maximal daily dose of tramadol is 400 mg.

**Meperidine (pethidine) and its modified structures:** meperidine (DEMEROL) is a phenylpiperidine derivative and predominantly stimulates µ opioid receptors. The pharmacological effects of meperidine on the CNS are very similar to those of morphine. The maximal single dose of meperidine is 100 mg, and the duration of the effective analgesia is about 3 hours. In clinical use, the effect of 100 mg meperidine is equivalent to 10 mg of morphine. Side effects of meperidine include respiratory depression, constriction of the pupil, increased pituitary hormone secretion, tremor, elevation of cerebrospinal fluid pressure, and CNS seizures. Meperidine releases histamine leading to the elevation of heart rate. Gastric motility is also reduced by meperidine.

**Pharmacokinetics of meperidine:** the drug is absorbed by all routes of application. Peak plasma concentration is detected after 45 minutes of administration. Meperidine is hydrolyzed and conjugated in the liver and excreted via the urine. Contraindications of meperidine are the same to those of opioids. Other meperidine-like drugs used in patient treatment include diphenoxylate (LOMOTIL), loperamide (IMODIUM), fentanyl (SUBLIMAZE), sufentanil (SUVENTA), alfentanil, and remifentanil (ULTIVA).

**Methadone (DOLOPHINE) and its derivatives:** methadone and its derivatives bind to µ receptors and exert pharmacological effects similar to those of morphine. The main effects of methadone are analgesic activity, extended duration of action, and efficacy by oral administration as well as suppression of withdrawal symptoms in physically dependent
patients. Untoward effects such as cough, bowel motility, increased biliary tone, and elevated secretion of pituitary hormones are observed. Peak concentrations of methadone and its congeners occur in the CNS within 2 hours, and their metabolites are excreted in the urine and bile. Indication for use of methadone include: (i) treatment of heroin addiction; (ii) relief of chronic pain; and (iii) treatment of opioid abstinence syndromes. The maximal single oral dose of methadone is 20 mg. Other analogs of methadone are propoxyphene (DARVON), levopropoxyphene, and napsylate (DARVON-N).

**Heroin:** diacetylmorphine (heroin) enters the brain more quickly than morphine. During the metabolism of heroin, heroin is hydrolyzed to morphine which results in a prolonged opioid effect. Heroin is excreted in the urine in free and conjugated forms. Heroin is not used in any medical therapy because of the quick development of tolerance and dependency.

**Opioid agonist/antagonists**

Butorphanol (STADOL), nalbuphine (NUBAIN), buprenorphine (BUPRENEX), and pentazocine (TALWIN) are competitive µ-receptor antagonists but exert their analgesic actions as agonists of κ receptors. These opioid agonist/antagonists mediate analgesic effect with less additive potential and respiratory depression in comparison with morphine, however, their clinical use is limited because of their undesirable side effects. Withdrawal syndrome develops following intake of these drugs, but over a longer period than in the case of morphine use. Typical doses of these opioid agonist/antagonists are generally between 10 mg and 100 mg.

**Opioid antagonists**

Members of this group of drugs have therapeutic utility in treatment of opioid overdose. The changes in the structure of morphine result in the antagonistic action at opioid receptors. Thus, substitution of the N-methyl group in the structure of morphine leads to nalorphine, levallorphan, naloxone (NARCAN), naltrexone (REVIA), and nalmefene, which are the most commonly used morphine antagonist agents worldwide. Some of these drugs such as nalorphine and levallorphan are not clean morphine antagonist agents because they have agonistic actions at κ receptors. Nalmefene, naloxon, and naltrexon are pure morphine antagonists having no agonistic effects on opioid receptors. Nalmefene (REVIX) is the most effective and potent opioid antagonist. These drugs are used intramuscularly or intravenously with concentrations of between 0.5 mg and 10 mg by a single injection. Naloxone is the most commonly used opioid antagonist due to its relatively short duration of action (about 30 to 45 min).

Other opioid antagonists which are relatively selective for individual types of opioid receptors are naltrindole (δ), norbinaltorphimine (κ), cypridime (μ), and β-funaltrexamine (μ). Morphine antagonist effects may be induced if opioid receptors have been previously activated. In individuals, who have no opioids present in their body (opioid-free subjects), morphine antagonists have no effect. After prolonged application of high doses of morphine antagonists, discontinuation of these agents is not followed by withdrawal symptoms. All opioid antagonists are metabolized in the liver by conjugation with glucuronic acid.

Therapeutic uses of opioid antagonists involve: (i) opioid overdose, (ii) opioid-induced respiratory depression, and (iii) the diagnosis of dependence on opioids. Naltrexon is also approved (iv) for the treatment of chronic alcoholism.
Antitussive agents

The antitussive agents are partial derivatives of the morphine molecule. Thus, codeine and hydrocodone (LORCET, LORTAB), which have phenantrene structures, serve to prevent cough. In addition, dextromethorphan (d-3-methoxy-N-methylmorphinan), a codeine analog, is a member of this group. Dextromethorphan has no analgesic or addictive properties and does not stimulate opioid receptors. This drug has a direct central effect which includes suppression of coughing. Coughing is a protective physiological mechanism that clears the respiratory system from the exogenous materials and promotes secretion. Cough should not be suppressed indiscriminately, although in many cases it must be prevented in order to promote sleep and avoid fatigue especially in elderly patients. In addition, cough must be prevented in patients suffering from neoplastic diseases. Other antitussive agents are carbetapentane, caramiphen, noscapine, pholcodine, and benzonatate (TESSALON).
CARDIOVASCULAR SYSTEM

In the following chapters, cardiovascular therapies are classified as follows:

1. Therapy of myocardial ischemia
2. Treatment of congestive heart failure
3. Antiarrhythmic drugs
4. Treatment of hypertension including the rennin-angiotensin system
5. Vasopressin and others affecting renal function
6. Diuretics
7. Therapy of hypercholesterolemia and dyslipidemia
8. Blood, pharmacology

1. Therapy of myocardial ischemia

Angina pectoris is caused by transient episodes of cardiac ischemia which are due to imbalance of the oxygen supply and demand in the myocardial tissue (Figure 2).

![Diagram of oxygen supply and demand]

**Figure 2.** The duration of ischemia leads to reversible or irreversible injury.

The decrease in diameter of vessels that characterizes coronary sclerosis impairs coronary blood circulation, and leads to symptoms of angina. Angina (angina pectoris, Prinzmetal angina, variant angina, unstable and stable angina) can lead to the development of coronary thrombosis and myocardial infarction. Angina is characterized as “heavy pain” and
discomfort radiating to the left shoulder and arm. Elderly, diabetic and hypertensive patients are more likely to have angina. Angina pectoris affects more than 22 million Europeans and North Americans. Angina pectoris can occur: (i) a stable pattern over years or (ii) can become unstable increasing its severity. In stable angina, the etiology is usually fixed coronary sclerosis, and on exertion or stress it can be superimposed in cardiac oxygen consumption. In patients with unstable angina, rupture of sclerotic plaques with platelet adhesion and aggregation can lead to the development (Figure 3) of coronary thrombosis, myocardial infarction, and sudden cardiac death caused by ventricular fibrillation (VF).

**Pathophysiology**

- Atherosclerotic disease
- Coronary vasoreactivity
- Thrombus

**Clinical presentation**

- Silent ischemia
- Stable angina
- Acute myocardial infarction
- Unstable angina

Figure 3. The pathophysiology and clinical presentation of sudden cardiac death. The pathophysiology of cardiac death includes athero- and coronary sclerosis, thrombus formation, and coronary vasoreactivity. The clinical presentation of cardiac death can be attributed to myocardial ischemia (silent), angina (stable, unstable), and acute myocardial infarction. VF: ventricular fibrillation.

The treatment of angina, depending on its form, may be accomplished by: (a) nitrovasodilators, (b) beta-adrenergic receptor blockers, (c) calcium channel antagonists, and (d) antiplatelet, antithrombotic, and antiintegrin agents combined with statins (stable and unstable angina) which are able to stabilize plaques. All groups listed above (a to d) improve
the balance of tissue oxygen supply and demand. This balance may be restored using antianginal drugs which reduce heart rate, contractility, and ventricular wall stress. The application of antiplatelet agents and heparin reduce coronary thrombosis. Antianginal agents reduce mortality by decreasing the incidence of sudden cardiac death related to ventricular fibrillation and associated with myocardial ischemia and infarction. These agents may be provided as elements of prophylactic or symptomatic treatments. The treatment of cardiac risk factors (e.g., cholesterol level) may reduce the progression of coronary sclerosis. Coronary bypass surgery, angioplasty and coronary stent deployment can also complement pharmacological treatment. Novel therapies which modify the expression of myocardial or vascular cell genes also hold potential as important strategies for therapy of the ischemic myocardium. The following subsections (a-d) summarize features of drugs with primary use in cardiac medicine.

(a) Nitrovasodilators

These agents are organic nitrates and potential sources of nitric oxide (NO), a potent signalling molecule. Organic nitrates are polyol esters of nitric acid, while organic nitrites are esters of nitrous acid. Nitrate esters (-CH2-O-NO2) and nitrite esters (-CH2-O-N=O) are a sequence of carbon, oxygen, and nitrogen, whereas nitro structures possess carbon and nitrogen bonds (-CH2=NO2). Organic nitrates are used for the therapy of ischemic myocardium. They include nitroglycerin, erythrityl tetranitrate, isosorbide mononitrate, and isosorbide dinitrate.

**Action mechanism of nitrates:** NO activates soluble guanylyl cyclase leading to the increased levels of cGMP. Increased cellular levels of cGMP promote dephosphorylation of the myosin light chains, reducing the content of cytosolic calcium ions, and leading to the relaxation of smooth muscle cells in vessels and various tissues. NO-dependent relaxation of vascular smooth muscle results in vasodilation. In addition, NO-activated guanylyl cyclase inhibits platelet aggregation and relaxes smooth muscle in the lung (bronchi) and gastrointestinal tract. Synthesis of NO is catalyzed by NO synthase which oxidizes the amino acid L-arginine to form NO. Three NO synthase isoforms exist: nNOS, eNOS, and iNOS, and they play a role, beside vasodilation, in neurotransmission, vasomotion, and immunomodulation. iNOS is the inducible form, and is able to produce substantial amounts of NO under physiological conditions.

**History:** Nitroglycerin was synthesized in 1846. Sobrero observed that a small amount of nitroglycerin placed on the tongue induced a severe headache. In 1857, amyl nitrite in inhaled form was identified as an agent relieved anginal pain within seconds. The application of sublingual nitroglycerin mimicks the effect of amyl nitrite; and acute anginal attack is relieved by this drug. The action mechanism of nitrates and the importance of endogenous NO was discovered by three Americans, Robert Furchgott, Louis Ignarro, and Ferid Murad, who were awarded the 1998 Nobel Prize in medicine for this work.

**Cardiovascular effects of nitrates:** At low doses, nitroglycerin dilates to a greater extent the veins than the arterioles. This venodilation reduces the size of left and right ventricular chambers and end-diastolic pressure. However, little change can be detected in systemic vascular resistance. Pulmonary vascular resistance and cardiac output are also reduced. Nitroglycerin produces arteriolar dilation in the face and neck and meningeal arterial vessels, leading to flush and headache. Coronary blood flow is increased transiently as a result of coronary dilation, but can reduce subsequently with the reduction of cardiac output and blood pressure. This latter can produce life-threatening hypotension and aggravating angina.

Preload is determined by the diastolic pressure that distends the ventricle (ventricular end-diastolic pressure). Elevated end-diastolic volume increases the ventricular wall tension.
Nitrates decrease venous return in the right atrium and ventricle, and as a consequence, reduce left ventricular end-diastolic volume, and decrease the consumption of oxygen in the tissue. Afterload is the impedance against which the left ventricle ejects. Reduced peripheral arteriolar resistance decreases afterload and thus cardiac work and oxygen consumption. Organic nitrates reduce both preload and afterload as a result of dilation of venous capacitance and arteriolar resistance vessels, respectively.

Absorption, fate, and excretion of nitrates: The metabolism of organic nitrates is complex, and may contribute to activation of enzymes including glutathione-organic nitrate reductase and mitochondrial aldehyde dehydrogenase enzymes.

The peak concentration of nitroglycerin is detected in the plasma within 4 minutes after sublingual application. The half life is about 3 minutes.

The major metabolic mechanism of isosorbide dinitrate is an enzymatic denitration followed by glucuronide conjugation. Peak plasma concentration of the drug may be detected after about 5 min in the plasma, and its half life is about 45 min. The active metabolite of isosorbide dinitrate is isosorbide-2-mononitrate and isosorbide-5-mononitrate with half life of 4 to 5 hours contributing to the therapeutic efficacy of the drug.

Isosorbide-5-monomonitrate is formulated in tablets and used orally for the prevention of various types of angina. This drug has longer duration of action than the previous agents.

Nitrate tolerance: Tolerance results from a reduced capacity of smooth muscles to convert nitrates to NO. In addition, other mechanisms have been also proposed to account for nitrate tolerance including neurohumoral activation, cellular depletion of sulfhydryl groups, and generation of oxygen, nitrogen, and oxygen-centered free radicals. However, inactivation of mitochondrial aldehyde dehydrogenase, the enzyme involved in biotransformation of nitrates (e.g., nitroglycerin), in nitrate tolerance is potentially associated with oxidative stress. The depletion of sulfhydryl groups leads to defect of biotransformation of nitrates to NO leading to nitrate tolerance.

Treatment of nitrate tolerance: The most effective treatment is to withdraw the application of nitrates for 12 hours in each day. Withdraw from nitrates is most efficient at night, accomplished by not taking the drug orally or by removing cutaneous nitroglycerin patch. To avoid the development of nitrate tolerance by orally administered nitrates, use of these drugs twice-daily is recommended.

Toxicity and side effects of nitrates: Headache may be severe, and may be reduced by decreasing the dose. Dizziness, weakness, drug rash, hypotension, and consciousness may also develop.

Drug interactions: Erectile dysfunction may develop, and the combination of nitrates with sildenafil and its derivative (tradalafil, vardenafil) which inhibit phosphodiesterase 5 enzyme (PDE5) can lead to extreme hypotension because of the formation of NO via cGMP signalling. The use of PDE5 inhibitors must be avoided with organic nitrates and alpha adrenergic receptor antagonists.

Therapeutic uses of nitrates:

Angina treatment: various types of angina (variant, unstable, stable angina): sublingual administration of nitrates is a convenient way to reduce the symptoms of acute angina. Pain is relieved within 3 minutes. Oral application of organic nitrates (e.g., isosorbide dinitrate) may prevent the development of anginal attacks. Transdermal nitroglycerin disks maintain a constant nitrate content in blood. In variant angina, calcium channel blockers can be used in combination with nitrates.
Treatment for myocardial infarction with non-ST-segment elevation: Nitrates can be combined with beta-receptor blockers. If the angina is unstable, treatment must be conducted as the case of myocardial infarction. Thus, morphine, beta-receptor blockers, heparine, and antiplatelet agents (e.g., aspirin, clopidogrel) must be applied in combination. Anti-integrin drugs directed against the platelet integrin GPIIb/IIIa (e.g., abciximab, tirofiban, eptifibatide) are effective with in combination with heparin. If coronary constriction is sustained, low doses of calcium channel antagonists can be also used. However, the degree of negative inotropic effect of Ca-channel blockers must be considered as part of a treatment regimen.

(b) Beta-adrenergic receptor blockers

Beta receptor blockers are able to reduce the frequency and severity of angina and improve the survival rate in patients who have had myocardial infarction. Beta adrenergic receptor blockers are not effective for the treatment of vasospastic angina. In other types of angina, propranolol, atenolol, and metoprolol have shown cardioprotective effects. These drugs decrease myocardial oxygen consumption because of their negative inotropic and chronotropic effects leading to a reduction in arterial systolic pressure. The combination of beta receptor blockers with nitrates is more effective as the application of these agents alone. Beta receptor blockers that do not have intrinsic sympathomimetic activity improve mortality rate in myocardial infarction.

(c) Calcium channel blockers

L-type or slow calcium channel blockers interfere with the entry of extracellular calcium into smooth muscle and cardiac myocytes because they inhibit calcium channel functions. These drugs also induce negative inotropic and chronotropic effects in the myocardium.

History: Fleckenstein, Godfraind and their colleagues reported in the 1960s that calcium channel antagonists (verapamil, gallopamil, nifedipine, cinnarizine, lidoflazine) block the calcium entry in cardiac and smooth muscles. Five classes of calcium blockers exist: (i) phenylalkylamines (verapamil, gallopamil), (ii) dihydropyridines (nifedipine, amlodipine, felodipine, isradipine, nicardipine, nisoldipine, nimodipine), (iii) benzothiazepines (diltiazem), (iv) diphenylpiperazines, and (v) diarylaminopropylamines (bepridil).

Action mechanisms of calcium channel blockers: Elevated cytosolic calcium results in an increased contraction in vascular smooth and cardiac muscle cells. The entry of extracellular calcium induces calcium-induced calcium release in the sarcoplasmic reticulum. Hormones and neurohormones increase calcium influx through receptor-operated calcium channels. Calcium channel blockers bind to the alpha-1 subunit of L-type calcium channels, thus, reducing calcium influx through the channel, and preventing actin-myosin complex and contraction.

Pharmacological properties of Ca-channel blockers: An elevation in cytosolic calcium ions results in an increased binding of calcium to calmodulin. The Ca-calmodulin complex activates the myosin light-chain kinase, resulting in the phosphorylation of myosin light chain. This phosphorylation promotes the formation of actin-myosin complex leading to contraction. The block of calcium channels is responsible for the negative inotropic and chronotropic effects. Calcium channel blockers decrease coronary vascular resistance and increase coronary blood flow, therefore these agents are useful for the prevention of angina. Hemodynamic effects of these drugs vary depending on routes of administration and the degree of ventricular dysfunction.
Absorption, excretion and adverse responses: The absorption of calcium channel blockers is complete after oral application, their bioavailability is decreased by first pass hepatic metabolism. These drugs are bound to plasma proteins, reaching their peak effects after 45 to 60 minutes. Their elimination half lives are between 3 and 60 hours. The metabolites of calcium channel blockers are inactive. Dizziness, hypotension, headache, flushing, nausea, peripheral edema, and coughing can be developed. In addition, bradycardia, AV nodal conduction disturbances, and exacerbation of heart failure may be detected. The use of calcium blockers to treat digitalis toxicity is contraindicated because of the exacerbation of AV nodal conduction disturbances.

Therapeutic uses of Ca-channel blockers: (i) Variant angina results from reduced flow rather than increased oxygen demand, and (ii) exertional angina resulting from exercise can be treated with Ca-antagonists. (iii) Unstable angina includes the administration of aspirin, heparin, nitrates, and beta blockers. Ca-channel blockers may be used if the underlying mechanism of unstable angina is vasospasm. (iv) Calcium channel blockers must not be used in myocardial infarction and have detrimental effect on mortality. (v) Calcium-channel antagonists can also be used as antiarrhythmic agents. (vi) Verapamil has been also used in the prophylaxis of migraine headaches. (vii) Felodipine, amlodipine, diltiazem, and nifedipine appear to provide the relief of Raynaud’s disease.

Contraindicating factors for use of beta receptor blockers include bronchospasm (the blockade of beta-2 receptors in the lung further aggravates the astma and induces asthma), Raynaud’s syndrome, and Prinzmetal angina. In these cases calcium channel blockers can be used for the treatment of angina. Calcium channel blockers and nitrates can be combined for the treatment vasospastic angina. The nitrates reduce preload, while calcium channel blockers reduce the afterload, and as a results excessive vasodilation and hypotension can be developed.

(d) Antiplatelet, antiintegrin, and antithrombotic agents combined with statins

Aspirin is the most widely known member of this group, and reduces the occurrence of myocardial infarction and mortality in patients suffered from chronic stable angina. Heparin and its low molecular weight fragments also reduce symptoms of unstable angina and prevent the development of myocardial infarction. Thrombin inhibitors such as hirudin and bivalirudin inhibit even the clot-bound thrombin. Intravenous inhibitors of platelet GPIIb/IIIa receptors (abciximab, tirofiban, eptifibatide) are effective in preventing the complication of acute coronary syndromes.

Peripheral vascular and coronary artery diseases may occur and overlap each other in most patients. The symptoms of peripheral artery diseases are provoked by exertion in the lower extremities (claudication). If the blood flow in the extremities becomes critically limited, peripheral ulcers and pain from ischemia can be debilitating. The treatment of claudication can be accomplished by aspirin, ADP antagonists such as clopidogrel and ticlopidine, and hyperlipidemic agents. Claudication can be successfully treated with pentoxyfylline and cilostazol. Pentoxyfylline has a methylxanthine structure, a “rheologic modifier”, and affects the structural integrity of red blood cells. Cilostazol is a PDE3 inhibitor, and increases the accumulation of cAMP in cells including platelets. cAMP accumulation inhibits platelet aggregation and induces vasodilation. Thus, cilostazol improves blood circulation in lower extremities. Other agents used for the treatment of claudication are naftidrofuryl, proprionyl, and levocarnitine.

Intracoronary stents can provoke angina and restenosis. “In-stent restenosis”, smooth muscle proliferation within the lumen of stented artery is a common pathological event. Therefore, antiproliferative therapy is required for the treatment of implanted stent-induced
proliferation. These drugs are paclitaxel (TAXOL) and sirolimus (RAPAMYCIN). Stent-induced damages in vascular endothelial cell layer lead to the development of thrombosis. Beside paclitaxel or sirolimus treatment, antiplatelet therapy with clopidogrel and aspirin can be done in stent implanted patients.

2). Treatment of congestive heart failure

Congestive heart failure (HF) is a major factor leading to morbidity and mortality. There are approximately 18 million established cases in North America and EU. About the same number of affected individuals has asymptomatic left ventricular dysfunction and, thus, at risk to developed HF. Annually, HF accounts for more than 1.5 million deaths in the two continents. Pharmacotherapies for HF have focused on volume overload (congestion) and cardiac dysfunction (heart failure). The treatment of HF includes diuretics and cardiac glycosides with extensive efforts directed at the development of new drugs leading to an improved contractile function.

Pathology of congestive HF is related to the circulatory homeostasis; therefore, it requires the stabilization of forward cardiac output (CO) and mean arterial pressure (MAP). Autoregulation determines the peripheral distribution of CO under physiological conditions; and circulation efficiency may supersede local autoregulation, if aggregate demand exceeds the delivery capacity of CO. Example of this kind of HF is hypovolemic shock. In hypovolemic shock, the sympathetic autonomic nervous system and the rennin-angiotensin system are activated. The vasoconstrictive effects of both systems increase peripheral vascular resistance, and as a result, blood flow is reduced. The redistribution of CO maintains the critical blood perfusion for critical tissues such as the central nervous system, the heart, and kidney. With the redistribution of CO, the reabsorption of sodium and water is increased.

Increased left ventricular volume results in an increase in the length of cardiac muscle fibres leading to stronger contractile force and enhanced ventricular stroke volume; this basic relationship between left ventricular filling and stroke volume is quantified in the Frank-Starling law. At the cellular level, changes associated with contractile dysfunction include calcium homeostasis and expression of contractile proteins. This signal transduction is related to the cytosolic free calcium ions released from sarcoplasmic reticulum and Na-Ca exchanger. As an additional mechanism, which is related to HF; and also to the cellular cAMP level.

Pharmacotherapy of congestive HF: Drug interventions used for HF are (i) diuretics, (ii) aldosterone antagonists, (iii) vasodilators, (iv) inhibitors of rennin – angiotensin system and AT1 receptor antagonists, (v) beta adrenergic receptor antagonists, (vi) cardiac glycosides, and (vii) beta adrenergic and dopaminergic agonists.

(i) Diuretics

The effects of these drugs are related to the retention of sodium and extracellular fluid volume allowing the heart to maintain left ventricular stroke volume. The increase in enddiastolic volume results in an elevated wall stress and increased ventricular chamber
Diuretics reduce the volume of extracellular fluid and preload, and parallel, the sodium dietary intake is advised. The diuretic agents are loop diuretics (furosemide = LASIX, bumetanide = BUMEX, torsemide = DEMADEX, and ethacrynic acid = EDECRIN), which inhibit a specific ion transport protein, the Na-K-2Cl symporter in the ascending limb of the Henle loop. Ethacrynic acid has to be reserved for patients who have allergic reactions to sulfonamides.

Thiazide diuretics (DIURIL, HYDRODIURIL) are widely used in combination for the treatment of hypertension, but their application is not common for the therapy of congestive HF. The action mechanism of thiazide agents involves the inhibition of Na-Cl cotransporter in the distal convoluted tubule. The application of thiazide diuretics results in a loss of potassium, therefore, potassium supply is mandatory during thiazide treatment.

K-sparing diuretics act in the collecting duct of nephron and inhibit sodium conductance channels in epithelial cells (amiloride, triamterene), or inhibit aldosterone’s effects (canrenone, spironolactone, eplerenone). All of these agents inhibit potassium and magnesium losses via the urine. Patients afflicted with HF require chronic application of diuretics to maintain euvoelema. Serum electrolyte contents and renal function must be monitored during the treatment.

(ii) Aldosterone antagonists

The rennin-angiotensin-aldosterone system is activated in cognitive HF. Aldosterone concentrations can be 20 times higher in patients afflicted with HF, therefore the antagonists of aldosterone (spironolactone) is a potential tool in the treatment of HF. Spironolactone causes severe hyperkalemia, therefore serum potassium contents must be monitored, and supplementation of potassium is contraindicated. The combination of spironolactone with ACE inhibitors is very effective in the treatment of HF. The most important adverse effects of spironolactone are electrolyte abnormalities including hyperkalemia.

(iii) Vasodilators

Nitrovasodilators (organic nitrates): These agents (nitroglycerin, isosorbide di- and mononitrate) relax vascular smooth muscle cells by the formation of nitric oxide. Nitrovasodilators reduce left ventricular filling pressure and pulmonary and systemic vascular resistance. The vasodilator mechanism of hydralazine (APRESOLINE) is unknown, and this drug is an effective antihypertonic agent having a moderate positive inotropic activity. Hydralazine is able to increase renal blood flow and can be used if ACE inhibitors are not tolerated by patients sufferd from HF.

(iv) Inhibitors of rennin – angiotensin system and AT1 receptor antagonists

The rennin-angiotensin system plays a basic role in the development of HF. Angiotensinogen (Figure 4) is cleaved by renin produced by the juxta glomerular cells in the kidney. Thus, angiotensin-I decapetide is formed from angiotensinogen. The angiotensin-converting enzyme (ACE) converts the angiotensin-I to the angiotensin-II octapeptide. While angiotensin-I is ineffective on smooth muscle, angiotensin-II produces a pronounced arterial vasoconstriction (Figure 4). In addition, angiotensin-II is a mediator of sodium and water retention through its effect on aldosterone secretion. Furthermore, angiotensin-II facilitates catecholamine release from neurons and adrenal medulla leading to cardiac arrhythmias, vascular hyperplasia, and myocardial hypertrophy. Thus, the inhibition of the formation of angiotensin-II is a key factor in the treatment of HF.
ACE inhibitors suppress both angiotensin-II and aldosterone productions, reduce the activity of sympathetic nervous system, and potentiate the effects of diuretics in HF. ACE is identical to kininase-II that degrades bradykinin that stimulates cGMP and NO production leading to vasodilatation. The inhibitors of ACE are more effective arterial than venous dilators. The reduction in afterload results in an elevated stroke volume and cardiac output.

If angiotensin-II is formed, its direct vasoconstrictor effect can be prevented by the blockade of angiotensin-1 (AT1) receptors. AT1 receptor antagonists can provide more potent reduction in blood pressure than ACE inhibitors do. AT2 receptors also exist in the cardiovascular system, and these AT2 receptors counterbalance the biological function of AT1 receptors under physiological conditions.

![Angiotensin System Diagram](image)

**Figure 4. The renin-angiotensin system.**

The first reported ACE inhibitor was captopril (CAPOTEN) followed by enalapril (VASOTEC), ramipril (ALTACE), lisinopril (VASOTEC), quinapril (ACCUPRIL), and fosinopril (MONOPRIL). These drugs are available for oral application between 5 mg/day to 30 mg/day in two divided doses for the treatment of HF and hypertension. ACE inhibitors can prevent ventricular dysfunction and mortality rate after acute myocardial infarction.

AT1 receptor antagonists (losartan, candesartan) can directly prevent the interaction between angiotensin-II and AT1 receptors, thus the angiotensin-II-induced vasoconstriction cannot be developed. The use of AT1 antagonists gives additive antihypertensive effect if used in combination with ACE inhibitors. The combined therapy with candesartan (AT1 receptor antagonist) and enalapril (ACE inhibitor) has excellent effects on ventricular remodelling and hemodynamics in comparison with therapy with either drug alone. Thus, AT1 antagonists are effective in the treatment of hypertension, cognitive heart failure, and diastolic heart failure.

(v) Beta adrenergic receptor antagonists

In HF the sympathetic nervous system is activated increasing contractility (inotropy), enhancing ventricular relaxation and filling (lusitropy), and elevating heart rate (chronotropy). Thus, the use of sympathomimetic drugs (e.g., dopamine and dobutamine) improve the short-
term relief of heart failure symptoms. However, paradoxically, for the long-term treatment of HF symptoms, the application of beta blockers is effective. As a conclusion, the use of beta receptor antagonists is related to the prevention of beta receptor-mediated adverse effects of catecholamines which is related to the imbalance of oxygen demand and supply of the myocardium.

Beta blockers used for the treatment of HF are metoprolol (LOPRESSOR, TOPROL XL), carvediol (COREG), and bisoprolol (ZEBETA).

Metoprolol is a selective beta-1 receptor antagonist and able to reduce the mortality in patients afflicted with heart failure. Bisoprolol is also a selective beta-1 receptor antagonist, and prevents the occurrence of sudden cardiac death originating from ventricular fibrillation. Thus, bisoprolol is an effective antiarrhythmic agent as well. Carvediol is a nonselective beta blocker having alpha-1 receptor antagonistic effect. Carvediol is able to reduce the mortality rate by 65% in patients.

Clinical application of beta receptor blockers: Beta receptor blockers can be used for the treatment of (i) heart failure, (ii) hypertension, and (iii) ventricular arrhythmias.

(vi) Cardiac glycosides

The therapeutic effects of glycosides are attributed to their positive inotropic effect and preventing the development of atrial fibrillation in failing heart. In addition, glycoside modulate the activity of autonomic nervous system which contribute to the management of heart failure. Cardiac glycosides consisting of three main chemical structures (Figure 6), including lactone ring, steroid structure, and various sugar residues. Today, digoxin (LANOXIN, LANOXICAPS) is the only cardiac glycoside used in the clinical therapy.

![Figure 5. Structure of digoxin.](image)

Action mechanism of cardiac glycosides: Glycosides are inhibitors of the active transport of sodium and potassium across cardiac cells. This effect is demonstrated by the binding of glycosides to the alpha subunit of Na-K-ATPase, the so called sodium pump. The binding and inhibition of glycosides to Na-K-ATPase are reversible in myocardial cells.
Sodium and calcium ions, during depolarization, enter the cell via L-type calcium channels and release the stored calcium ions from the sarcoplasmic reticulum (SR) into the cytosol via the ryanodine receptor. The sodium- and calcium-induced calcium releases increase the free calcium content in the cytosol, leading to contraction via the formation of actin-myosin complexes. During relaxation and repolarization, cytosolic free calcium ions is re-sequestered by SERCA (sarcoplasmic reticular Ca-ATPase), and as a result, the cytosolic calcium content is reduced leading to relaxation.

**Electrophysiological effects of glycosides:** Glycosides decrease automaticity and increase diastolic resting membrane potential in the atrium and AV node. This effect is related to the increase in vagal tone, and as a consequence, reduction in sympathetic activity. The result is sinus bradycardia and various degrees of AV block. Cardiac glycosides, at higher doses, can increase sympathetic activity leading to cardiac arrhythmias.

**Pharmacokinetics of cardiac glycosides:** Digoxin’s half life is about 48 hours in healthy human beings. In patients suffering from heart failure, the application of digoxin is once-a-day, if the renal function is normal. The bioavailability of digoxin (LANOXICAPS, LANOXIN) applied orally is about 80%. The intravenous use of digoxin is suggested, if oral application is impractical. Digoxin is a first-line glycoside agent used for the treatment of congestive heart failure. Additionally, digoxin can be used for the treatment of atrial fibrillation.

**Toxicity of digoxin:** Overdose of digoxin and the symptoms of digoxin toxicity have been significantly reduced in the past 30 years due to development of new alternative drugs and therapies for the treatment of heart failure. The toxic symptoms of digoxin relate to various degrees of AV block and bradycardia. Digoxin toxicity may be treated with atropine, potassium supply, and lidocain or phenytoin as antiarrhythmic agents. Antidigoxin immunotherapy with purified Fab (DIGIBIND) from bovine antidigoxin antisera is also available as a new therapy.

(vii) Beta adrenergic and dopaminergic agonists

Dopamine (DOPAMINE) and dobutamine (DOBUTREX) are beta adrenergic receptor agonists most often used for the treatment of short-term heart failure. These drugs stimulate dopamine-1 (D1) and beta adrenergic receptors via stimulation of the Gs protein-adenyly cyclase-cAMP-PKA (phosphokinase) pathway. PKA phosphorylates a number of proteins that promote calcium-dependent contraction and speed relaxation.

Dopamine, at low doses (less than 2 microgram/kg/min infusion rate), produces vasodilation by stimulating (i) D1 receptors in the smooth muscle of vessels, stimulating (ii) presynaptic D2 receptors on sympathetic nerves by inhibiting norepinephrine release. At intermediate doses (between 2 and 5 microgram/kg/min infusion rate), dopamine stimulates beta1 receptors in the heart, and D1 and B1 receptors in vascular sympathetic neurons. At high concentrations (15 microgram/kg/min infusion rate), dopamine stimulates alpha adrenergic (alpha1) receptors leading to vasoconstriction.

Dobutamine is used for the treatment of systolic dysfunction and congestive HF. The effect of dobutamine is induced by the stimulation of B1 and B2 adrenergic receptors, resulting in increased cardiac output. The infusion rate of dobutamine is 2-3 microgram/kg/min. Dobutamine does not stimulate D1 and D2 adrenergic receptors, thus no vasoconstriction can be developed even at higher doses. The side effects of the drug are cardiac arrhythmias.

Phosphodiesterase inhibitors: Phosphodiesterase inhibitors (PDE) block the degradation of cAMP in the cell. The accumulation of cellular cAMP leads to positive inotropic effect in the heart and vasodilation in the peripheral vessels. This dual effect on the
myocardium and vessels classifies these drugs as “ino-dilators”. Clinical application of theophylline and caffeine as PDE inhibitors are limited, and generally inamrinone and milrinone are used.

Inamrinone and milrinone are selective inhibitors of PDE3. These agents stimulate myocardial contractility and relaxation via the increased concentrations of cAMP. Both drugs are effective for short term treatment of severe heart failure. Thrombocytopenia (10%) occurs in patients treated with inamrinone, but is relatively rare in application of milrinone. These agents have beneficial effects on systolic and diastolic heart function.

3). Antiarrhythmic drugs

The consequences and prevention of coronary artery diseases, despite many decades of efforts and characterization of molecular and cellular changes that occur during myocardial ischemia, have been intensively investigated in identification and control of the pathophysiological mechanisms responsible for cardiac injury. In the search for mechanisms of cardiac ischemia-induced pathways that may be amenable to manipulation, a number of potential candidates have been identified and have been the subject of many investigations. It is highly probable that a number of interaction mechanisms combine to cause damage resulting from ischemia of the myocardium and a variety of such triggers have been postulated including e.g., ionic disturbances, fatty acid metabolism, α and β adrenergic receptors, platelet activating factor, endothelin, and free radicals. These and many other factors influence action potential (AP) and the function of various ion channels especially sodium, potassium, and calcium. In some arrhythmias treatments may be specifically targeted.

Antiarrhythmic therapy can be accomplished on two ways: (i) termination of ongoing arrhythmias; and (ii) prevention of development of arrhythmias. The flow of ions across cardiac membranes generates the currents that produce AP. The changes in AP by various antiarrhythmic drugs can be explained at molecular and cellular levels. The antiarrhythmic drugs exert various actions and may be beneficial or harmful depending on the individual patient.

The cardiac cell at rest maintains transmembrane potential at 80 mV to 90 mV negative to the exterior. This transmembrane potential is controlled by Na-K-ATPase, the so called Na-K-pump. Antiarrhythmic agents can change the movement of sodium and potassium ions across cell membranes and control the function of cardiac cells. Electrophysiological methods are capable of measuring the function of individual ion channels of cardiac cells and their proteins leading to better insight into the action of antiarrhythmic drugs. The cardiac AP can be divided in five different phases (Figure 6).

![Figure 6. Cardiac Action Potential](image)

Phase “0” is the depolarization phase, Na channels are opened, and sodium ions are able to penetrate via the Na-channels in the cell. Phase 1 is the “notch” phase (short repolarization phase, when transient outward potassium channels are activated. During phase 2
(plateau), calcium (L-type and T-type) and potassium channels ("delayed rectifier") are activated, leading to an increase in intracellular calcium ions, and an out-flux of potassium ions from intracellular sites. Phase 3 is the so called repolarize phase when Na-channels are still open and sodium ions enter the intracellular site from the extracellular site. Phase 4 is the "depolarization phase" when the Na-K-ATPase is activated, and potassium ions return to the intracellular space by active transport from the extracellular space, and sodium ions are pumped from the intracellular site into the extracellular site.

In cardiac ischemia, some channels are activated such as ATP-sensitive K-channels, resulting in increased intracellular potassium ion current, which is increased through the cell membrane into extracellular spaces, leading to hyperpolarization. In addition, under ischemic conditions, intracellular sodium and calcium ion concentrations are elevated causing necrosis and apoptosis (cell death).

Electrocardiogram (ECG): Under physiological condition impulses are generated in the sinus node (right atrium). As the impulse leaves the sinus node, it propagates through the atria leading to atrial systole, and the “P” wave of the ECG (Figure 7). Propagation is slowed in the AV node, and this can be seen and measured as “PQ” distance on the ECG. If an impulse exits in the AV node, it enters the ventricular conduction system producing left ventricular systolic contraction. The sign (depolarization state) of the contraction of left ventricle (systole) is represented by the “QRS” complex on the ECG. Ventricular repolarization (diastole) leads to the appearance of the “T” wave on the ECG.

The ECG can give the clinicians a rough guide and important information about cellular, physiological, and pathological properties of cardiac tissues and the heart. Each cardiac cell interacts with many neighbours, thus the impulses spread rapidly, and the heart contracts similarly a single huge cell, such as a syncytium.

Mechanisms of cardiac arrhythmias:

Three processes which have been classified as mechanisms of arrhythmias are (a) increased automaticity, (b) triggered automaticity, and (c) re-entry mechanism.

Increased automaticity (a) is related to beta adrenergic stimulation and hypokalemia which increase the “phase 4 slop” of action potential accelerating pacemaker rates, while acetylcholine decreases pacemaker rate and “phase 4 slop”. If impulses propagate normal or abnormal automaticity to excite the rest of the myocardium, cardiac arrhythmias develop.

Triggered automaticity and afterdepolarization (b) occur under pathological conditions, if the normal AP is interrupted or followed by abnormal depolarization, leading to abnormal cardiac rhythms as shown in Figure 8. Two forms of triggered arrhythmias are known: (1) The normal AP is followed by a delayed afterdepolarization (DAD); (2) and if the
“phase 3” repolarization is interrupted by an early afterdepolarization (EAD). EAD can develop under clinical conditions when the heart rate and extracellular potassium content is low. If cardiac repolarization (phase 3) is prolonged, the long QT syndrome and “torsades de pointes” ventricular tachycardia can be generated.

![Diagram](image)

**Figure 8.**

The re-entry mechanism (c) can develop if two different parts of the heart have heterogeneous electrophysiological properties. The classical re-entry mechanism is the Wolff-Parkinson-White (WPW) syndrome developed between the right atrium and left ventricle (AV node). If the AV node is not in the refractory stage, the propagation impulse returns to the left atrium as a circuit. Thus, WPW syndrome can result in re-entrant tachycardia and atrial flutter.

**Mechanisms of antiarrhythmic drugs:**

The major action of antiarrhythmic drugs is the blockade of sodium, calcium, potassium channels, and beta-1 adrenergic receptors. Antiarrhythmic agents bind to specific sites on the ion channel proteins to modify their function, and thus, prevent the development of DAD, EAD, and re-entry arrhythmias. Antiarrhythmic agents are classified as: (1) sodium channel blockers, (2) calcium channel blockers, (3) beta adrenergic receptor blockers, and (4) drugs prolonging the duration of action potential.

1. **Sodium channel blockers:** If sodium channels are blocked excitability threshold is increased, and a bigger membrane depolarization is required to bring sodium channels from the rest to open stages. The blockade of sodium channels decreases conduction velocity and increases the duration of QRS complex on the electrocardiogram. Sodium channel blockers affect the phases “0” (depolarization) and “4” (decreasing “phase 4” slope) in AP. Drugs which block sodium channels are quinidine, disopyramide, moricizine, propafenone, flecainide, lidocaine, procainamide, mexiletine, and phenytoin (antiarrhythmic and antiepileptic agent).

2. **Calcium channel blockers commonly used for the treatment of angina and hypertension:** Among calcium channel blockers, only verapamil (CALAN, ISOPTIN, VERELAN) and diltiazem (CARDIZEM, TIAZAC, DILACOR) block calcium channels in the myocardium at therapeutic doses. These drugs prolong PR interval and have metabolites that exert calcium channel blocking actions. Both verapamil and diltiazem can increase the concentration of digoxin in the serum.

3. **Beta adrenergic receptor blockers:** The stimulation of beta adrenergic receptors increases inward calcium current, and the magnitude of repolarizing potassium and chloride currents. As a result, under pathological conditions, DAD- and EAD-related arrhythmias can...
develop. Beta adrenergic receptor blockers inhibit the aforementioned effects, and the drugs can be antiarrhythmic by reducing heart rate and reducing intracellular calcium overload. Beta adrenergic receptor blockers also inhibit the increase of intracellular sodium leading to slow heart rate.

Side effects of beta adrenergic receptor blockers are fatigue, bronchospasm (blockade of beta-2 receptors), hypotension, depression, aggravation of heart failure, and impotence. Abrupt discontinuation of these agents can cause rebound effects such as hypertension, angina, and cardiac arrhythmias.

Beta adrenergic blockers can be selective, blocking beta-1 adrenergic receptors, or nonselective, blocking both beta-1 and beta-2 receptors. Table 1 below shows the selective and nonselective structures.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Acebutolol</td>
<td>selective β₁ blocker</td>
</tr>
<tr>
<td>Alprenolol</td>
<td>selective β₁ blocker</td>
</tr>
<tr>
<td>Atenolol</td>
<td>selective β₁ blocker</td>
</tr>
<tr>
<td>Betaxolol</td>
<td>selective β₁ blocker</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>selective β₁ blocker</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>selective β₁ blocker</td>
</tr>
<tr>
<td>Nebivololum</td>
<td>selective β₁ blocker, used in essential hypertension!</td>
</tr>
<tr>
<td>Esmolol</td>
<td>selective β₁ blocker</td>
</tr>
<tr>
<td>Oxprenolol</td>
<td>nonselective β₁,₂ blocker</td>
</tr>
<tr>
<td>Pindolol</td>
<td>nonselective β₁,₂ blocker</td>
</tr>
<tr>
<td>Propranolol</td>
<td>nonselective β₁,₂ blocker</td>
</tr>
<tr>
<td>Sotalol</td>
<td>nonselective β₁,₂ blocker</td>
</tr>
<tr>
<td>Timolol</td>
<td>nonselective β₁,₂ blocker, used in glaucoma</td>
</tr>
</tbody>
</table>

Table 1. Selective and nonselective beta receptor blockers.

Mainly acebutolol, sotalol, propranolol, esmolol, and metoprolol are used for the treatment of cardiac arrhythmias.

(4) Drugs prolonging the duration of action potential (AP): These drugs block potassium channels, although an increase in inward sodium current also may cause AP prolongation. Increased duration of AP reflects in the increase of QT interval and refractoriness, and therefore these drugs are effective for the treatment of re-entry arrhythmias. Potassium channel blockers also interact with beta adrenergic receptors (e.g., sotalol) or other channels (e.g., amiodarone and quinidine). The pure AP prolonging drugs are dofetilide and ibutilide.

Application of antiarrhythmic drugs: In atrial fibrillation, (i) AV nodal blocking drugs include digitalis, verapamil, diltiazem, or beta adrenergic blocking agents, (ii) maintaining normal rhythm by quinidine, flecainide, and amiodarone can be used. It’s important to note that, under some conditions, antiarrhythmic drugs (e.g., verapamil) can cause or aggravate cardiac arrhythmias (proarrhythmic effects). Therefore, calcium sensitizers, e.g., levosimendan, can sensitize the myocardium to calcium, without increased intracellular free calcium contents, which avoids the proarrhythmic effect of the drug.

Properties of most common antiarrhythmic drugs:
Quinidine (QUINIDINE) has been used as antiarrhythmic agent for the treatment of atrial fibrillation and flutter since 1920s. The drug blocks sodium and various potassium currents. The function of sodium channels is inhibited (“0 phase”) in open state, and as a consequence, the duration of QRS complex is increased by 20% at therapeutic concentrations. Quinidine also prolongs the QT interval by approximately 25%, thus the duration of AP is increased. At higher concentrations (>2 micromol), the drug blocks L-type calcium channels.

Adverse effects of quinidine are diarrhea, thrombocytopenia, hepatitis, bone marrow depression, headache, tinnitus, and “torsades de pointes” VT. Quinidine can exacerbate the various types of heart failure. The drug undergoes hepatic oxidation, and about 20% is excreted by kidneys in unchanged form. Therapeutic plasma concentrations are between 2 and 5 microgram/ml. Quinidine is an inhibitor of CYP-450 enzymes, therefore, the parallel administration of quinidine with digoxin, morphine, and beta adrenergic blockers can elicit their toxic effects. Barbiturates, cimetidine, and verapamil can elevate the plasma concentration of quinidine.

Amiodarone (CORDARONE, PACERONE) blocks the influx of sodium and calcium ions (in “0 phase” an “phase 3”), and outward potassium current. On the ECG, the prolongation of PR, QRS, and QT intervals can be detected, thus, the final result is bradycardia. Therapeutic concentration of amiodarone is about 2 microgram/ml in the plasma. Elimination of the drug is slow, therefore, oral delivery must be used once a day. Amiodaron inhibits CYP enzymes, therefore the dosages of warfarin, digoxin, and other antiarrhythmics have to be reduced during amiodarone treatment. Side effects are hypotension, nausea, pulmonary fibrosis, pneumonia, hepatic and pulmonary dysfunction.

Dysopiramide (NORPACE) is used in atrial flutter or atrial fibrillation to protect the left ventricle against the development of ventricular fibrillation. Dysopiramide blocks sodium channels but does not prolong the duration of action potential. The drug has anticholinergic actions which are responsible for the adverse effects. Thus, glaucoma, constipation, urinary retention, dry mouth, and heart failure can develop. Dysopiramide is eliminated by the liver and excreted via the kidney in unchanged form. Drug interaction is developed with the concomitant administration of phenytoin.

Dofetilide (TIKOSYN) is a potent potassium channel blocker, acting by blockade of the delayed rectifier potassium current (I\(_{Kr}\)) in “phase 2” and “phase 3” of action potential. Dofetilide can induce “torsade de pointes” ventricular tachycardia as a side effect. The drug is excreted in unchanged form via the kidney and urine. The drug cannot be used in patients with renal failure or with inhibitors of renal ion transports.

Flecainide (TAMBOCOR) blocks sodium current in “phase 0” and delayed rectifier potassium current (I\(_{Kr}\)) in “phase 2” and “phase 3” of action potential. The drug prolongs PR, QRS, and QT intervals on ECGs. The side effects of the drug are blurred vision, exacerbated congestive heart failure, arrhythmias (proarrhythmic effect), and AV blockage. The elimination of flecainide occurs by hepatic metabolism, and in unchanged form via renal excretion. The optimal plasma concentration of the drug is 1 microgram/ml.

Ibutilide (CORVERT) activates inward Na\(^+\) current and blocks the delayed rectifier potassium current (I\(_{Kr}\)). The drug is used for the conversion of atrial fibrillation and flutter to normal sinus rhythm. The major side effect of ibutilide is “torsades de pointes” ventricular tachycardia (in about 6-7% of patients). The drug is eliminated by hepatic metabolism, and the half life is about 10 hours.

Lidocaine (XYLOCAINE) is used for the treatment of ventricular arrhythmias by the intravenous route especially for the termination of ventricular tachycardia and fibrillation. The drug also has a local anesthetic effect. These effects are explained by the blocking of Na\(^+\) channels in both the heart and neurons. Lidocaine has no beneficial effect in the treatment of atrial fibrillation or flutter. The drug does not have affect the duration PR and QRS complex,
however the QT interval is slightly shortened in lidocaine-treated patients. The drug is eliminated by hepatic metabolism, and the half life is about 2 hours in the serum after intravenous administration. The therapeutic range of lidocaine is between 1.5 and 3.0 microgram/ml in the serum.

**Mexiletine** (MEXITIL) and **tocainide** (TONOCARD) is derived from the basic molecular structure of lidocaine to reduce the first-pass hepatic metabolism and permit oral application. Mexiletine and tocainide can be used in combination with quinidine and sotalol to increase the efficacy and reduce the side effects of antiarrhythmics. Mexiletine and tocainide are effective for the treatment of “long QT” syndrome.

**Moricizine** (ETHMOZINE) is a sodium channel blocker used for the treatment of ventricular arrhythmias. The drug is metabolized by the liver. Although moricizine has a short half life in the body (about 90 min), its antiarrhythmic effect persists for 7 to 8 hours, suggesting that its metabolite has still antiarrhythmic activity.

**Propafenone** (RYTHMOL) blocks sodium channels in “phase 0” and “phase 2” of AP, as well the potassium channels in “phase 2” and “phase 3”. The drug prolongs duration of the PQ and QRS complexes. Propafenone has beta adrenergic receptor antagonist effects leading to bradycardia. The drug is eliminated by hepatic and renal routes. Propafenone can be carefully administered together with quinidine and fluoxetine, because propafenone blocks the function of cytochrome P-450 enzymes in the liver.

**Sotalol** (BETAPACE) is a nonselective beta adrenergic receptor antagonist blocking various K⁺ currents. In addition, sotalol blocks Na⁺ influx in the “phase 0” of action potential. Thus, the duration of action potential is increased, leading to the prolongation of QT interval on the ECG. The drug slows AV nodal conduction. Sometimes sotalol causes ‘torsades de pointes’ ventricular tachycardia (proarrhythmic effect) if the serum K⁺ level is low.

**Cardiac glycosides** (LANOXIN) have positive inotropic effects and are used for the treatment of heart failure. The drug shortens AP in the atrium and slows the impulse conductance in the AV node. Thus, digoxin protects the ventricle against atrial fibrillation. Digoxin prolongs PR interval on the ECG. With severe digoxin intoxication severe hyperkalemia, because of the poisoning of Na-K-ATPase, bradycardia and VF can develop.

**Magnesium** sulphate is used for the treatment of ‘torsades de pointes’ ventricular tachycardia with doses of 1 g to 2 g. Magnesium is a natural Ca²⁺ antagonist, therefore, magnesium can be used for the treatment of digitalis overdosage.
4). Treatment of hypertension including the rennin-angiotensin system

Hypertension, if sustained, causes pathological changes in the vasculature and the heart. Hypertension is the primary cause of the stroke, and a major risk factor of coronary diseases and myocardial infraction. The definition of hypertension is an elevated and sustained blood pressure above 140/90 mmHg. If systolic blood pressure is extremely high (>210 mmHg), endothelial injury, intimal thickening, and arteriolar occlusion develop leading to the failure of the kidney, brain, heart, pulmonary failure, and edema formation.

Treatment of hypertension is associated with the reduction of elevated diastolic pressure leading to a reduction of morbidity and mortality of patients. Antihypertensive drugs lower blood pressure, peripheral resistance, and cardiac output. Such drug therapy significantly reduces the risk of stroke, cardiac failure, infarction, and renal insufficiency. The simultaneous use of antihypertensive drugs with a variety of action mechanisms can reduce adverse effects. Genome scanning can lead to identification of novel genes that have a significant impact on the development of hypertension.

Antihypertensive agents can be classified according to their action mechanisms and sites of action. Thus, the antihypertensive agent groups are: (i) Diuretics; (ii) Sympatholytic drugs; (iii) Calcium-channel blockers; (iv) Angiotensin-converting enzyme inhibitors; (v) Angiotensin II receptor antagonists; and (vi) Direct vasodilators.

(i) Diuretics

The drug categories that include diuretics as antihypertensive agents are thiazides, loop diuretics, and K-sparing agents. These diuretics have antihypertensive effects if used alone, and enhance the efficacy of all antihypertensive drugs.

Thiazides (chlorthalidone: HYGROTON, hydrochlorothiazide: HYDRODIURIL) open Ca-activated K-channels leading to hyperpolarization and vasodilatation. Thiazides inhibit carbonic anhydrase causing edema reduction. In addition, the blockage of Na-Cl-cotransporters leads to urination and reduction in blood pressure. The maximum daily dose of thiazides is 25 mg. Urinary K-loss by thiazides must be replaced by potassium salts. However, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists will attenuate thiazide-induced K⁺ loss to a certain degree.

Thiazides inhibit renal Ca²⁺ excretion leading to hypercalcemia, therefore these drugs are also useful tools for the treatment of osteoporosis or hypercalciuria. Because of potassium depletion, ventricular tachycardia and ventricular fibrillation can develop. All thiazides cross the placenta but do not have adverse effects on the fetus.

Loop diuretics (furosemide, bumetanide, torsemide, ethacrynic acid) are particularly useful for the treatment of azotemia (high level of urea in the blood), and severe edema associated with congestive heart failure and ascites.

K-sparing diuretics (amiloride, spironolactone, triamterene) lower blood pressure in patients afflicted with hypertension. These diuretic drugs may not be used in patients afflicted with hyperkalemia. Renal insufficiency is a contraindication for the use of K-sparing diuretics. The coadministration of these diuretics with ACE inhibitors or angiotensin-receptor antagonists magnifies the risk of hyperkalemia.

(ii) Sympatholytic drugs

The antihypertensive effect of beta adrenergic receptor blockers is the blockade of beta adrenergic receptors in the juxtaglomerular complex by reducing rennin secretion and
diminishing of circulating angiotensin II in concert with the direct cardiac effect. In addition, beta blockers are able to change peripheral adrenergic neuronal function and increase prostacyclin production leading to vasodilatation.

Side effects of beta blockers are asthma (due to beta-2 receptor blockade) and sinus and/or AV nodal conduction dysfunction in the heart. Sudden discontinuation of beta adrenergic receptor blockers produce “withdrawal syndrome” by causing enhanced tissue sensitivity to catecholamines leading to exacerbation of coronary artery diseases.

Drug interactions of beta adrenergic receptor blockers can be happened with the coadministration of indomethacin (blunting the antihypertensive effect) and other beta adrenergic receptor antagonists. Epinephrine can induce severe hypertension with the administration of beta receptor antagonists. Bradycardia is the result of the reflex vagal stimulation.

Beta adrenergic receptor antagonists are effective therapy for all degrees of hypertension. These drugs also have antiischemic and antiarrhythmic effects. These drugs (propranolol, metoprolol) are successfully used for the treatment of myocardial infarction, ischemic heart disease, and congestive heart failure.

Alpha-1 adrenergic receptor antagonists (prazosin: MINIPRESS, terazosin: HYTRIN, doxazosin: CARDURA) reduce arteriolar resistance, increase venous capacitance; and in addition, they are also able to reduce triglycerides and LDL cholesterol levels in the plasma. These drugs are not recommended alone for the treatment of hypertension, therefore the combination of alpha-1 adrenergic receptor antagonists is suggested with beta receptor blockers and/or diuretics. Alpha-1 adrenergic receptor antagonists are useful drugs for the treatment of patients afflicted with benign prostate hyperplasia and as a result they are able to improve urinary symptoms. The alpha-1 and beta adrenergic receptor antagonists, labetalol (NORMODYNE) and carvediol (COREG) are often used in combination. The ratio of alpha and beta antagonist potency for these drugs is about 1:10. Labetalol and carvediol are also potent antihypertensive agents.

Centrally acting antihypertensive agents include methyldopa (ALDOMET), clonidine (CATAPRES), guanabenz (WYTENSIN), and guanfacine (TENEX).

Methyldopa is a ‘pro drug’ exerting its antihypertensive effect via an active metabolite. Methyldopa is metabolized to alpha-methyldopamine, which is converted to alpha-methylnorepinephrine. Alpha-methylnorepinephrine replaces norepinephrine in the vesicles of neurons, and during its release by nerve stimuli does not stimulate alpha-1 receptors. Thus, the final result is vasodilatation. In addition, alpha-methylnorepinephrine stimulates presynaptic alpha-2 receptors in the CNS leading to the blockade of neurotransmitter release of catecholamines.

The duration of action of a single dose of methyldopa is about 24 hours. Side effects of methyldopa are parkinsonian signs, reduction in libido, hyperprolactinemia causing gynecomastia and galactorrhea. Methyldopa is a preferred antihypertensive agent for the treatment of hypertension during pregnancy based on its safety for the mother and fetus. Maximal daily dose of the drug is 2 grams divided in two portions.

Clonidine, guanabenz, and guanfacine are alpha-2 adrenergic receptor agonist. These agents stimulate alpha-2 receptors in the CNS resulting in a reduction in norepinephrine outflow from the CNS. Vasodilatation occurs as a result along with reduced blood pressure. Adverse effects include sedation, xerostomia, dry eyes, sleep disturbances with nightmares, depression, parotid gland swelling and pain. Withdrawal syndrome (tachycardia, high blood pressure) can be seen if the application of drugs is suddenly stopped. Diuretics potentiate the hypotensive effects of these alpha-2 receptor agonists. Clonidine is used for the diagnosis of pheochromocytoma. A single oral dose (0.3 mg) of clonidine can reduce the extremely high blood pressure at normal within 3 hours.
Guanadrel specifically inhibits the function of postganglionic adrenergic neurons in the periphery. Guanadrel is an exogenous false neurotransmitter like alpha-methyl-norepinephrine and does not stimulate postsynaptic alpha-1 receptors. Guanadrel is accumulated and stored in vesicles as norepinephrine. Guanadrel blocks sympathetic ganglions leading to a reduction in peripheral vascular resistance, and inhibition of alpha-1 receptor mediated vasoconstriction. The maximum effect on blood pressure develops after 6 to 8 hours. Antidepressants, cocaine, ephedrine, and amphetamine or amphetamine-like compounds block the effects of guanadrel.

Reserpine is an alkaloid extracted from Rauwolfia serpentina which interferes with the function of the sympathetic nervous system. The drug binds to the vesicles of norepinephrine stores and causes damage to storage capacity. Finally the vesicles will empty and no release of norepinephrine occurs from the neurons, resulting in reduction of blood pressure. Reserpine induces the depletion of other biogenic amines such as dopamine and serotonin. Adverse effects of reserpine are due to its effects on the CNS. Thus, depression, Parkinson-like syndrome, and peptic ulcer can develop.

(iii) Calcium-channel blockers

The use of calcium channel blockers is a basic strategy in patients afflicted with hypertension. Verapamil, amlodipine, felodipine, isradipine, nifedipine, and diltiazem block calcium entry in the cell leading to vasodilatation. These drugs, depending on the molecular structure, have antiischemic and antiarrhythmic effects as well. All calcium channel blockers are effective in monotherapy of mild and moderate hypertension. Side effects are headache, dizziness, flushing, peripheral edema, constipation, and urinary retention. Cardiac side effects as AV nodal block and conduction disturbances can be detected on the ECG. Drug interaction may occur when calcium antagonists are given with digoxin. The coadministration of Ca-channel blockers with quinidine can cause excessive hypotension.

(iv) Angiotensin-converting enzyme (ACE) inhibitors

These drugs reduce the level of angiotensin II in the plasma as an important result of the prevention of the development of hypertension. Captopril was the first agent to be developed for the treatment of hypertension as an ACE inhibitor. A new generation of ACE inhibitors includes enalapril, lisinopril, quinapril, benazepril, moexipril, fosinopril, trandolapril, and perindopril. The ACE inhibitors have a special advantage in the treatment of diabetes slowing the progression of diabetes-induced glumerulopathy. ACE inhibitors, in the treatment of postmyocardial infarction, have been shown to improve cardiac function.

The attenuation of aldosterone production by ACE inhibitors changes potassium homeostasis. Patients with diabetic nephropathy are at a greater risk of hyperkalemia. ACE inhibitors are contraindicated in pregnancy. These drugs are approved for one dose daily and their effects last for 24 hours.

(v) Angiotensin II receptor antagonists

Angiotensin II receptor antagonists produce their effects by binding to the AT-1 receptors. The members of this group are losartan (COZAR), candesartan (ATACAND), irbesartan (AVAPRO), valsartan (DIOVAN), telmisartan (MICARDIS), and eprosartan (TEVETEN). These drugs antagonize the effects of angiotensin II, resulting in smooth muscle relaxation, promoting vasodilation, reducing plasma volume, and decreasing cellular hypertrophy.
Two subtypes of angiotensin II receptors exist, AT1 and AT2: The AT1 receptors are located in vascular and myocardial tissues, in the brain, the kidney, and adrenal glomerulosa cells which secrete aldosterone. The AT2 receptors are in the CNS, the adrenal medulla, and the kidney where they play a role in vascular development, and responsible antigrowth and antiproliferative responses. Adverse effects are hypotension, hyperkalemia, and diminished renal function. The AT1 receptor blockers can be combined with thiazide diuretics.

(vi) Direct vasodilators

This group of antihypertensive agents includes hydralazine (APRESOLINE), sodium nitroprusside and diazoxide, and $K^+_{ATP}$ channel openers (minoxidil: LONITEN).

Hydralazine directly causes the relaxation of arteriolar smooth muscle leading to reduction of blood pressure. The drug decreases vascular resistance of arterioles in the heart, the brain, and kidney. Hydralazine is well absorbed in the gastrointestinal tract with a half-life of one hour, and maintains 12-hour hypotensive effect. Side effects are palpitation, angina pectoris, tachycardia, nausea, dizziness, flushing, and immunological (lupus syndrome) reaction. Hydralazine can be combined with beta-blockers and diuretics. However, hydralazine is not a first line drug in the treatment of hypertension.

Sodium nitroprusside releases nitric oxide (NO), which activates a guanylyl cyclase (cyclic GMP) signal leading to vasodilatation in vascular smooth muscles. The drug is a nonselective vasodilator. NO formation is much less in hypertensive patients in comparison with intact human beings. Thus, nitroprusside is an effective antihypertensive agent as a result of its stimulation of NO production in endothelial cells. Tolerance is not developed to nitroprusside as it is the case of the application of nitroglycerine or other organic nitrates.

Nitroprusside is an unstable molecule, which dilates both venules and arteriols, thus, as a consequence afterload and cardiac output are reduced in patients treated with nitroprusside. The hypotensive effect appears within 1 minute of intravenous injection and disappears after 4 minutes. Side effects of the drug are originated from its metabolites of cyanide and thiocyanate. These are anorexia, fatigue, nausea, disorientation, and hypothyroidism by inhibition of iodine uptake in the thyroid gland. Diazoxide (HYPERSTAT) has the same effects as nitroprussid.

The active metabolite of the drug activates $K^+_{ATP}$ channels by maintaining their open state. The resulting $K^+_{ATP}$ efflux causes membrane hyperpolarization, leading to vasorelaxation of smooth muscles in vessels. Minoxidil induces rennin secretion, and has slight hypoglycemic effect and hypercholesterolemic effects as well. The main route of minoxidil elimination is via the hepatic metabolism; and about 20% of it is excreted in unchanged form via the urine.

Adverse effects of minoxidil: Retention of salts and water are increased in proximal tubules of the kidney leading to antinatriuretic effects. Drug-induced retention of salt and water requires large doses of loop diuretics to prevent edema formation. Myocardial ischemia also can be induced by the drug in patients with coronary diseases. Minoxidil is best reserved for the treatment of severe hypertension especially in patients with renal insufficiency. Minoxidil cannot be used alone, drug combinations are necessary, mainly with beta receptor blockers. The daily dose of minoxidil is about 1.25 mg which can be increased gradually up to 40 mg/day, in single or divided doses.

5). Vasopressin and other drugs affecting renal function

Arginine vasopressin (antidiuretic hormone = ADH) is the primary hormone that regulates fluid osmolality in the body. Vasopressin (or vasopressin-like hormones) can be
found in mammalian, nonmammalian vertebrates, and invertebrates. Vasopressin is the hormone that regulates the conservation of water in the body. The hormone is released from the posterior pituitary if water deprivation causes an increased plasma osmolality, and the cardiovascular system is hypovolemic, or hypotension develops. In vertebrates, vasopressin acts on the renal collecting duct. The hormone increases the permeability of cell membranes to water, permitting water to passively move in extracellular compartments. Vasopressin is a potent vasoconstrictive agent and a neurotransmitter as well. The drug acts on the CNS and produces the secretion of adrenocorticotrop hormone (ACTH). Vasopressin also promotes the release of coagulation factors in vascular endothelial cells increasing platelet aggregation.

Vasopressin and oxytocin are synthesized in the supraoptic nucleus and paraventricular nucleus. The process of axonal transport of hormones is rapid, and the hormone-laden granules arrive at their target within 30 minutes. Vasopressin is synthesized in the CNS, the heart, and adrenal gland. Stress increases the synthesis of vasopressin in the aforementioned organs. Increased vasopressin synthesis stimulates catecholamine secretion from chromaffin cells stimulating aldosterone synthesis.

Many well known drugs and molecules are able to stimulate vasopressin secretion. These are vincristine, tricyclic antidepressants, nicotine, epinephrine, acetylcholine (via nicotinic receptors), dopamine (via D1 and D2 receptors), glutamine, prostaglandins, angiotensin II, substance P, vasoactive intestinal polypeptide, and cholecystokinin. Inhibitors of vasopressin secretion include ethanol, glucocorticoids, haloperidol, promethazine, fluphenazine, opioids (via kappa receptors), gamma-aminobutyric acid, and atrial natriuretic peptide.

Vasopressin receptors include V1a, V1b, and V2. The V1a receptor is the most widely distributed type of vasopressin receptor. It is located in vascular smooth muscle, myometrium, adrenal gland, bladder, platelets, adipocytes, spleen, testis, kidney, and CNS structures. The distribution of V1b receptors is very limited, they can be found in the anterior pituitary, the pancreas, and adrenal medulla. V2 receptors are present in epithelial cells, vascular endothelial cells, and in the renal collecting duct system. Vasopressin receptors are heptahelical G protein-coupled receptors. In addition, two putative receptors can be included in the V1a, V1b, and V2 receptor families: one of them is vasopressin activated Ca-mobilizing receptor, which binds vasopressin and increases intracellular Ca ion levels. The second one is a dual angiotensin II – vasopressin heptahelical receptor that activates adenylyl cyclase in response to vasopressin and angiotensin II.

Vasopressin binds to V1 receptors and activates Go – PLC pathway leading to the generation of IP3 and diacylglycerol. These mediators increase the intracellular Ca2+ concentration and activate protein kinase C (PKC), and as a consequence, vasoconstriction, platelet aggregation, glycogenolysis, ACTH release, and growth of smooth muscle cells occur (Figure 9).
Figure 9. Vasoconstriction via V₁ receptors.

Cells of the renal collecting duct express V₂ receptors. Vasopressin binding to these receptors couples to Gₛ proteins to stimulate adenylyl cyclase activity. This results in an increase in cellular cAMP content and protein kinase A (PKA) activity, triggering an increased rate of insertion of water channel-containing vesicles by increasing the water permeability through the apical membrane. Aquaporins are water channel proteins that allow water to cross cell membranes.

V₂ receptor activation also increases urea permeability in the inner medullary collecting duct. The increase in water and urea permeability in the collecting duct, and V₂ receptor activation increases Na⁺ transport that affects Na⁺ - K⁺ - Cl⁻ symporters. V₂ receptors are responsible for the increased water permeability in the collecting duct. Vasopressin increases water permeability at a concentration of 50 fM or less in the collecting duct.

Under conditions of dehydration in patients, the osmolality of plasma is increased, vasopressin concentration is elevated, and the permeability of collecting duct to water is increased. The osmotic gradient between the diluted tubular urine and the hypertonic renal intestinal fluid gives for the osmotic flux of water out of the collecting duct. The final osmolality of urine is as high as 1100 mOsm/kg in humans. V₂ receptor stimulation causes increased Na⁺ transport in the cortical collecting duct, and this synergizes with aldosterone to increase Na⁺ reabsorption in patients suffering from hypovolemia.

Drug interactions: Although the mechanism is still obscure, carbamazepine enhances the antidiuretic effects of vasopressin. Nonsteroid anti-inflammatory drugs (NSAIDs) increase the antidiuretic response to vasopressin via reduced prostaglandin production. This occurs due to the capacity of prostaglandins to attenuate the antidiuretic response of vasopressin. Moreover, NSAIDs inhibit prostaglandin synthesis. Lithium (used for the treatment of manic depression) reduces V₂-receptor mediated stimulation of adenylyl cyclase leading to less cAMP production and water reabsorption.
Vasopressin (ADH) causes vasoconstriction via the stimulation of V1 receptors in the brain, coronary arteries, skin, skeletal muscle, pancreas, gastrointestinal tract, and thyroid gland. The effects of vasopressin are reduced cardiac output, reduced heart rate, and coronary constriction. In the development of angina pectoris vasopressin plays an important role via the stimulation of V1 receptors in the coronaries. However, the stimulation of V2 receptors causes vasodilatation in some blood vessels.

Other effects of vasopressin: Vasopressin stimulates the contraction of smooth muscle in the uterus (via oxytocin receptors) and gastrointestinal tract (via V1 receptors). Platelets store vasopressin, therefore the stimulation of V1 receptors in platelets induces platelet aggregation. The stimulation of V2 receptors by vasopressin or desmopressin enhances circulating levels of factor VIII and von Willebrand factor leading to the formation of thrombus.

Vasopressin agonists and antagonists: Vasopressin and oxytocin have very similar structures (each consisting of 8 amino acids); and their agonists and antagonists can bind to each other’s receptors. The antidiuretic effect of desmopressin (peptide-like agonist) is 3000 times greater than vasopressin, therefore desmopressin is used for the treatment central diabetes insipidus.

Vasopressin receptor antagonists affect V1 or V2 receptors. These agents are nonpeptide antagonists, relcovaptan (selective V1 antagonist) and lixivaptan (selective V2 receptor antagonist). These drugs can be used for the treatment of heart failure and hypertension. Peptide-like vasopressin antagonists (derivatives of arginine vasopressin) are not selective and bind to both V1 and V2 vasopressin receptors.

Diabetes insipidus (DI) is an impaired renal conservation of water including: (i) inadequate secretion of vasopressin from the hypophysis (central diabetes insipidus); and (ii) an insufficient renal response to vasopressin (nephrogenic diabetes insipidus). Patients with DI excrete large volumes of dilute urine (less than 200 mOsm/kg), typically (more than 30 liter/day). In DI, glucose in the urine cannot be detected. Central DI can be distinguished from the nephrogenic DI by the application of desmopressin which reduces the volume of urine to 3 liter/day and increases its osmolality to 1000 mOsmol/kg. Desmopressin has no effects in patients suffering from nephrogenic DI (the lack of V1 and V2 receptors).

Central DI is caused by head injury (surgical or traumatic) in the region of pituitary or hypothalamus, tumors, cerebral aneurysms, CNS ischemia, and brain infections. Familial central DI is autosomal dominant (chromosome 20) leading to vasopressin deficiency. Antidiuretic peptides (e.g., vasopressin or desmopressin) are the primary therapy for central DI. Some of the patients cannot tolerate antidiuretic peptides because of allergic reactions. In these cases chlorpropamide, an oral sulfonylurea, potentiates the action of small or residual amounts of circulating vasopressin, and reduces urine volume in central DI. Carbamazepine and clofibrate are also able to reduce urine volume in central DI patients. All of these agents are ineffective in nephrogenic DI.

Hypercaldcemia, hypokalemia, renal failure, lithium, clozapine can induce nephrogenic DI. The reason is the mutation or lack of V2 receptors in the kidney. Vasopressin is available in the circulation but the peptide cannot bind to V2 receptors because of their lack, mutation, or insensitivity to vasopressin. Thiazide diuretics paradoxically reduce the polyuria in patients with nephrogenic DI. The response is good to thiazides, and the volume of urine can be reduced by 60% daily. The action mechanism of thiazide diuretics is completely unknown in nephrogenic DI.

Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is a disease of water excretion with hyponatremia and hypoosmolality. The mechanism involves inappropriate secretion of vasopressin. This syndrome leads to lethargy, anorexia, muscle cramps, coma, convulsions, and death. Infections, tumors, CNS injuries, and pulmonary
diseases can lead to the development of SIADH. The treatment of hypotonicity with SIADH includes water restriction, iv administration of hypertonic saline, and drugs that inhibit the effect of vasopressin to increase water permeability in collecting ducts. An inhibitor of vasopressin action in collecting ducts is demeclocycline, a tetracycline derivative, is the preferred drug for the treatment of SIADH.

**Therapeutic uses:** Two antidiuretic peptides are used for therapy: vasopressin (PITRESSIN) and desmopressin acetate (DDAVP). V1 receptor-mediated vasoconstriction is used to reduce bleeding in acute hemorrhagic gastritis, burn wound excision, liver transplant, and uterine myoma resection. V2 receptor-mediated applications are central DI with V2-receptor agonists, and polyuria and polydipsia are also well controlled by V2 agonists. The duration of the effect of desmopressin is about 20 hours, and its dose is 20 to 40 microgram/day nasally. Vasopressin is used for the treatment of bleeding time (shortening) in type I von Willebrand’s disease.

**Pharmacokinetics and toxicity of vasopressin:** The duration of antidiuretic action after intramuscular or subcutaneous injection is about 4 to 8 hours. The half life of vasopressin is about 30 minutes in the plasma. The side effects are mediated via V1 receptors. Desmopressin is less toxic than vasopressin. Cutaneous vasoconstriction, coronary constriction, reduced cardiac output, and gangrene have been encountered in patients receiving vasopressin. V2 receptor-mediated adverse effects include water intoxication. Intranasal application causes local oedema, rhinorrhoe, irritation, pruritus, and ulceration.
6). Diuretics

Diuretic drugs regulate and increase the sodium excretion and urine flow to adjust the volume and composition of body fluids in hypertension, heart failure, cirrhosis, brain and lung oedema, and renal failure.

The basic unit forming urine is the nephron consisting of a filtering system called the glomerulus connected to a long tubule that reabsorbs the glomerular ultrafiltrate including water, ions, and other components. A single afferent arteriole penetrates the glomerulus in each nephron to form the glomerular capillary nexus. The kidney is composed about 1.1 million nephrons in humans.

The kidney filters a huge quantity of plasma. The two human kidneys produce about 120 ml/min of ultrafiltrate, and only 1 ml/min of urine. Thus, 99% of ultrafiltrate is reabsorbed under physiological condition.

In the proximal tubule, which is permeable to water, approximately 65% of the filtered sodium is reabsorbed. Thus, the reabsorbed sodium is followed by water reabsorption. The descending limb of the loop of Henle is highly permeable to water, but with low permeability to sodium, chloride, and urea. The ascending limb of the Henle loop actively reabsorbs the sodium and chloride ions, but is impermeable to water. About 25% of sodium ion is reabsorbed in the loop of Henle. The ascending limb of Henle is followed anatomically by the distal convoluted tubule. This structure actively transports sodium and chloride ions, but is impermeable to water, leading to formation of a fluid that is hypotonic. The sodium(reabsorption) – potassium(excretion) exchange occurs in the distal convoluted tubule. Therefore, diuretics can cause potassium loss. Fine control of ultrafiltrate composition and volume occurs in the collecting duct. Here, the final electrolyte composition and urine volume is adjusted by the adrenal steroid aldosterone, and the antidiuretic hormone (ADH) produced in the hypophysis-hypothalamic system. In the absence of ADH, the collecting duct is impermeable to water and the diluted urine is flushed away. In the presence of ADH, the collecting duct is permeable to water, and water is reabsorbed. The collecting duct has a low permeability to urea, thus, urea is concentrated in the fluid.

Various molecules can cross the renal epithelial cell membranes by various mechanisms. If water flows across cell membranes, the solute molecules (a) are passively transported into the direction of water flow. This transport mechanism is known as solvent drag. Lipoid soluble molecules can be dissolved in the membrane and diffused across the cell membrane by simple diffusion (b) down their electrochemical gradients. Many solutes have limited lipoid solubility and rely on integral carrier proteins embedded in the membrane providing a pore through which the molecule can diffuse passively. This transport is known (c) as channel mediated diffusion. In addition, some molecules can bind to an integral protein leading to a change in conformation (d), and the complex crosses the cell membrane in the direction of electrochemical gradient (facilitated or carrier mediated diffusion). If the molecule moves against an electrochemical gradient, it does so via ATP-mediated active transport (e). If the energy is derived from ATP, and is required for the transport of two different molecules through the cell membrane in the same direction (f), the mechanism is termed symport cotransport. Under symport cotransport conditions, but where the transport direction of the two molecules is opposite (g), the membrane transport mechanism is termed antiport (countertransport). A diagrammatic representation of these transport mechanisms is shown in the Figure 10 below. There are at least 9 different cotransporter and countertransporter proteins for different organic acids and bases in the kidney. The ions (sodium, potassium, calcium, magnesium, and chloride) and water are usually transported by passive or active transports in the various parts of the glomerular duct.
The classification of diuretics based on their sites of action includes (a) inhibitors of carbonic anhydrase, (b) osmotic diuretics, (c) inhibitors of Na-K-Cl symport (loop diuretics, high-ceiling diuretics), (d) inhibitors of Na-Cl symport (thiazide diuretics), (e) inhibitors of renal epithelial Na-channels (K-sparing diuretics), and (f) antagonists of aldosterone (K-sparing diuretics).

(a) Inhibitors of carbonic anhydrase

Acetazolamide (DIAMOX) is the first carbonic anhydrase inhibitor discovered to play an important role in renal physiology and pharmacology. Other inhibitors of carbonic anhydrase include dichlorphenamide (DARANIDE) and methazolamide (GLAUCTABS). The site of action for these drugs is epithelial cells of the proximal tubular system. Carbonic anhydrase plays a key role in the production of H\textsubscript{2}CO\textsubscript{3}. Its dissociation to H\textsuperscript{+} and -HCO\textsubscript{3} leads to Na\textsuperscript{+} and H\textsuperscript{+} exchange between the lumen of proximal tubule and epithelial cell leading to Na\textsuperscript{+} and water reabsorption and H\textsuperscript{+} secretion. The inhibitors of carbonic anhydrase lead to the lack of H\textsubscript{2}CO\textsubscript{3} production which does not provide H\textsuperscript{+} by dissociation, thus the Na\textsuperscript{+} and water reabsorption is inhibited, and the final volume of urine is substantially increased (Figure 11).

![Diagram of tubule and epithelial cell](image)

Figure 11. The role of carbonic anhidrase in the proximal tubule.

Although the proximal tubule is the primary action site for carbonic anhydrase inhibitors, carbonic anhydrase is also involved in the collecting duct system, which is the secondary site of action of these drugs. This inhibition results in a 35\% of \textsuperscript{3}HCO\textsubscript{3} excretion in
the urine. In addition Na\(^+\) ion and water reabsorption is inhibited in the proximal tubule, leading to increased volume of urine. The increased concentration of Na\(^+\) stimulates Na\(^+\) - K\(^+\) exchange in the proximal tubule, therefore carbonic anhydrase inhibitors produce hypokalemia. Potassium replacement is therefore mandatory in patients receiving carbonic anhydrase inhibitors.

The proximal tubule is the primary action site of carbonic anhydrase inhibitors. Carbonic anhydrase is also active in the collecting duct system, which is a secondary site of action for these drugs. This inhibition results in 35% of HCO\(_3^-\) excretion in the urine. In addition Na\(^+\) ions and water reabsorption is inhibited in the proximal tubule leading to the increased volume of urine. The increased concentration of Na\(^+\) stimulate the Na\(^+\) - K\(^+\) exchange in the distal tubule, therefore carbonic anhydrase inhibitors produce hypokalemia. Thus, K\(^+\) replacement is mandatory in patients receiving carbonic anhydrase inhibitors.

Other actions of carbonic anhydrase inhibitors: Carbonic anhydrase enzyme is also present in eye, gastric mucosa, pancreas, erythrocytes, and central nervous system. The inhibition of carbonic anhydrase reduces intraocular pressure, prevents the development of epileptic seizures, and diminishes gastric acid secretion. Acetazolamide causes vasodilation by opening vascular Ca\(^{2+}\) activated K\(^+\) channels.

Toxicity and adverse effects of carbonic anhydrase inhibitors: These drugs are sulphonamide derivatives causing bone marrow depression, allergic reactions, drowsiness, metabolic and respiratory acidosis. The long term use of carbonic anhydrase inhibitors can suspend their own diuretic effect due to metabolic acidosis leading to elevated H\(^+\) leading to the H\(^+\) - Na\(^+\) exchange in the epithelial cells of the proximal tubule. Thus, the diuretic effect is not developed.

(b) Osmotic diuretics

Osmotic diuretics are freely filtered at the glomerulus remaining in the tubules, pharmacologically inert. The osmotic agents glycerine (OSMOGLYN), isosorbide (ISMOTIC), urea (UREAPHIL), and mannitol (OSMITROL) are osmotic diuretics. The drugs stay in the proximal tubule, and absorb Na\(^+\) and water. In addition, osmotic diuretics expand the extracellular fluid volume, reduce rennin release, and diminish blood viscosity. Thus, renal blood flow is increased, and the filtrate and urine production is increased. Osmotic diuretics inhibit the reabsorption of Mg\(^{2+}\) interfere with various transport processes in the ascending limb leading to urination.

In summary, osmotic diuretic agents act in the proximal tubule and the Henle loop. As diuretic agents, glycerine and isosorbide can be given orally, whereas urea and mannitol must be given intravenously. Extraction of water and sodium, as side effects, leads to hyponatremia and dehydration. Mannitol and urea are contraindicated in patients with cranial bleeding. The metabolite of glycerine may cause hyperglycemia.

Therapeutic uses of osmotic diuretics: Osmotic diuretics are used in acute renal failure and acute tubular necrosis. Mannitol and urea are used for the treatment of dialysis disequilibrium syndrome because they increase the osmolality of the extracellular fluid compartment and shift water back into the extracellular space. Osmotic diuretics are also used for the treatment eye and brain oedema. The drugs reduce intraocular pressure (glaucoma) and cerebral oedema.

(c) Inhibitors of Na-K-Cl symport (loop diuretics, high-ceiling diuretics)

These drugs inhibit the activity of of Na-K-Cl symporter in the ascending limb of the Henle loop. Therefore, these drugs are called loop diuretics, and because of their high
effectiveness they are also called high-ceiling diuretics. These drugs are furosemide (LASIX), bumetanide (BUMEX), ethacrynic acid (EDECRIN), and torsemide (DEMADEX). Because of the high Na⁺ content in the proximal tubule, Na⁺ is absorbed followed by K⁺ excretion leading to cellular K⁺ loss. Therefore, K⁺ replacement is mandatory during the use of loop diuretics.

Other effects of loop diuretics include: stimulation of renin release, and stimulation of prostacyclin formation (the precise mechanism is unknown). About 60% of these diuretics (e.g., furosemide) is excreted in unchanged form in the urine. Most side effects of loop diuretics are related to abnormalities of fluid and electrolyte balance such as hypotension, circulatory collapse, and thromboembolic episodes. The development of hypokalemia can result in cardiac arrhythmias. The loss of Mg²⁺ and Ca²⁺ via urination causes hypomagnesemia and hypocalcemia. Therefore (Ca²⁺ loss), the application of loop diuretics must be avoided in osteopenia.

Drug interactions occur with various drugs including sulfonylureas (hyperglycemia), propranolol, lithium, digitalis glycosides, anticoagulants, and thiazide diuretics. The main application of loop diuretics is (A) treatment of acute pulmonary oedema, (B) chronic congestive heart failure, and (C) hypertension; and oedema (D) originating from nephritic syndrome refractory to other diuretics, therefore, loop diuretics are used for this therapy.

(d) Inhibitors of Na-Cl symport (thiazide diuretics)

These drugs increase NaCl excretion and Na⁺ transport in both the distal and proximal tubules. The distal convoluted tubule is the primary action site of thiazides. The proximal tubule is the secondary site of action of thiazides. Thiazide diuretics inhibit the Na⁺ - Cl⁻ symporter function in the distal convoluted tubule. The Na⁺ - Cl⁻ symporter (called ENCC1) is expressed in the kidney and is localized to the apical membrane of distal convoluted tubule epithelial cells. Thiazides increase the excretion of K⁺ as do loop diuretics.

Toxicity and adverse effects of thiazides: These drugs cause headache, weakness, nausea, vomiting, diarrhea, constipation, pancreatitis, photosensitivity and skin rashes, and electrolyte imbalance. The latter side effect includes hypotension, hypokalemia, hypernatremia, metabolic alkalosis, hypomagnesemia, and hypercalcemia. The K⁺ replacement is mandatory during the application of thiazide diuretic agents.

Drug interaction and therapeutic uses of thiazides: Thiazides reduce the effects of anticoagulants, sulfonylureas, and insulin. These diuretics can increase the effects of anesthetics, lithium, loop diuretics, digitalis glycosides, diazoxide, and vitamin D. The diuretic effect of thiazides can be reduced by nonselective or selective COX2 inhibitors (nonsteroid anti-inflammatory drugs). Corticosteroids also increase the risk of hypokalemia induced by thiazides. Lethal drug interaction (tachycardia and fibrillation) may develop if thiazides and quinidine are coadministered.

Therapeutic application of thiazides includes heart failure associated with oedema, hepatic cirrhosis, chronic renal failure, and acute glomerulonephritis. These drugs reduce blood pressure if they are applied alone or combination with other antihypertensive agents. Thiazides reduce urinary Ca²⁺ excretion, therefore, these drugs are useful tools for the treatment of osteoporosis. Thiazides, are used for the treatment of nephrogenic diabetes insipidus by reducing the volume of urine by 50% to 60%.

(e) Inhibitors of renal epithelial Na-channels (K-sparing diuretics)

Clinical use of these drugs includes treatment of patients with triamterene, a pyrazinoyl guanidine structure, (DYRENIUM) and amiloride, a pteridine structure,
(MIDAMOR). These drugs increase Na\(^+\) and Cl\(^-\) excretion. Triamterene and amiloride are classified as K\(^+\)-sparing diuretics.

The action site of both drugs is in the late distal tubule and collecting duct. Epithelial Na-channels provide, under physiological conditions, a conductive pathway for the Na\(^+\) into the cell down the electrochemical gradient created by the basolateral Na\(^+\) pump. The voltage difference provides a driving force for the secretion of K\(^+\) into the lumen via the potassium channels. The drugs of this group block the Na\(^+\) pump and Na\(^+\) penetration, and the secretion of K\(^+\) into the lumen.

Absorption, elimination: Amiloride is eliminated in unchanged form in the urine. Triamterene is metabolized to 4 hydroxytriamterene (an active metabolite) in the liver, and this active metabolite is excreted in the urine. The diuretic effect of the active metabolite is prolonged, and toxic effects may be detected if hepatic diseases are present in patients.

Drug interactions and therapeutic uses: The most frequent adverse effects of these drugs are hyperkalemia which may become life threatening. These drugs are contraindicated if patients suffered from hyperkalemia. The coadministration of NSAIDs with amiloride can cause the development of severe hyperkalemia. Triamterene reduces glucose tolerance, induces photosensitization, interstitial nephritis, and renal stone formation. Amiloride causes nausea, diarrhea, and headache. Amiloride and triamterene are rarely used alone, usually used in combination with other diuretics.

(f) Antagonists of aldosterone (K-sparing diuretics)

Mineralocorticoids induce the retention of salts and water and increase the excretion of H\(^+\) and K\(^+\) in the urine. The members of this group are spironolactone (ALDACTONE), eplerenone (INSPRA), and canrenoate.

Action mechanism: Mineralocorticoids (e.g., aldosterone) bind to their receptors in the epithelial cells of distal tubule and collecting duct increasing expression of aldosterone-induced proteins and Na\(^+\) transport via the epithelial cell membranes. Consequently, the driving force of Na\(^+\) transport in epithelial cells is followed by the secretion of H\(^+\) and K\(^+\) into the tubular lumen. Aldosterone antagonists inhibit the binding of aldosterone in epithelial cells blocking the secretion of H\(^+\) and K\(^+\) into the tubule, thus the reabsorption of Na\(^+\) (and water) from the tubule is also inhibited. Aldosterone antagonists are the only diuretics that do not require access and are not present in the tubular lumen to induce diuresis.

Side effects, absorption, and elimination: Aldosterone antagonists induce confusion, gynecomastia, impotence, irregular menstrual cycles, diarrhea, gastritis, gastric bleeding, and peptic ulcer. Spironolactone and its active metabolite (canrenone) prolong a long lasting effect of the drug, as long as for 20 hours. The drug is metabolized by cytochrome P450 enzymes (CYP3A4) in the liver. Potassium replacement is contraindicated.

Toxicity, contraindications, and drug interactions: Aldosterone antagonists can cause life-threatening hyperkalemia. Potassium administration of various drugs in the form of potassium salt is contraindicated. These drugs may induce metabolic acidosis in cirrhotic patients. Salicylates reduce the tubular secretion of canrenone and spironolactone. The effect of digitalis glycosides may be reduced with the simultaneous application of aldosterone antagonists.

Therapeutic uses of aldosterone antagonists: These drugs are used in the treatment of oedema and hypertension together with thiazide diuretics. In this combination, the perturbation of K\(^+\) homeostasis is reduced. Spironolactone is especially useful for the treatment of primerey hyperaldosteronism such as adrenal adenoma or bilateral adrenal hyperplasia; and refractory oedema associated with hepatic cirrhosis, and severe ascites. In
patients suffering from myocardial infarction complicated by left systolic dysfunction, the application of eplerenone reduces the mortality rate.

The following figure (Figure 12) shows and summarizes the structure of nephron, and active and passive transport processes of various molecules and ions in the different sections of the nephron.

![Diagram of nephron transport processes](image_url)

Figure 12. Active and passive transports in the different sections of the nephron.
This chapter provides a summary of endogenous and exogenous lipoprotein transport mechanisms, including triglycerides, cholesterol, and an introduction and to clinical relevance of various lipoprotein disorders focusing on coronary artery disease. Hyperlipidemia and hypercholesterolemia are major causes of the development of atherosclerosis and sclerosis-associated diseases such as coronary heart disease (CHD), stroke-related cerebrovascular disease, and peripheral vascular disease. These diseases account for more than 50% of morbidity and mortality of middle-aged and elderly adults. Dyslipidemia is a risk factor contributing to the development of mechanisms that reduce cholesterol levels. Related drugs possess beneficial effects in patients including the entire spectrum of cholesterol levels by reducing of low-density lipoprotein cholesterol (LDL-C) levels. Appropriate drug therapy may reduce the development of CHD by 30%. In addition, severe hypertriglyceridemia (>1000 mg/dl) may induce pancreatitis, therefore, the prevention of pancreatitis by various drugs is required. Furthermore, hypertriglyceridemia is frequently occurred as a component of metabolic syndrome (X-syndrome), which includes insulin resistance, hypertension, low HDL-C levels, and obesity leading to development of CHD. The X-syndrome affects about 25% of adult population and is very common in patients suffering from CHD. Hyperlipidemia (increased levels of triglycerides and/or cholesterol) and diminished HDL-C levels affect various concentrations of plasma lipoproteins. Other intermediate factors such as genetic, mutations, diet, exercise, and diabetes also affect the degree and severity of hyperlipidemia.

Lipoprotein metabolism:
Lipids and proteins are the components of lipoproteins. The lipid components consist of free and esterified cholesterol, triglycerids, and phospholipids. The protein constituents, named as apolipoproteins or apoproteins, give functional stability to the lipoproteins, and also could serve as ligands in lipoprotein-receptor interactions and cofactors in enzymatic processes that control and regulate lipoprotein metabolism. The major groups of lipoproteins and their major apoprotein components are in the Table 2 below.

<table>
<thead>
<tr>
<th>Lipoprotein</th>
<th>Lipid constituents</th>
<th>Major apoproteins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chylomicrons and remnants</td>
<td>Dietary triglycerids, cholesterol</td>
<td>B-48, ApoE, A-I, A-IV, C-I, C-II, C-III</td>
</tr>
<tr>
<td>VLDL</td>
<td>Endogenous triglycerides</td>
<td>B-100, ApoE, C-I, C-II, C-III</td>
</tr>
<tr>
<td>IDL</td>
<td>Cholesteryl esters, endogenous triglycerids</td>
<td>B-100, ApoE, C-II, C-III</td>
</tr>
<tr>
<td>LDL</td>
<td>Cholesteryl esters</td>
<td>B-100</td>
</tr>
<tr>
<td>HDL</td>
<td>Phospholipids, cholesteryl esters</td>
<td>A-I, A-II, ApoE, C-I, C-II, C-III</td>
</tr>
<tr>
<td>Lp (a)</td>
<td>Cholesteryl esters</td>
<td>B-100, apo(a)</td>
</tr>
</tbody>
</table>

Table 2. The major groups of lipoproteins.
Very low density lipoproteins (VLDL) are formed if triglyceride production is stimulated by increased flux of free fatty acids or by increased fatty acid synthesis in the liver. ApoE, Apo-B100, C-I, C-II, and C-III are synthesized by the liver and incorporated in VLDL. ApoE plays a major impact in triglyceride-rich lipoprotein metabolism and participates in the redistribution of lipids in various tissues. In addition, ApoE determines the catabolism of apoE containing lipoproteins by binding to cell surface proteoglycans and LDL receptors. Three alleles of ApoE genes exist and code for the 3 major components of ApoE including E2, E3, and E4 with about 8%, 77%, and 15%, respectively.

Low density lipoproteins (LDL): These molecules are derived from the catabolism of intermediate density lipoproteins (IDL). Mutations in the LDL receptor gene have been identified in the absence of LDL receptors causing high levels of plasma LDL and familial hypercholesterolemia. The liver expresses LDL receptors, and these receptors remove about 75% of LDL from the plasma. Thus, the increase of the numbers of LDL receptors is the most effective way to reduce LDL contents in the plasma. Estrogens and Tyroxine increase gene expression, leading to high numbers of LDL receptors; and as a consequence, plasma LDL levels are reduced. This is the most effective pharmacological treatment by statins for hypercholesterolemia. If cellular cholesterol content is reduced, the sterol regulatory element binding proteins (SREBPs) undergo proteolytic cleavage in the Golgi system leading to the expression of LDL receptors and activation of other enzymes, and the final result is the modification of cholesterol biosynthesis.

High density lipoproteins (HDL) and their metabolic products are very complex with ApoA-I, the major constituent of HDL particles. HDL deficiency is related to a mutation of the ApoA-I gene; and is associated with accelerated atherogenesis (new vessel formation).
HDL are protective lipoproteins that reduce the risk of CHD. This protection is related to the participation of HDL in reverse cholesterol transport, which requires that excess cholesterol level in cells be transferred to the liver for excretion. HDL also possesses antiinflammatory, anticoagulant, antioxidant, and profibrinolytic activities.

Hyperlipidemia, atherosclerosis: Hyperlipidemia and atherosclerosis are the main cause of the development of CHD (chronic heart disease), and its risk factors are high LDL-C, reduced HDL-C, smoking, elevated blood pressure, type-2 diabetes, and family history of premature birth. The control of the aforementioned risk factors is especially crucial in preventing development of CHD. These risk factors account for about 80%-85% of CHD development. In summary, it is generally accepted that (i) elevated plasma cholesterol levels contribute to development of CHD, (ii) diets rich in animal fat and cholesterol (saturated) raise cholesterol levels, and (iii) the reduction in cholesterol levels reduces the development of CHD. The treatment of CHD is complex including recommendations (a) to increase exercise, (b) to reduce daily caloric intake from fat and from saturated and trans fats, (c) eat a variety of fish at least twice a week including other foods rich in alpha-linolenic acid. Two fish meals in a week are very important for patients who have previously suffered from myocardial infarction in order to avoid the risk of sudden cardiac death. Patients having carotid vascular disease, aortic aneurism, and diabetes must immediately begin lipid-lowering drug therapy. Before the starting of any drug therapy, secondary causes of hyperlipidemia must be excluded.

Statins are the recommended first-line drug therapy to reduce CHD risk factors above 50 years of age. It is of interest to note that plasma cholesterol levels also correlate positively with risk of ischemic stroke; and clinical studies show that statins diminish episodes of stroke and transient cerebral ischemic attacks. Diabetes is an extremely high risk factor for the development of CHD. Diabetic dyslipidemia is characterized by high triglyceride levels, low levels of HDL-C, and elevations in total cholesterol and LDL-C contents. Thus, the treatment of of dyslipidemia in diabetic patients is the same as for patients suffering from CHD, irrespective of whether diabetic patients have had previously an event of CHD. Mainly simvastatin, pravastatin, and lovastatin are used for the treatment of hyperlipidemia, atherosclerosis, and diabetic dyslipidemia.

Treatment of hypertriglyceridemia, dyslipidemia, and hyperlipidemia

Hypertriglyceridemia and dyslipidemia are associated with an increased risk of CHD. Reduction of triglycerids may be achieved using statins and nicotinic acid (NILACIN). In addition, another drug combination involves application of statins with fibrates. The aim of this treatment is to increase HDL-C levels. This may be achieved, in addition to drug combination therapies, with diet by application of dietary foods. Thus, statins may be combined with bile acid-binding resins such as cholestyramine and colestipol leading to a greater reduction in LDL-C than can be atchieved with statines alone.

The following grups can be used for treatments of hypertriglyceridemia, dyslipidemia, and hyperlipidemia:
  a. Statins
  b. Bile-acid sequestrants
  c. Nicotinic acid
  d. PPAR activators (fibric acid derivatives)
  e. Ezetimibe (an inhibitor of cholesterol uptake)
  f. Inhibitors of cholesteryl ester transfer protein
**a. Statins**

The statins are the most effective and well-tolerated agents for treatment of hypertriglyceridemia and dyslipidemia. Statins were isolated from *Penicillium citrinum* (mold), and identified as inhibitors of cholesterol biosynthesis. Satins inhibit the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which catalyzes a critical rate limiting step in the biosynthesis of cholesterol. The major effect of statin drugs is the reduction of LDL levels. Statins reduce blood cholesterol levels by inhibiting hepatic cholesterol synthesis, which results in increased expression of LDL receptor gene. The most frequently used statins are simvastatin, pravastatin, lovastatin, fluvastatin, rosuvastatin, and atorvastatin in reducing the episods of CHD, cerebrovascular strokes, and mortality. Statins have antiinflammatory activity and inhibit platelet aggregation and the formation of trombi.

Application, absorption, excretion of statins: All statins are orally administered. Plasma concentrations of statins peak within 3 hours; and their half-lives are about 4 hours, except in the case of rosuvastatin and atorvastatin, which have about 20 hours of half-lives. More than 70% of statins are metabolized and excreted by the liver with subsequent elimination in the feces.

Adverse effects and interactions: The statins increase levels of hepatic transaminases, but no cases of liver failure associated with use of these drugs has been reported. The major side effect of statins is myopathy. Although the incidence of myopathy is relatively low (less than 0.01%), but the risk of rhabdomyolysis and myopathy is significantly increased in proportion to plasma statin levels. Statins are not recommended during pregnancy. The statin interactions may occur with fibrates, macrolide antibiotics, gemfibrozil, warfarin, and various antifungal drugs.

**b. Bile-acid sequestrants**

The resins of cholestyramine (QUESTRAN) and colestipol (COLESTID) have favorable safety profile since they are not absorbed from the gastrointestinal tract. These resins are frequently used in combinations with statins, however, their application alone may reduce the the LDL-C level by 25%. Colesevelam (WELCHOL) is a bile acid sequestant and is able to reduce LDL-C level by 18% at its higher dose. The effective doses of these resins are 10 to 20 g/day and two weeks are sufficient to reduce LDL-C by 18% to 25%. The application is oral, and they are mixed with water and runk as slurry. Sometimes, as side effects, constipation and dyspepsia may occur. These resins bind and interfere with the absorption of various drugs, therefore, applications of resins should be avoided if other therapy is necessary.

**c. Nicotinic acid**

Nicotinic acid (Niacin) affects all lipid parameters and is used for the treatment of dyslipidemia. Nicotinic acid inhibits the lipolysis of triglycerides reducing the transport of free fatty acids and reduces the triglyceride synthesis in the liver. Acipimox is a nicotinic acid related structure having the same effect. Nicotinic acid stimulates HM74b-Gi adenylyl cyclase pathway in adipocytes inhibiting cAMP production, decreasing lipase activity and triglycerider lipolysis, and the release of free fatty acids.

Nicotinic acid is completely absorbed from the gastrointestinal sytem with a peak plasma concentration detectable within one hour; and the half-life is also about one hour, following which it is excreted in via urine. Adverse effects of nicotinic acid are flushing, skin rashes, pruritus, dry skeen, dyspepsia, nausea, vomiting, and diarrhea. The most frequently
developed side effects are elevated serum transaminases and hyperglycemia. The maximum dose of nicotinic acid is 2 g daily.

d. PPAR activators (fibric acid derivatives)

It has been suggested that lowering of lipoprotein levels and many related homeostatic functions mediate interaction of peroxisome proliferator activated receptors (PPARs). Three PPARs isophorms exist (alpha, beta, and gamma), and fibrates bind to PPARs alpha, which is primarily expressed in brown adipose tissue, liver, kidney, skeletal muscle, and heart. Fibrates are able to decrease triglyceride levels through PPAR-alpha stimulation of fatty acid oxidation, and increase LPL synthesis. Increased LPL levels may result in clearance of the triglyceride-rich lipoproteins. In addition, the PPAR-alpha stimulation by fibrates increases HDL levels. Fibrates are the drugs of choice for the treatment of severe hypertriglyceridemia and chylomicronemia. In chylomicronemia, fibrates combined with low fat diet to keep triglyceride levels below 1000 mg/dl preventing development of pancreatitis.

Fibrates are absorbed efficiently if applied orally during meals; and peak plasma concentrations may be reached within 2 to 4 hours. Fibrates are excreted as glucuronide conjugates in the urine, and a smaller amount in the feces. Side effects are gastrointestinal motility disturbances, hair loss, rash, urticaria, fatigue, headache, anemia, and impotence. Myopathy syndrome can also occur. Doses of fibrates are usually 200 mg to 2,000 mg daily. The most frequently used fibrates are gemfibrozil (LOPID), fenofibrate (LOFIBRA). If statins and fibrates are combined, attention must be given to development of myopathy.

e. Ezetimibe (an inhibitor of cholesterol uptake)

Ezetimibe (ZETIA) inhibits cholesterol absorption by enterocytes in the intestine, and lowers the total and LDL-C levels. Ezetimibe blocks a specific transport process in jejunal enterocytes, which takes up cholesterol from the intestinal lumen. Thus, ezetimibe is able to reduce LDL-C levels about 20% if it is applied as monotherapy. The combination of ezetimibe with statins provides additional substantial reduction in the levels of LDL-C.

Ezetimibe is insoluble in water, glucuronidated in the intestinal epithelium, absorbed, and participates in the enterohepatic circulation. Adverse effects of ezetimibe are negligible, however, allergic reactions may develop. Its daily dose is about 10 to 20 mg.

f. Inhibitor of cholesteryl ester transfer protein

Cholesteryl ester transfer proteins (CETPs) are synthesized by processes in the liver that mediate the transfer of cholesteryl esters from HDL to triglyceride lipoproteins and LDL in exchange for triglyceride. Torcetrapib is an inhibitor of CETPs that stabilizes the association of CETPs with its lipoprotein substrate leading to a nonfunctional complex. Torcetrapib elevates the levels of HDL-C by 50 % to 100 % leading to inhibition of vascular diseases in dyslipidemic patients.

8). Blood, Pharmacology

During the course of a lifetime, vertebrate blood cells require continuous reproduction and replacement. This process is called hematopoiesis. The most intensive hematopoietic activity involves replacement of red blood and white blood cells, and platelets, as a result of anemia, systematic infection, and thrombocytopenia, respectively.
The hematopoietic process is very complex including at least nine distinct blood-cell lineages. The process occurs in cavities of the skull, pelvis, and proximal long bones. It involves communication and interactions among progenitor and hematopoietic stem cells, macromolecules of the marrow stroma, and a number of various hematopoietic growth factors. In addition, hematopoiesis requires a constant supply of minerals such as copper, iron, and cobalt; and vitamins including B-12, ascorbic acid, pyridoxine, riboflavin, and folic acid. Deficiencies of hematopoiesis result in the development of various anemias. This chapter describes the roles of (I) hematopoietic growth factors, (II) drugs effective against anemias, and (III) vitamin B12 and folic acid for the treatment of megaloblastic anemias.

(I) Hematopoietic growth factors

Hematopoiesis, under physiological conditions, produces daily about 400 billion cells. This production is very well controlled and regulated and may be increased severalfold if necessary. The process relies on a small number of multipotent progenitors, which develop pluripotent hematopoietic stem cells. These pluripotent hematopoietic stem cells are capable of differentiating, and influencing various cellular and humoral factors to produce diverse forms of mature blood cells.

Stem cell differentiation proceeds through a series of steps, resulting in structures called burst forming units (BFU) and colony forming units (CFU) for each of the major cell lines (as discussed in detail in the Chapter of Cancer and Antineoplastic Drugs, see Figure 18 on page 89). These progenitors (BFU, CFU) are able to further proliferate and differentiate increasing their numbers by many fold. Together with additional growth factors (see, Figure 18 on page 89) such as granulocyte colony stimulating factor (G-CSF) and macrophage colony stimulating factor (GM-CSF) can additionally amplify differentiated blood cell products by 30-fold or more.

Lymphopoietic and hematopoietic growth factors are produced by marrow cells and various peripheral tissues. They are very effective at very low concentrations and affect at least two or three cell lineages. Most growth factors synergistically interact with and stimulate other growth factors, a process named networking. Growth factors act at various points in the processes of cell differentiation, proliferation, and mature cell function. Many growth factors exist, the most important of which are: (a) erythropoietins, (b) myeloid growth factors, and (c) thrombopoietic growth factors.

(a) Erythropoietins

Erythropoietin is not the sole regulator of the proliferation of progenitors (colony forming units: CFU) and their immediate progeny but it is the most important. In the absence of erythropoietin several types of anemia are developed. Erythropoiesis is controlled by the kidney, which detects changes in oxygen delivery and modulates the secretion of erythropoietin. This process is regulated by hypoxia-inducible factor (HIF-1), which is a heterodimeric (HIF-1-alpha and HIF-1-beta) transcription factor, that increases the expression of hypoxia-inducible genes including erythropoietin and vascular endothelial growth factor.

Erythropoietin is encoded by a gene on chromosome 7 in humans, and expressed by peritubular interstitial cells in the kidney. Erythropoietin consists of 193 amino acids, and its molecular mass is about 30,000 daltons. The molecule binds to the receptor of erythroid progenitors in the marrow and is internalized. Under conditions of hypoxemia or anemia, the level of serum erythropoietin may rise by hundredfold or more. As a consequence, marrow progenitor cell survival, proliferation, and maturation are significantly increased. This process
can be disrupted by kidney failure, deficiency in essential vitamins or iron, and marrow damage.

Currently available preparations of recombinant human erythropoietin (epoetin alpha) for intravenous and subcutaneous therapeutic use include EPOGEN, PROCRIT, and EPREX. The half-life of epoetin alpha is about 8 hours in the plasma. Injections of epoetin alpha can be administered three times per week, which is sufficient to sustain the effect of marrow progenitors. Recently two other preparations, erythropoiesis-stimulating protein (NESP) and darbapoetin alpha (ARANESP), have been approved for clinical use with the same indications as those of epoetin alpha.

Therapeutic use of erythropoietins is conducted for various anemias, e.g., anemias associated with surgery, patients with AIDS-related anemia, hemodialysis, chronic kidney diseases, cancer chemotherapy, prematurity, and chronic inflammations. Erythropoietin therapy affects functional iron deficiency, which is the result of mobilization of iron from iron stores to support erythropoiesis. During erythropoietin therapy the supplementation of iron is recommended, especially if serum ferritin is below 100 microgram/liter. Weekly hematocrit monitoring is also recommended.

Side effects of the application of erythropoietins include serious thromboembolic events such as thrombophlebitis, pulmonary embolism, thrombosis of retinal artery, ischemic heart diseases, congestive heart failure, and microvascular thrombosis. In addition, high blood pressure, headache, nausea, vomiting, diarrhea, epileptic seizures, and flu-like symptoms can occur. Folic acid and vitamin B12 deficiencies also have been observed in patients treated with erythropoietins.

(b) Myeloid growth factors

Myeloid growth factors are glycoproteins that induce proliferation and differentiations of myeloid cell lines. Many myeloid growth factors have been produced by recombinant methods such as granulocyte and macrophage colony stimulating factor (GM-CSF), granulocyte colony stimulating factor (G-CSF), colony stimulating factor (CSF-1), and interleukin-3. Myeloid growth factors are produced by different cells including endothelial cells, T cells, macrophages, and fibroblasts. Myeloid growth factors are very effective at low concentrations and bind to membrane cytokine receptors to activate the JAK/STAT signal transduction pathway.

For example, GM-CSF is able to stimulate the proliferation, differentiation, and function of various myeloid cell lineages. GM-CSF also acts synergistically with other growth factors (seen Figure 18 on page 89) i.e., erythropoietin and burst forming unit (BFU). GM-CSF stimulates the colony forming unit of granulocyte erythropoietin megakaryocyte macrophage (CFU-GEMM), colony forming unit of granulocyte/macrophage (CFU-GM), colony forming unit of erythropoietin (CFU-E), and colony forming unit megakaryocyte (CFU-Meg) to enhance cell production. GM-CSF also increases the migration, phagocytosis, superoxide production, and cell mediated toxicity of monocytes, eosinophils, and neutrophils. Sargramostim (LEUKINE) is subcutaneously or intravenously used at a daily maximum dose of 500 microgram/m2 body surface.

Granulocyte colony stimulating factor (G-CSF) activity is restricted to neutrophils and their progenitors (see Figure 18 on page 89), leading to proliferation, differentiation, and function. G-CSF acts on the colony forming unit of granulocyte (CFU-G), interleukin-3, and GM-CSF, stimulating other cell lines. This factor also increases cytotoxic and phagocytic functions of neutrophils. G-CSF is able to mobilize hematopoietic stem cells from the marrow into peripheral blood. Recombinant human G-CSF filgrastim (NEUPOGEN) is produced by E. coli. Filgrastim is used for the treatment of neutropenia and cancer chemotherapy and
reduces morbidity associated with fungal and bacterial infections. Filgrastim is also useful for patients undergoing peripheral blood stem cell collection for stem cell transplantation, since it promotes CD34+ progenitor cell production in the marrow. The maximum daily dose of filgrastim is 20 microgram/kg. The pegylated form of recombinant human G-CSF is pegfilgrastim (NEULASTA).

(c) Thrombopoietic growth factors (interleukin-11 and thrombopoietin)

Interleukin-11 is a 178 amino acid protein, which stimulates intestinal epithelial cell growth, hematopoiesis; and osteoclastogenesis, and inhibits adipogenesis. Recombinant human interleukin-11, oprelvekin (NEUMEGA), is a bacterially derived polypeptide of 177 amino acids, and is administered daily at doses of 25 to 50 microgram/kg, leading to a thrombopoietic response within 5 to 10 days. Oprelvekin is used in patients subjected to chemotherapy and displaying severe thrombocytopenia (platelet count is less than 20,000/microliter). The side effects of oprelvekin therapy are cardiac symptoms, fluid retention, edema, shortness of breath, blurred vision, erythema, rash, and paresthesia.

Thrombopoietin is a member of cytokine family that predominantly stimulates megakaryopoiesis. Thrombopoietin consists of 332 amino acids that is mainly produced by marrowstromal cells and the liver. Treatment with recombinant thrombopoietin accelerates the recovery of platelet counts. Two different forms of recombinant thrombopoietin have been developed for human use. One of them is a truncated version of the native polypeptide, called recombinant human megakaryocyte growth and development factor (rHuMGDF). The second form is the full-length polypeptide, called recombinant human thrombopoietin (rHuTPO), which is produced in various mammalian tissues.

In clinical use, recombinant human thrombopoietin decreases the duration of severe thrombocytopenia and increases platelet counts. After the application of a single bonus injection of rHuMGDF, platelet counts were significantly increased after 4 days. However, platelet activation and aggregation are not affected; and the risk of thromboembolic diseases is not increased. The immunogenicity of these thrombopoietic agents is a concern, therefore, small organic molecules are under development that may avoid complication associated with large recombinant proteins.

(II) Drugs effective against anemias

The iron and its salts

In humans, the iron deficiency is a very common nutritional cause of anemia. It may originate from malabsorption, blood loss, inadequate iron intake, or an increased iron requirement, e.i., in pregnancy. Beside erytron, iron is also an essential factor of heme and metalloflavoprotein enzymes including catalase, peroxidase, cytochromes, xanthine oxidase, and the mitochondrial alpha glycedrophosphate oxydase. Iron deficiency is associated with learning and behavioral difficulties in children, impaired temperature regulation; and catecholamine metabolism metabolic disfunction.

Hemoglobin is the dominant molecule in iron metabolism. Hemoglobin contains four iron atoms contributing to about 1.0-1.2 mg of iron per milliliter of red blood cells. Essential iron-containing compounds include myoglobin and a variety of heme iron-dependent enzymes. Ferritin and apoferritin are iron-protein complexes that exist as individual molecules or aggregates. Each ferritin molecule contains about 4000 of iron atoms, and ferritin aggregate is termed as hemosiderin.
Homeostatic iron sequestration and exchange is accomplished by transferrin in the plasma. Iron is subsequently delivered from transferrin to intracellular sites by transferrin receptors via the cell membrane. The cell regulates the expression of transferrin receptors, and if too much iron is available, the expression of transferrin receptors is reduced. The daily flux of iron is about 40 mg in adults. The main internal distribution of iron involves the erythron and reticuloendothelial cells (Figure 14, below). Approximately 80% of the iron from the plasma enters the erythroid marrow to be packaged into new erythrocytes. Simultaneously, a certain portion of iron is returned to the plasma bound to transferrin. Another portion of iron is sequestered into ferritin stores in reticuloendothelial cells; and returns to the circulation. A minor portion of iron, in defective cells, is transferred to reticuloendothelial cells during maturation, bypassing the circulating blood. Substantial iron loss can be observed (i) in pregnancy, (ii) anemia results from dietary intake of iron, (iii) blood loss and (iv) menstruating women.

![Iron Metabolism Diagram]

Figure 14. The iron metabolism.

Substantial iron loss can occur during menstruation; during blood donation; during bleeding in the gastrointestinal tract; and as a result of lack of iron absorption and uptake from the intestine. Physiological iron absorption is about 1 mg to 2 mg per day, increased up to 4
mg if bleeding occurs. The Figure above is based on the 11th edition of Goodman and Gilman’s, 2005, The McGraw Hill Companies Inc., USA.

Figure 15. Iron Absorption. The Figure is based on the 8th edition of Goodman and Gilman’s 1990, Pergamon Press.

Physiological homeostatic iron absorption begins in the stomach. Acidification occurs in this organ followed by absorption in the bowel lumen and mucosa as either inorganic or heme iron (Figure 15.). Both inorganic and heme iron are absorbed by the duodenum small intestine followed by a direct transport process into the blood or storage as mucosal ferritin. Transferrin, from the blood, enters various tissues and binds to tissue receptors participating e.g., in heme formation, or is stored in ferritin form.

Treatment of iron deficiency: Orally applied ferrous sulfate (Fe²⁺), the hydrated salt of iron, is the choice treatment for iron deficiency. Ferrous salts are absorbed three times better than ferric (Fe³⁺) salts. Many substances including surface-acting agents, amino acids, vitamins, and carbohydrates are able to enhance the absorption of ferrous iron. Unfortunately, increased iron uptake is associated with increased side effects such as heartburn, gastric discomfort, nausea, constipation, and diarrhea. The treatment of iron-deficiency anemia involves administration of about 200 mg/day of iron, increased to 15 mg/day to 30 mg/day in pregnant women. If oral iron therapy fails, parenteral iron administration can be done. Parenteral iron therapy may only be used when clearly indicated, since anaphylactoid reactions can occur in 2% of patients receiving such treatment.

Copper
Clinical cases associated with hypocupremia are relatively rare, however, anemias have been observed in individuals who underwent intestinal bypass surgery; and also in malnourished children. In humans, the outstanding clinical cases are leukopenia, particularly granulocytopenia and anemia. Daly oral doses of cupric sulfate up to 1 mg to 2 mg are appropriate.

Pyridoxin (Vitamin B6)
Pyridoxin may improve hematopoiesis in patients suffering from hereditary or acquired sideroblastic anemia. Such patients characteristically have impaired hemoglobin synthesis and accumulate iron in perinuclear mitochondria of erythroid precursor cells. Sideroblastic anemias are associated with a number of drugs used for inflammatory disease and neoplastic disorders. The daily dose of pyridoxin is about 50 mg. For adequate therapy, pyridoxin is given for at least three months, and its response can be monitored by measuring reticulocyte count and hemoglobin levels.

(III) Vitamin B12 and folic acid for the treatment of megaloblastic anemias
Deficiency of vitamin B12 and/or folic acid impairs the synthesis of DNA in all cells in which chromosomal division and replication are taking place. The hematopoietic system is extremely sensitive to deficiencies of vitamin B12 and folic acid. The first sign of deficiency of vitamin B12 and folic acid is megaloblastic anemia, which is the abnormal poroduction of red blood cells, and this is termed pernicious anemia.

In the intracellular space, vitamin B12 is closely related to two active coenzymes: methylcobalamin and deoxyadenosylcobalamin. Deoxyadenosylcobalamin is a cofactor for mitochondrial mutase that promotes the isomerization of L-methylmalonyl CoA to succinyl CoA, a critical step in carbohydrate and lipid metabolisms. Methylcobalamin contributes to the methionine synthase reaction, which is an important reaction for physiological metabolism of folate. The folate-cobalamin interaction is a critical process for purine and pyrimidine regulation, and as a consequence, DNA synthesis. Deficiencies of vitamin B12 or folic acid; and the decreased synthesis of methionine and S-adenosylmethionine interfere with protein synthesis including polyamin synthesis. The lack of these physiological processes along with the deficiency of vitamin B12 or folic acid, promote development of megaloblastic anemia. In addition, deficiency of vitamin B12 is responsible for the development of various neurological symptoms and disorders. Demages to myelin sheaths of neurons are the most obvious lesion in neuropathies.

Source, absorption, distribution, and elimination of vitamin B12: The primary source of B12 is from various bacteria that grow in soil, water, and intestinal lumen of animals that synthesize vitamin B12. Unfortunately, vegetables do not produce vitamin B12. The daily requirement of B12 is between 3 to 5 micrograms.

Pharmacokinetics: B12 of dietary origin, complexes with salivary binding proteins and bound to gastric intrinsic factor. The vitamin B12 – gastric intrinsic factor complex reacts with receptors on the mucosal cell surface in the ileum; and subsequently transported actively into the circulation. After absorption, vitamin B12 binds to transcobalamin II for entry into cells. About 3 micrograms daily vitamin B12 is secreted into bile; and half of that is not reabsorbed. The other half participates in the enterohepatic cycle. Thus, gastric surgery or atrophy is a general cause of deficiency of vitamin B12. Vitamin B12 deficiency has a major impact on the function of the hematopoietic and nervous systems. Deficiency of vitamin B12 can cause irreversible damage to the central nervous system. Inadequate intake of vitamin B12 leads to defective DNA replication. The content of vitamin B12 deficiency can be monitored by the measurements of serum vitamin B12 content, or the level of serum.
methylmalonic acid. Vitamin B12 therapy is available in injected or oral forms. Treatment of vitamin B12 deficiency may also be done by intramuscular or subcutaneous administration of cyanocobalamin. Vitamin B12 should be given prophylactically in cases of B12 deficiency. If vitamin B12 therapy is started, it must be maintained for life.

Folic acid has a pteroyl-monohepta-glutamate (PteGlu) structure. Following absorption, PteGlu is quickly reduced to tetrahydrofolic acid (H₄PteGlu) as an effective agent. Many foods derived from vegetables or animal products are rich in folates. The daily necessary intake of folic acid is about 400 micrograms, but in pregnant and lactating women dosage requirements are higher. When folate is absorbed, it is quickly transported to cells as CH₃ - H₄PteGlu. Following the uptake of CH₃ - H₄PteGlu in tissues and cells, it serves as a methyl group donor for the formation methylcobalamin. Unused folate by cells is stored as polyglutamates.

Folate deficiency occurs as a consequence of disease of the small intestine that interferes with the enterohepatic circulation of folate, and its absorption from food. Folate deficiency can lead to hemolytic and megaloblastic anemias. In addition, the lack of folate can cause anencephaly. Folate deficiency is also connected to vitamin B12 metabolism. However, megaloblastic anemia, which is a consequence of folate deficiency cannot be distinguished from the vitamin B12-induced deficiency. Folate deficiency can be diagnosed by the measurement of folate in plasma and red blood cells. The physiological folate level in plasma is in the range of between 9 nmol to 45 nmol. Folic acid intake is available in oral tablets containing pteroylglutamic acid, and injected form. Folic acid (leucovorin, citrovorum factor) is a formyl derivative of tetrahydrofolic acid.

Folic acid has no toxic side effects at therapeutic doses. However, high doses of folic acid can lead to the suspension of the antiepileptic effects of antiepileptic drugs leading to the increased frequency of epileptic seizures. Folic acid treatment can be done concomitantly with vitamin B12 in patients afflicted with megaloblastic anemia. The daily therapeutic dose of folic acid is 100 microgram.
CANCERS AND ANTINEOPLASTIC DRUGS

Treatment of various types of cancer may be accomplished by surgery, radiations, and pharmacological intervention. A combination of radiations, surgery, and antitumor agents is required in many cases. In the present chapter, the pharmacological treatment of various cancers is discussed. The action mechanisms of antineoplastic agents, which modify the purine, pyrimidine, DNA, RNA, and protein synthesis can be summarized Figure 16 below:

Figure 16. Action mechanisms of antineoplastic agents

It is important to note that many antineoplastic drugs can be used for the therapy of various diseases unrelated to the tumor therapy. For instance, (i) methotrexate and cyclophoshamide are useful for the treatment a rheumatoid arthritis. Sickle cell anemia (ii) can be treated with hydroxyurea and 5-azacytadine, (iii) methotrexate is a beneficial tool for
treatment of psoriasis and allograft rejection, (iv) azathioprine is used for immunosuppressive therapy, and (v) leucovorin, acyclovir, and trimetrexate are effective agents against infective diseases.

To understand the action mechanisms of antitumor agents, understanding the cell cycle is crucial. The majority of antineoplastic agents act by damaging DNA structure. The toxicity of antitumor agents is more effective in the “S” phase, while e.g., vinca alkaloids and taxane structures block the “M” phase. The cell cycle phases are shown in the Figure 17 below, and the locus of action sites of some antitumor drugs are also depicted.

Figure 17. The cell cycle. S: DNA synthesis. G1 is the gap period between mitosis (M phase) and DNA synthesis (S phase). G2: premitotic phase. G0: resting phase, a subphase of G1. The action sites of some antineoplastic agents are also shown.

The agents used for the treatment of neoplastic diseases can be divided into 5 main groups (A-E below).

A). Alkylating agents
B). Antimetabolites
C). Natural extracts and products, and antibiotics
D). Miscellaneous agents
E). Hormones and Hormone-like agents

Their characteristics are discussed as follows:

A). Alkylating agents

The alkylating agent group (A) used in the tumor therapy can be further devided in six subgroups. These are

A1). Nitrogen mustard structures
A1). Nitrogen mustards

Nitrogen mustard gas was used as a neurotoxic agent in World War I. The molecule causes burn damage to skin, eye, mucosa, and other organs. Later, in the 1940s, various nitrogen mustard structures were applied for the treatment of cancer chemotherapy in patients afflicted with various lymphomas. Nitrogen mustard agents are alkylating molecules that disturb DNA synthesis and cell division. In nondividing, resting cells, the damage to DNA activates a "checkpoint" that depends on the presence of the normal p53 gene. Tumor tissues, thus, are blocked in G1 and S interphase and either repair DNA alkylation and/or undergo apoptosis. By contrast, malignant tissues with mutant or absent p53 genes fail to suspend cell-cycle progression, don’t undergo apoptosis, showing resistance to these drugs.

Members of the nitrogen mustard family include mechloretamine (MUSTARGEN), cyclophosphamide (CYTOXAN, NEOSAR), ifosfamide (IFEX), melphalan (ALKERAN), and chlorambucil (LEUKERAN).

Toxicities of alkylating agents used in tumor therapies are relatively intensive compared to other therapeutic agents, e.g., antihypertensive agents, diuretic or antidiabetic drugs. Thus, the most common toxic effects of alkylating agents are bone marrow toxicity, mucosal toxicity, and neurotoxicity. Myelosuppression, suppression of all blood elements, humoral immunity, nausea, vomiting, cerebellar ataxia, coma, nephrotoxicity, epileptic seizures, ulceration, the damage of reproductive systems are frequently caused by application of alkylating agents.

The alkylating drugs are used for the treatment of both Hodgkin’s and non-Hodgkin’s lymphoma (cancer of the lymphoid system), acute and chronic lymphocytic leukemia, multiple myeloma, neuroblastoma, lung, ovary, breast, cervix, and testis cancers, and soft-tissue sarcoma.

Absorption, fate, and excretion: Alkylating agents are well absorbed by oral administration. Beside oral administration, the intravenous application of these drugs is required in many cases. In certain cases, the combination of oral and intravenous applications must be used, and the duration of therapy may be sustained over a timeframe for months or years. Alkylating agents are inactivated and metabolized by the liver and excreted in the urine. Their half life in the plasma is about 8 hours.

A2). Ethylenimines and methylmelamines

The members of this group include altretamine (HEXALEN) and thiotepa (THIOPLEX). The precise mechanism of these agents is unknown. These drugs are used for the treatment of ovarian cancer at doses of 200 to 300 mg/m² body surface for the first 3 to 8 days, and then, these doses can be repeated each month for 6 to 8 cycles. Altretamine and thiotepa can be combined with cisplatin or alkylating antitumor agents and can be also used for the treatment of bladder and breast cancers, and Hodgkin’s disease.

The main toxic effects of altretamine and thiotepa are myelosuppression, neurotoxicity, depression, confusion, hallucination, renal failure, mucositis, coma, and epileptic seizures.
A3). Alkyl sulfonate agents

Busulfan (MYLERAN, BUSULFEX), an alkyl sulfonate agent, is used for treatment of chronic myelocytic leukemia (CML). The drug reduces the number of granulocytes after two weeks following onset of application. Maximum dosage is 8 mg daily delivered orally. Anticonvulsant therapy must be used concomitantly to protect neurons against epileptic-like seizures. Toxic effects of the drug are myelosuppression, thrombocytopenia, impotence, sterility, amenorrhea, hypotension, and cataracts. Busulfan is used in combination with cyclophosphamide.

A4). Nitrosourea structures

Carmustine (BICNU, GLIADEL), lomustine, semustine, and streptozotocin (ZANOSAR) are the members of the nitrosourea structure group. The action mechanism of these drugs is alkylation of DNA at O6-guanine position. „Mustines” can be used for the treatment of Hodgkin’s and non-Hodgkin’s lymphomas, melanomas, and primary brain tumors. Streptozotocin is used intravenously for the treatment of malignant pancreatic islet cell carcinoma.

Side effects of these agents are pulmonary fibrosis, renal failure, secondary leukemia, hepatic toxicity, anemia, and leukopenia. Streptozotocin may also induce diabetes due to its ability to ablate insulin producing beta-islet cells of the pancreas. The dose of „mustines” is 200 mg/m² intravenously on the fist day, repeated weekly at the same dosage for six weeks. Streptozotocin can be administered intravenously to a maximum concentration of 1500 mg/m² weekly for six weeks.

A5). Triazenes and methylhydrazines

The triazene group includes dacarbazine (DTIC-DOME) and temozolomide (TEMODAR). These molecules have nonspecific action on tumors, and kill tumor cells in various phases of the cell cycle. Dacarbazine and temozolomide alkylates DNA at the position of O6-guanine bases. Applications of triazenes include malignant melanomas, Hodgkin’s lymphomas, gliomas, and soft tissue carcinomas. These drugs are frequently combined with radiation therapy. Side effects are nausea, vomiting, myelosuppression, leukopenia, fever, myalgias, hepatotoxicity and dermatitis. The drugs are given intravenously at a concentration of 200 mg/m2/day for 4 to 6 days, and then repeated four/five times every three weeks.

Procarbazine (MATULANE) is the only agent of methylhydrazines which is used for the treatment of Hodgkin’s lymphoma and malignant brain tumor in clinical chemotherapy. Procarbazine is well absorbed after oral administration and penetrates the blood brain barrier distributing readily to the CNS. The drug is metabolized in the liver and eliminated in the urine. The therapeutic dose of procarbazine is 100 mg/m²/day for 2 weeks alone or in combination with other antineoplastic agents. The toxic effects of procarbazine are thrombocytopenia, leukopenia, gastrointestinal and neurological symptoms. Procarbazine has MAO inhibition activity, therefore, hypertension may also develop.

A6). Platinium complexes

The platinium complexes were initially identified as antiproliferative drugs. Cisplatin (PLATINOL) is the most active and frequently used agent in antitumor therapy versus the other platinium complexes such as carboplatin and oxaliplatin. These drugs are used for the treatment of various cancers including ovarian, colon, bladder, esophagus, testis, and lung.
Platinium complexes react with DNA forming cross-links between platinium and guanines of DNA strands leading to the inhibition of DNA replication and transcription. The „platins” are effective mainly in the „S” phase. Platinium complexes are mutagenic, teratogenic and carcinogenic. Cisplatin can only be given intravenously. The therapeutic dose of cisplatin is 20 mg/m^2/day for a week, and this dose must be repeated for 4 weeks. Side effects include ototoxicity, nephrotoxicity, vomiting, neuropathy, myelosuppression, anemia, electrolyte imbalance (Na, K, Ca), bronchoconstriction, hypotension, tachycardia, and facial edema. Platinium complexes can be used in combination with vinblastine, ifosfamide, etoposide, and bleomycin.

B). Antimetabolites

The antimetabolites include three distinct molecular structures, namely the B1). Folic acid analogs, B2). Pyrimidine and cytidine analogs, and B3). Purine analogs. The incorporation of the aforementioned molecular structures in DNA and RNA synthesis leads to transcription of abnormal proteins resulting in indirect inhibition of the „S” and „M” phases of cell cycles.

B1). Folic acid analogs

Folic acid is crucial dietary factor for DNA (purine and thymidylate) and RNA (purine) synthesis. Folic acid analogs provide the „first strike” in remission of various leukemias, choriocharcinoma, and solid tumors. In the systemic treatment of these cancers, methotrexate has played a critical and pivotal role. Methotrexate (METHOTREXATE) is an inhibitor of the enzyme dihydrofolate reductase (DHFR), and also directly inhibits the so-called folate-dependent enzyme systems of de novo thymidylate and purine synthesis. A major focus of drug discovery has been development of antifolate analogs targeting the folate-dependent enzyme systems. Thus, the primary action mechanism of methotrexate is inhibition of the function of DHFR. Folic acid and its analogs are poorly permeable to the blood brain barrier, therefore, a transport mechanism (e.g., the presence of folate receptors) is required for entry into mammalian cells. Recently, lipid soluble folate antagonists have been produced. These agents, trimetrexate (NEUTREXIN) and pemetrexed (ALIMTA) can penetrate the blood brain barrier relatively easily. Toxic effects of methotrexate and its analogs include in myelosuppression, mucositis, pneumonitis, psoriasis, cirrhosis, and rheumatoid arthritis.

Folic acid analogs are absorbed from the gastrointestinal tract, but the injection of these drugs can be better controlled. The highest dose of methotrexate is 25 mg/m^2 (oral and/or intravenous) weekly followed by a rest period at least for 2 days. This protocol may be repeated for at least 5 weeks. Folic acid analogs are used for treatment of breast, neck, head, and lung cancer, bladder cancer, osteogenic sarcoma, choriocarcinoma, and lymphocytic leukemia. Therapy with folic acid analogs can be combined with dactinomycin and leucovorin. Toxic effects of folic acid analogs include damage to bone marrow, intestinal epithelium, and renal function. In addition, meningismus, seizures, coma, and inflammatory responses may occur.

B2). Pyrimidine and cytidine analogs

Pyrimidine analogs inhibit RNA and DNA synthesis and function on various ways. For instance, fluoropyrimidines and purine analogs block the synthesis of DNA precursors. Adenosine and cytidine nucleoside analogs are incorporated into the nascent DNA chain blocking its function and elongation. The pyrimidine analog agents include gemcitabine,
capecitabine (XELODA), fludarabine, decitabine, fluorouracil, floxuridine (FUDR), and idoxuridine. Leucovorin and oxaliplatin are commonly used with „citabine” and fluorouracil structures for the treatment of metastatic colorectal cancer. Other uses of pyrimidine and purine analogs are for breast, ostomach, esophageal, head, neck, and pancreatic tumors. Purine analogs are useful tools for the therapy of chronic lymphocytic leukemia, small cell non Hodgkin’s lymphoma; and hairy cell leukemia. Oral application and absorption of these drugs are very unpredictable, therefore, intravenous application is typically used. The maximum doses of these agents are 600 mg/m² in each week for 6 weeks. Clinical manifestation of side effects includes nausea, diarrhea, mucosal ulceration, shock, hair loss, dermatitis, hyperpigmentation, and cardiac ischemia.

Cytarabine (Ara-C, DEPOCYT, CYTOSAR-U) is a cytidine analog antimetabolite (pyrimidine base) and used for the treatment of acute myelocytic leukemia (AML), inhibiting its recurrence. The incorporation of cytarabine in nascent DNA chains prevents the replication and translation of DNA. Cytarabine stimulates various intracellular signals that determine whether cells survive or undergo apoptosis. Cytarabine promotes PKC (protein kinase C) and NF-kappaB (cell damage response factor) activities leading to apoptotic cell death in tumor cells. The drug must be used intravenously at an initial concentration of 300 mg/m² continued at 50 mg/m² in every second week. Side effects of cytarabine reflected include myelosuppression, thrombocytopenia, stomatitis, conjunctivitis, pulmonary edema, dermatitis, seizures, and coma. Other cytidine analogs are azacitidine and gemcitabine. These drugs incorporate in the DNA and RNA, stimulating the expression of silenced genes. Azacitidine and gemcitabine (GEMZAR) are useful tools for the treatment of leukemia, esophageal, bladder, ovarian, pancreatic, and non-small cell lung tumors.

B3). Purine analogs

Pentostatin (NIPENT) and 6-mercaptopurine (6-MP) (PURINETHOL), as a purine analogs, were the first effective agents for the treatment of hairy cell and other leukemias. Other members of this group include fludarabine (FLUDARA), and cladribine (LEUSTATIN). 6-Thioguanine (6-TG) and 6-MP are substrates for hypoxanthine guanine phosphoribosyl transferase and are converted to ribonucleotids 6-thioguanosine-5-monophosphate (6-thioGMP) and 6 thioguanosine-5'-monophosphate (TIMP). TIMP accumulates intracellularly and inhibits the first step in de novo synthesis of purine rings in DNA synthesis. Purine analogs are frequently combined with methotrexate. The typical oral dose of 6-MP is 100 mg/m²/day. Side effects of 6-MP include depression of bone marrow, hyperuricemia, anemia, anorexia, vomiting, and hepatic necrosis.

Fludarabine, as an antimetabolite that inhibits DNA polymerase, DNA ligase, DNA primase, and ribonucleotid reductase. The drug is incorporated with DNA and RNA chains, inhibiting protein syntheis. It also activates apoptosis in tumor cells. Fludarabine is used intravenously at a daily dose of 30 mg/m² for 5 days; and this dose can be repeated every 4th week up to three cycles. Fludarabine is useful for the treatment of chronic lymphocytic leukemia (CLL), non-Hodgkin’s lymphoma, promyelocytic leukemia, and cutaneous T-cell lymphoma. Fludarabine is also a potent immunosuppressive agent. The side effects of this drug are similar to 6-MP.

Cladribine has potent activity against CLL and hairy cell leukemia. Cladribine is incorporated into nascent DNA chains after intracellular phosphorylation. Beside, DNA fragmentation, the purine analog cladribine depletes intracellular ATP and NAD, and induces apoptosis. The dose of cladribine, as a single course, is 0.1 mg/kg/day for 7 days. Toxic effects also can be manifested in myelosuppression, thrombocytopenia, high fever, skin rashes, nausea, and infections.
Pentostatin is a potent inhibitor of adenosine deaminase (ADA) which is related to immunodeficiency by inhibiting T- and B-cell functions. The inhibition of ADA leads to the accumulation of intracellular adenosine, which blocks DNA and RNA synthesis. Pentostatin is able to induce apoptosis in leukemic cells. The drug is administered intravenously at a concentration of 4 mg/m^2 every 2nd week for the treatment of hairy cell leukemia, CLL, CML (chronic myelocytic leukemia), and non-Hodgkin’s lymphoma. Side effects may include neurological symptoms, renal complications, fever, and functional damage to the lung.

C). Natural extracts and products, and antibiotics

This group of therapeutic agents includes a diverse range of molecules such as (C1) vinca alkaloids, (C2) taxanes, (C3) camptothecin analogs, (C4) epipodophyllotoxins, (C5) antibiotics including bleomycins and mitomycin, and (C6) enzymes.

C1). Vinca alkaloids

The vinca alkaloids, vinblastine (VELBAN), vincristine (ONCOVIN), vinleurosine, and vinrosidine, are derived from Catharanthus roseus (Madagascar), and are used for the treatment of various tumors including leukemias, lymphomas, large cell non-Hodgkin’s and Hodgkin’s lymphoma, neuroblastoma, testicular, bladder, lung, and breast cancers. The vinca alkaloids block the cell cycles in the mitosis (M) phase. The effect is especially pronounced in the microtubules by binding to beta-tubulin. Side effects of vinca alkaloids manifest in hair loss, myelosuppression, motor function damage, gastrointestinal disturbances, stomatitis, obstriction, and coma. The doses of vinca alkaloids, depending on the type and progression of tumors, are between 2 mg/m^2 and 40 mg/m^2 of body surface in every 3 weeks.

C2). Taxanes

Paclitaxel (TAXOL) was the first alkaloid isolated from the yew tree and used for cancer therapy. Paclitaxel was followed by a semisynthetic molecule named docetaxel (TAXOTERE). These taxanes inhibit the mitosis (M phase) by binding to different sites of beta-tubulin. The drugs are used for the therapy of breast, lung, ovarian, bladder, and neck tumors. Taxanes are used in combination with doxorubicin and cisplatin, thus, the side effects of drugs are reduced. Toxic effects include neutropenia, myalgia, mucositis, ventricular tachycardia, pulmonary edema, and respiratory failure. Doses of taxanes are 80 to 175 mg/m^2 in infusion once in every three weeks.

C3). Camptothecin analogs

Camptothecin was isolated from the Camptotheca acuminata (Chinese tree). Camptothecin and its analogs (topotecan as HYCAMTIN, irinotecan as CAMPTOSAR) target the DNA topoisomerases. DNA topoisomerases diminish torsional stress in supercoiled DNA becoming relaxed and untangled to enable replication, repair, and transcription. Camptothecin inhibits the function of topoisomerase I, and as a consequence, the transcription of DNA is blocked. Camptothecin is effective in the “G2” phase of the cell cycle, thus, the mitosis (“M” phase) is prevented in tumor cells. Camptothecin induces the transcription of c-fos and c-jun (early response genes) in association with internucleosomal DNA fragmentation leading to apoptotic cell death. Camptothecin analogs are used in therapy for ovarian, small-cell lung, colon, and lung cancers. Side effects involve neutropenia, thrombocytopenia, mucositis, diarrhea, fever, fatigue, and rash. Camptothecin and its analogs are used
intravenously at concentrations of 1.5 mg/m\(^2\) to 350 mg/m\(^2\) per day for 5 consecutive days every 3rd week.

C4). Epipodophyllotoxins

Podophyllotoxins are extracted from the Podophyllum peltatum (“may-apple”) and were used as folk by remedies in native American Indian tribes. Two synthetic derivatives of epipodophyllotoxins: etoposide (TOPOSAR, ETOPOPHOS) and teniposide (VUMON), are used clinically. These agents form a complex with topoisomerase II and DNA, and prevent the normal dissociation of topoisomerase binding to DNA. The enzyme binds to free ends of the broken DNA strands, leading to an accumulation of DNA breaks and apoptotic cell death. Etoposide and teniposide affect and block the cell cycle in the S and G2 phases. These agents are effective against testicular, lung, and breast tumors. In addition, they are used for the treatment of Hodgkin’s and non-Hodgkin’s lymphomas, leukemias, and Kaposi’s sarcoma. Side effects include dermatitis, fever, flebitis, diarrhea, stomatitis, and liver damage. Intravenous doses of etoposide and teniposide range are between 50 mg/m\(^2\) and 160 mg/m\(^2\) per day for 4 days. Etoposide can be used orally for 21 days with a daily dose of 50 mg/m\(^2\).

C5). Antibiotics including bleomycins and mitomycin

The first antitumor antibiotics were isolated from Streptomyces bacteria. The most effective and therapeutically useful antibiotic-antitumor agent is actinomycin D (COSMEGEN). Actinomycin D binds to double helical DNA, resulting in blockade of DNA transcription by RNA polymerase. Actinomycin D is used for treatment of rhabdomyosarcoma and Wilm’s (kidney tumor) tumors. Side effects include neurological symptoms, erythema, extravasation, pigmentation and inflammation. During the treatment of these tumors, actinomycin D is combined with surgery, radiotherapy, vincristine, and cyclophosphamide. Actinomycin D is used for treatment of Kaposi’s sarcoma and soft tissue sarcomas. Doses of actinomycin D range from 10 to 15 ug/kg intravenously for 5 days, with repetition of this course at intervals of 3 weeks.

Other important antitumor antibiotics are anthracyclins structures including daunorubicin (CERUBIDINE), doxorubicin (ADRIAMYCIN), epirubicin, idarubicin, and mitoxantrone, which are produced by Streptococcus peucetius. Daunorubicin and doxorubicin are used for the treatment of AIDS related Kaposi’s sarcoma.

Bleomycins are a family of DNA-cleaving antibiotics that include bleomycins A2 and B2 groups (BLENOXANE) produced by Streptococcus verticillus. Bleomycins cause oxidative degradation of nucleotides, leading to single and double stranded breaks in cancer cell’s DNA. These drugs affect the G2 phase of the cell cycle resulting in chromosomal aberrations, chromatid breaks, fragments, gaps, and translocations. Bleomycins are effective against cervix and testicular tumors, and various lymphomas. Bleomycin has less myelosuppressive effect in comparison with other antitumor agents, therefore its combination with other antineoplastic agents is preferred. However, hyperpigmentation, hyperkeratosis, erythema, and ulceration may occur as side effects. The dose of bleomycin is 30 units/m\(^2\) weekly by intravenous or intramuscular route.

Mitomycin (MUTAMYCIN) is the product of Streptococcus caesipitosus with limited clinical use to its toxicity. Mitomycin is used in therapy for breast, bladder, lung, anal, and colorectal tumors. As an alkylating agent, mitomycin inhibits DNA synthesis and cross-links DNA at sites of adenine and guanine incorporation. Mitomycin additionally causes single-strand DNA breaks and chromosome fragmentation. Toxic effects include myelosuppression, neurological abnormalities, pneumonia, leucopenia, diarrhea, vomiting, fever, dermatitis,
renal failure, and uremic syndrome. Typical dosage of this drug by intravenous application is 30 mg/m² every 6 weeks.

C6. Enzymes

L-asparaginase (ELSPAR) is the first enzyme applied in chemotherapy. Its main use is as an antileukemic agent. Normal tissues synthesize L-asparagine at levels sufficient for protein synthesis. L-asparaginase catalyzes the conversion of L-asparagine to aspartic acid, and depletes reserves of asparagine needed for protein synthesis by malignant cells. L-asparaginase is administered in combination with methotrexate, doxorubicin, prednisone, and vincristine for the treatment of various lymphomas. L-asparaginase is given intravenously at dosages of 6,000 to 10,000 international units (IU) every third day for 4 weeks. Pegaspargase (PEG-L-asparaginase) is conjugated to the 5 kDalton unit of polyethylene glycol, leading to long half-life (six days) in the body. Typically it is administered intramuscularly at a dose of 2500 IU/m² per week. L-asparaginase or PEG-L-asparaginase has less toxic effects in comparison with other antineoplastic agents. However, hypersensitive reactions, bone marrow and gastrointestinal damage, hyperglycemia, thromboses, and intracranial hemorrhage can occur as side effects.

D). Miscellaneous agents

This family includes (1) hydroxyurea, (2) thalidomide, (3) estramustine, bortezomib, mitotane, (4) differentiating agents: ATRA and arsenic trioxide, (5) protein tyrosine kinase inhibitors (imatinib, gefitinib, erlotinib), and (6) biological response modifiers.

D1). Hydroxyurea

Hydroxyurea (HYDREA, DROXIA) may be administered orally at doses of 15 mg/kg to 80 mg/kg every 3rd day for the treatment of various myeloproliferative syndromes, thrombocytosis, venous thrombosis, chronic myelocytic leukemia (CLM), and sickle cell disease. Hydroxyurea blocks activity of the enzyme ribonucleoside diphosphate reductase. This enzyme catalyzes the conversion of ribonucleotides to deoxyribonucleotides, a critical step, in DNA biosynthesis. Side effects of hydroxyurea include megaloblastic anemia, leukopenia, gastrointestinal symptoms, and pneumonitis. Hydroxyurea is a potent teratogen agent in animals.

D2). Thalidomide

Thalidomide was introduced for the pregnancy related morning sickness, but due to its teratogenicity the drug was withdrawn from the market. However, in 1998, it was reintroduced for the medication of erythema nodosum leprosum and multiple myeloma. Thalidomide has antiproliferative and proapoptotic antitumor effects by inhibition of transcriptional activity of NF-kappaB and its antiapoptotic target genes e.g., caspase inhibitor c1AP-2 (cellular inhibitor of apoptosis 2) and A1/Bfl-1 (a member of antiapoptotic Bel-2 family). Adverse effects of thalidomide include constipation, sedation, neuropathy, sensory loss, weakness, and muscle cramps. Maximal daily dose of thalidomide is 200 mg. Also included in this family of drugs are lenalidomide, a derivative of thalidomide.

D3). Estramustine, bortezomib, mitotane
Estramustine (EMCYT) is a compound structurally related to nitrogen mustard and frequently used in combination with estradiol. Estramustine is not an alkylating agent. The drug binds to beta tubulin causing antimitotic action. Clinical use of estramustine is in the treatment of prostate cancers at a daily oral dose of 16 mg/kg. Side effects include myelosuppression, impotence, gynecomastia, angioedema, and fluid retention.

Bortezomib (VELCADE) inhibits chymotrypsin activity by binding to the 26S proteosome. The consequence of proteosome inhibition is the downregulation of NF-kappaB, a basic transcription factor that promotes cell survival. NF-kappaB activates cell adhesion molecules (ICAM-1, VCAM-1, and VEGF) promoting cell proliferation and survival. Bortezomib is used for the treatment of multiple myeloma (MM) at an intravenous concentration of 1.3 mg/m² given on days 1, 4, 8, and 11 of every 21 day cycle. Side effects include neutropenia, neuropathy, fatigue, nausea, dehydration, diarrhea, and anemia.

Mitotane (LYSODREN) is a useful tool for the treatment of tumors derived from adrenocortical cells. Mitotane reduces the level and production of adrenocorticosteroids. Accordingly, the drug is used for treatment of Cushing’s syndrome (hyperadrenocorticism). The daily dose of mitotane is 6 grams divided into three portions, continued for 3 months. Spiranolactone (a diuretic agent) cannot be given simultaneously, because it interferes with the effects of mitotane. The side effects of mitotane are relatively minor in comparison with other antineoplastic agents.

D4). Differentiating agents: ATRA and arsenic trioxide

One of the crucial features of malignant transformation is inhibition of differentiation. For example, altered activity of the PML (progressive multifocal leukoencephalopathy) gene results in blockage of differentiation leading to acute promyelocytic leukemia (APL). For tumor treatment, the differentiating agent, tretinoin (all-trans-retinoic acid: ATRA) may produce complete remission of APL at an oral daily dose of 45 mg/m². Side effects of ATRA include hepatic enzyme abnormalities, dry skin, hyperlipidemia, and retinoic acid syndrome (characterized by weight gain, pleural effusion, dyspnea, and fever).

Arsenic trioxide (ATO) as a heavy metal structure was used for the treatment of syphilis, parasitic disease, and chronic myelocytic leukemia (CML) in the 19th and 20th centuries. ATO has been recently used for therapy of APL. The action mechanism of ATO summarized as follows: (i) free radical generation; and (ii) angiogenesis inhibition effects. In addition, ATO promotes (iii) the degradation of NF-kappaB, stimulates (iv) angiogenesis and inhibits apoptotic responses. These four effects lead to the inhibition of tumor development. Side effects of ATO include hepatic enzyme elevations, fatigue, hyperglycemia, and the lengthening of QT interval on the ECG which is related to the inhibition of K⁺ channel function in the myocardium. The dose of ATO is 0.15 mg/kg/day for 2 months until remission is clinically established.

D5). Protein tyrosine kinase inhibitors (imatinib, gefitinib, erlotinib)

Protein kinases are critical components of signal transduction that transmit various messages to the nucleus altering gene transcription and DNA synthesis. The human genome codes for more than 500 protein kinases and over 100 protein phosphatases which are enzymes that regulate activity of protein kinases. The protein kinases can be classed into 3 major groups: (i) tyrosine kinases (with specific activity on tyrosine groups), (ii) serine/threonine kinases (with specific activity on serine and threonine structures), and (iii) kinases with nonspecific activity on tyrosine, serine, and threonine residues. Activation of protein tyrosine kinases has been demonstrated in various human neoplasms; and therefore
are molecular targets for tumor therapies. Three protein tyrosine kinase inhibitors (imatinib, gefitinib, and erlotinib) are available for treatment of CML, gastrointestinal tumors, non-small cell lung cancer, and bronchoalveolar tumors. Side effects include anorexia, nausea, vomiting, acne, pruritus, fluid retention and edema, rash, and bleeding. Doses of imatinib (GLIVEC), gefitinib (IRESSA), and erlotinib (TARCEVA) administered orally, range from 200 mg/day and 600 mg/day for 6-10 weeks.

D6). Biological response modifiers

This family of protein drugs augments patient’s naturally occurring antitumor responses, and also acts indirectly or directly on tumor cells. Included in this category are: (a) interferons, (b) interleukins, (c) hematopoietic growth factors (e.g., erythropoietin), (d) myeloid growth factors: filgrastim (granulocyte colony-stimulating factor: G-CSF) and sargramostim (granulocyte macrophage colony-stimulating factor: GM-CSF). (e) tumor necrosis factor (TNF), and monoclonal antibodies (e.g., trastuzumab, cetuximab, rituximab).

D6).a Interferons

Interferons (INFs) possess antiviral, immunomodulating, and antiproliferative effects. The two most important interferons are interferon alpha (INF-α) and interferon beta (INF-β). INF-α and INF-β stimulate the cytotoxic activity of lymphocytes, macrophages, and natural killer cells. The action mechanism of interferon is the inhibition of protein synthesis. Interferons are used as intramuscular or subcutaneous injections. The therapeutic use of INFs includes various diseases such as virus infections, multiple sclerosis, chronic hepatitis B virus (HBV) infection, chronic hepatitis C virus (HCV) infection, and Kaposi’s sarcoma in HIV infected patients. Side effects are influenza-like syndrome, fever, headache, diarrhea, confusions, CNS seizures, and depression. The doses of INF-α and INF-β are between 1 and 2 million of IU.

D6).b Interleukins

IL-2 (T-cell growth factor) promotes cytolytic T-cell responses against tumor cells. Because the half-life of IL-2 is relatively short (10 to 80 min), continuous infusion (2 million IU/day) is recommended for 5 days every 2nd week. IL-2 is used for the treatment of hairy cell leukemia, Kaposi’s sarcoma (tumor manifested in the skin and its vessels), renal and bladder tumors, multiple myeloma, and malignant melanoma. Hypotension, anemia, arrhythmias diarrhea, fever, and confusion can be manifested as side effects.

D6).c Hematopoietic growth factors (e.g., erythropoietin)

The formation of blood cells is a very complex process. Hematopoietic stem cells are marrow cells having self-renewal potential and are able to differentiate into nine different blood cell lineages, and expressing a number of soluble hematopoietic growth factors. Clinical application of hematopoietic growth factors is used in treatment of hematological diseases, infections, cancer chemotherapy, and bone marrow transplantation. Hematopoiesis requires additional natural products that include vitamins (B-12, Vitamin C, pyridoxine), folic acid, and minerals (iron, cobalt, and cooper). Deficiencies of the aforementioned nutrients result in various anemias or failure of hematopoiesis. The short lifespan of blood cells requires their continuous reproduction and replacement (which is the definition of
hematopoiesis). This process involves cell-cell interactions and lymphopoietic and hematopoietic growth factors.

Stem cells present in bone marrow are pluripotent, giving rise to megakaryocytes, granulocytes, lymphocytes, monocytes, and erythrocytes. Pluripotent stem cells and growth factors give rise to progenitors as colony-forming units leading to differentiation into functional leukocytes. Growth factors are protein hormones, which after discovery were named erythropoietin. The gene encoding erythropoietin has recently been cloned. Other growth factors such as granulocyte colony stimulating factor (G-CSF), and granulocyte and macrophage colony stimulating factor (GM-CSF) have critical role in the differentiation of blood cells (Figure 18). The first step in differentiation is development of burst forming units (BFU) or colony forming units (CFU) of major cell lines including each of the major cell lines such as colony forming unit of granulocyte/macrophage (CFU-GM), burst forming unit-erythrocyte (BFU-E). These cell lines are able to further proliferate and differentiate. This differentiation process requires presence of interleuki-3 (IL-3) and GM-CSF (Figure 18). These progenitors develop into colony forming cells and units e.g., granulocyte colony forming cells (G-CFC), monocyte cell forming cells (M-CFC), colony forming unit of erythropoietin (CFU-E) or colony forming unit megakaryocyte (CFU-Meg).

Erythropoietin (EPREX, EPOGEN) is produced by peritubular cells around the proximal tubule in the kidney. Its molecular weight is about 34,000 D. Renal synthesis and secretion of erythropoietin is increased approximately 100-fold under hypoxic or ischemic conditions. Erythropoietin production is controlled by BFU-E and CFU-E. This protein is responsible for erythropoiesis, and is the basic regulator of the progenitors and maturation of erythroblasts, and release of reticulocytes into circulation. Erythropoietin (15 to 150 units/kg/day for weeks) is intravenously administered for treatment of anemia in renal failure. In addition, it has beneficial effects in acquired immunodeficiency syndrome (AIDS) when coadministered with zidovudine (AZT); and anemia associated with cancer therapy. Side effects of erythropoietin can include hypertension and CNS seizures.
Figure 18. Differentiation in marrow cell lines.

Shown here are lines of differentiation for colony forming units of granulocyte erythroidopietin megakaryocyte macrophage (CFU-GEMM); Colony stimulating factor (CSF-1); granulocyte colony stimulating factor (G-CSF); granulocyte and macrophage colony stimulating factor (GM-CSF); burst forming units (BFU); burst forming unit-erythrocyte (BFU-E); burst forming unit-megakaryocyte (BFU-Meg); colony forming unit megakaryocyte (CFU-Meg); colony forming unit of granulocyte/macrophage (CFU-GM); colony forming unit of erythropoietin (CFU-E); monocyte cell forming cells (M-CFC); granulocyte colony forming cells (G-CFC); red blood cells (RBC).

D6)d Myeloid growth factors: filgrastim (granulocyte colony-stimulating factor: G-CSF) and sargramostim (granulocyte macrophage colony-stimulating factor: GM-CSF)

Myeloid growth factors are generated naturally by various cells such as fibroblasts, macrophages, endothelial cells, and T-cells. GM-CSF (sargramostim) is able to stimulate proliferation, differentiation, and functions of various myeloid cell lines. GM-CSF also stimulates expression of CFU-GM, CFU-GEMM, CFU-Meg, CFU-E, and CFU-M. This protein increases phagocytosis; and production of superoxide radicals, antibody-dependent
cell-mediated toxicity of eosinophils, neutrophils, and monocytes. GM-CSF (sargramostim, LEUKINE) is used for the long-term survival of transplanted organs and tissues preventing the early graft failure. The protein mobilizes CD34+ progenitor cells after myeloablative chemotherapy in patients. Side effects include diarrhea, fever, dyspnea, hypotension, arrhythmias, and rash. Sargramostim is used at a maximal daily dose of 500 ug/m² administered as an infusion.

         Human recombinant granulocyte colony-stimulating factor (G-CSF, filgrastim, NEUPOGEN) is produced in E. coli. Filgrastim stimulates CFU-G, increasing neutrophil granulocyte production, and enhancing the phagocytic and cytotoxic function of neutrophils. The drug is a useful tool for the treatment of neutropenia, and high dose tumor chemotherapy. In addition, filgrastim is effective against bacterial and fungal infections. The dose of this drug is 20 ug/kg/day for 3 weeks. Pegylated recombinant human G-CSF (pegfilgrastim, NEULASTA) increases the effectiveness and duration of action of G-CSF.

D(6).e Tumor necrosis factor (TNF), and monoclonal antibodies (e.g., trastuzumab, cetuximab, rituximab)

Tumor necrosis factor (TNF) is involved in inflammatory processes, and secreted by monocytes and macrophages. TNF-alpha and TNF-beta are recognized by cell-surface receptors producing proinflammatory responses. Glucocorticoids interfere with the synthesis of TNF. TNF-alpha is for the treatment of some tumors.

Tumor cells express various antigens that are targets for monoclonal antibody-based therapy. Monoclonal antibodies are used for the treatment of lymphoid malignancies such as B-cell lymphoma, and br monoclonal antibody breast cancers. The action mechanism of TNF-based drugs involves apoptosis induction via monoclonal antibodies that include part of a TNF molecule. Categories of this drug class include trastuzumab (HERCEPTIN), cetuximab (ERBITUX), and rituximab (RITUXAN) which are “naked monoclonal antibodies” frequently used in tumor therapy.

E). Hormones and hormone-like agents

This group includes 1). Glucocorticoids, 2). Progestins, 3). Estrogens and androgens, 4). Aromatase inhibitors, and 5). Anti-androgen therapy in prostate tumor.

E1). Glucocorticoids

The effects and pharmacology of glucocorticoids are discussed in the „Hormons” chapter, and only hormone-based antitumor therapy considered here. Glucocorticoids possess lympholytic effects and suppress mitosis in lymphocytes, therefore glucocorticoids are primarily used for the treatment of malignant lymphoma and acute leukemia including Hodgkin’s and non-Hodgkin’s lymphoma; and multiple myeloma. Remission of tumors occurs more rapidly with glucocorticoids than with antimetabolites. Prednisone and dexamethasone are frequently combined with vincristine, methotrexate, and l-asparaginase at concentrations of 6 to 60 mg/day. Dexamethasone is able to significantly reduce cancer-related edema formation. Glucocorticoid therapies are frequently combined with radiotherapy. Abrupt discontinuation of glucocorticoids is contraindicated due to adverse impact on the condition of the patient prognosis. If glucocorticoids are used chronically, a wide range of side effects is manifested including psychosis, immunosuppression, osteoporosis, and glucose intolerance.
E2). Progestins

Progestins are used as second line hormonal therapy for the treatment of hormone-dependent breast cancer and endometrial carcinoma. In addition, this group of anticancer agents is suggested for the treatment of hormone dependent cancers in the presence of AIDS infection. Progestins are also used for increasing the appetite in cachectic patients. Progesterone is poorly absorbed if given orally, therefore it is used as an intramuscular injection with an oil carrier. Hydroxyprogesterone and medroxyprogesterone (DEPO-PROVERA) are applied at a maximal weekly intramuscular dose of 1000 mg. Megestrol acetate (MEGACE) is primarily used for the treatment of endometrial cancer at a maximal dose of 320 mg/day. Indications for use of progestins include metastatic prostate and kidney tumors.

E3). Estrogens and androgens

Estrogens and androgens are used for the treatment of mammary gland and prostate tumors. If distant metastases are present in patients, hormone treatment becomes the primary therapy instead of surgery and radiation therapy.

To decrease the concentrations of endogenous androgens and inhibit their effects, bilateral orchectomy, antiandrogens, and administration of gonadotropin releasing hormone (GnRH) agonists or antagonists are suggested. The side effects of androgens include increased appetite, weight gain, and well-being feeling. Although, androgen therapy produces regression of cancer and tissue metastases, neoplastic cells are not completely eliminated. The level of prostate specific antigen (PSA) in plasma is a general marker of the response. If mutation of androgen receptors occurs, prostatic cancers become refractory to androgen deprivation.

Mammary tumors can be treated with both estrogens and androgens. Antagonization of estrogen effects is effective as exemplified remission of disease achieved with oophorectomy. Tamoxifen, an anti-estrogen agent, is used for the therapy of breast tumors. The presence or absence of estrogen receptors (ER) and progesteron receptors (PR) led to the selection of patients for hormone therapies. Patients with PR- or ER-positive (presence of receptors) tumors may experience beneficial response to hormone therapy. Conversely, for patients who have no ER- and PR-receptors (ER- and PR-negative tumors) hormonal therapy is completely ineffective. A detectable response to hormone therapy requires about 3 months. Treatment and remission using hormonal therapy may last for many years.

Another tool for treatment of hormone-receptor positive breast cancers are anti-estrogen therapies. These approaches include the application of: (i) selective estrogen-receptor modulators (SERMs); (ii) selective estrogen-receptor downregulators (SERDs); and (iii) aromatase inhibitors (AIs).

(i) Tamoxifen (NOLVADEX), toremifene (FARESTON), idoxifene, and droloxifene are the major representative SERM drugs. Tamoxifen and toremifene are the most frequently used drugs for the treatment of breast cancer as antiestrogen therapeutic agents. Tamoxifen is prescribed for prevention, adjuvant therapy, and therapy of advanced breast tumors. Tamoxifen inhibits the binding of estradiol to the estrogen receptors (ER). The maximal oral dose of tamoxifen is 20 mg/day in ER positive tumors, and treatment may continue for years. Tamoxifen is ineffective against ER-negative tumors. Retinal degeneration, hair loss, vomiting, vaginal bleeding, pruritus, and dermatitis can occur as side effects. Tamoxifen also promotes development of endometrial tumors and thromboembolic events in older postmenopausal patients.
(ii) SERDs include fluvestran (FASLODEX) and related compounds which are under clinical investigation. The drug is used for the treatment of hormone receptor-positive metastatic breast cancer in postmenopausal women. Fulvestrant is a steroidal antiestrogen molecule that binds to the ER, accelerates ER degradation, and reduces ER numbers. Fulvestrant is injected intramuscularly at a single dose of 250 mg per month. Adverse side effects include nausea, pain, headache, and vasodilation.

(iii). Aromatase is the product of CYP19 gene. Aromatase inhibitors (AIs) as potential tools against breast cancers are discussed just below in section E4.

E4). Aromatase inhibitors

The aromatase enzyme is responsible for conversion of androstenedione and testosterone to estrone (E1) and estriol (E2). AIs inhibit aromatase activity leading to profound estrogen deprivation in postmenopausal women. AIs can be divided into three groups: (i) First generation AIs (steroid analogues of androstenedione); (ii) second generation AIs (nonsteroid structures); and (iii) third generation AIs (steroid and nonsteroid structures).

A major representative agent first generation AI is aminogluthethimide (CYTADREN) which inhibits the synthesis of adrenocortical steroids. The dose of aminogluthethimide is 250 mg/kg/day coadministered with hydrocortisone. The coadministration of hydrocortisone is necessary to prevent the unwanted adrenal suppression.

Second generation of AIs includes formestane (LENTARON), a type 1 steroid inactivator, fadrozole and rogletimide (nonsteroid structures) that are able to inhibit aromatase enzyme activity in women afflicted with ER-positive breast cancers. These agents are administered by intramuscular injection. The latest derivative of formestane is exemestane, currently the most frequently used drug in this class.

Third generation AIs (can be nonsteroid or steroid structures) is used for the treatment of early-stage and advanced breast tumors. The nonsteroid agents are anastrozole (ARIMIDEX) and letrozole (FEMARA). These drugs are administered at a daily maximum dose of 10 mg. Side effects include vaginal bleeding, ischemic cerebrovascular events, deep vein trombosis, and pulmonary embolism.

A representative steroid agent of the third generation of AIs is exemestane (AROMASIN), an orally administered analog of the natural substrate of androstenedione, which lowers estrogen levels. Exemestane irreversibly inactivates the function of aromatase at a daily dose of 25 mg/kg. Exemestane is used for treatment of ER-positive breast cancer in postmenopausal women. The side effects of exemestane (fatigue, peripheral edema, increased appetite) are not common and very well tolerated by patients.

E5). Anti-androgen therapy in prostate tumors

Surgical castration (bilateral orchiectomy) or hormonal therapy (medical castration) is an effective treatment for prostate cancer. Androgen deprivation therapy (ADT) is the major treatment of prostate cancer. A well-tolerated form of ADT includes chemical suppression of pituitary activity with gonadotropin releasing hormone (GnRH) agonists. GnRH agonist agents cause an initial rise in levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), followed by inhibition of gonadotropin release. The result is reduction of testicular production of testosterone (chemical castration). GnRH agonist agents include triptorelin (TRELSTAR), goserelin (ZOLADEX), buserelin (SUPREFACT), and leuprolide (LUPRON). Complete androgen blockade may be accomplished with a combination of androgen receptor blockers (see below) and GnRH agonist agents.
Androgen receptor blockers that inhibit the natural ligands of the androgen receptor (AR), are called anti-androgens. Use of these drugs blocks androgen production and release from adrenals. AR blockers include two groups: (i) steroid-like (cyproterone: ANDROCUR, megestrol); and (ii) compounds with nonsteroid structure such as flutamide (EULEXIN), nilutamide (NILANDRON), and bicalutamide (CASODEX). Nonsteroid AR blockers inhibit ligand binding and AR translocation from the cytoplasm to the nucleus. Nonsteroid AR blockers cause gynecomastia and decreased libido. The daily dose of nonsteroid AR blockers cannot exceed 150 mg, and may be applied for months.
Gastrointestinal tract function and pharmacotherapy strategies for management of stomach and bowel diseases are discussed in this chapter. Following subchapters within this section describe treatments of the gastrointestinal disorders including: (i) stomach, (ii) bowel motility, laxatives, antiemetic agents, biliary and pancreatic diseases, (iii) and the treatment of inflammatory bowel disease (IBD).

(i) The stomach

Gastric acids and pepsin are necessary for maintaining of the normal physiological function of the stomach. The primary esophageal defense is a barrier to the reflux of gastric contents protecting the esophagus. When this barrier fails and reflux occurs, dyspepsia and erosive esophagitis develop. Therapies for reflux disorders are focused on reducing gastric acidity, increasing the esophageal sphincter pressure and stimulating gastric motility. Mucus and bicarbonate protect the stomach via increased local production of prostaglandins in the gastric mucosa of the stomach. If the function of this defense mechanism is damaged, gastric and duodenal ulcers may develop.

Gastric acid secretion in the stomach is dependent on the secretion of protons by parietal cells (Fig. 19). This process is complex, and determined by neuronal (acetylcholine), paracrine (histamine), and endocrine (gastrin) factors and their receptors: muscarin3 (M3), histamine2 (H2), and cholecystokinin2 (CCK2), respectively. The H2 receptor activates Gq-protein adenyl cyclase–cAMP pathway. The cAMP and Ca2+ dependent pathways activate the H+-K+ATPase (proton pump) system which contributes to the K+-H+ exchange via the parietal cell membrane of the stomach. The ACh (M3 receptor) couples the Gq protein-PLC-IP3-Ca2+ pathway in parietal cells of the stomach. Another important component of the gastric acid secretion system is the vagal nerve. ACh release from vagal fibers directly stimulates gastric acid secretion through M3 receptors in parietal cells of the stomach. In addition, enterochromaffin-like (ECL) cells located closely to parietal cells contribute to histamine gastric secretion.

Figure 19. Mechanisms of gastric proton secretion.

Gastrin is the most important inducer of acid secretion in the stomach. This mediator up-regulates acid secretion by stimulating the release of histamine in ECL cells. The activity of gastrin is regulated by somatostatin, which antagonizes gastric acid secretion. Somatostatin
analogs therefore can be an important therapeutic strategy against the development of gastrointestinal ulcus.

Three major pharmacological strategies have been developed for management of peptic acid disorders. These may be summarized as follows:

a). Inhibitors of the proton pump (K$^+$-H$^+$ pump)
b). H2 receptor antagonists
c). Antacids, ascid supressants and cytoprotectants

a). Inhibitors of the proton pump (K$^+$-H$^+$ pump)

Gastric acid secretion is suppressed by proton pump inhibitors. These drugs are able to reduce the daily gastric acid secretion by as much as 90%. The proton pump inhibitors include omeprazole (RAPINEX, ZEGERID), esomeprazole (NEXIUM), lansoprazole (PREVACID), rabeprazole (ACIPHEX), pantoprazole (PROTONIX). These drugs are activated by an acid environment, followed by binding of activated forms with sulfhydryl groups of cysteines, thus, inactivating the function of the K$^+$-H$^+$ pump.

Proton pump inhibitors are quickly absorbed and metabolized by hepatic CYP2C19 and CYP3A4 enzymes in the liver. The proton pump inhibitor effect is developed after 3 to 4 days by the application of a single daily dose of these agents. The therapeutic effect may last for 2 to 4 days after final dosing. Chronic treatment with proton pump inhibitors decreases the absorption of vitamin B12.

Proton pump inhibitors are used for promoting the healing of gastric and duodenal ulcers, and the treatment of gastroesophageal diseases including erosive esophagitis. These drugs are also the mainstay in the pharmacotherapy of pathological hypersecretory conditions including the Zollinger-Ellison disease. Additionally, the proton pump inhibitors are able to diminish the risk of duodenal ulcer recurrence associated with H. pylori infections, an effect which may demonstrate therapeutic synergy with astaxanthin a carotenoid antioxidant, which has also shown effectiveness in counteracting H. pylori-related pathologies.

b). H2 receptor antagonists

H2 receptor antagonists are drugs that inhibit acid production in the basolateral membrane of parietal cells. These agents include cimetidine (TAGAMET), ranitidine (ZANTAC), nizatidine (AXID), and famotidine (PEPCID). These H2 receptor antagonists are less effective than proton pump inhibitors, but are able to suppress gastric acid secretion by 60 to 70%. Each of these agents is available for oral and parenteral application.

H2 receptor antagonist agents are quickly absorbed after oral application. The main site for metabolism of these drugs is the kidney by filtration and renal tubular secretion, however about 20% of H2 receptor antagonists are metabolized in the liver. These agents are well-tolerated by patients with minor side effects, including headache, fatigue, constipation, diarrhea, and muscular pain. H2 receptor antagonists penetrate the placenta, and are excreted in milk. The main therapeutic indications of H2 receptor antagonist are gastric and duodenal ulcers, and prevention of stress-induced ulcers.

c). Antacids, ascid supressants and cytoprotectants
CaCO₃ quickly and effectively neutralizes gastric proton, but the formation of CO₂ can cause nausea, belching, abdominal distention, and flatulence. Mg²⁺ and Al³⁺ hydroxide are orally-delivered agents, which both provide a relatively sustained proton neutralizing effect. These antacids are frequently combined with H₂ receptor antagonists. MAGALDRATE is a hydroxy-magnesium-aluminate complex which is degraded by gastric acid to magnesium- and aluminiumhydroxide leading to a therapeutic effect.

Antacids may affect the activity of a number of drugs such as antifungals, thyroid hormones, and allopurinol. Changes in effectiveness of these drugs are related to absorption, bioavailability and excretion rates. Drug interactions can be avoided by taking antacids 2 or 3 hours before or after applications of other drugs.

Acid suppressants, pirenzepine and telzepine, the M (muscarinic) receptor antagonists can diminish acid production by 50% and have been used to treat peptic ulcers in patients. The ACh receptor is the M3 (muscarinic 3) receptor on parietal cells, and these drugs are able to suppress neural stimulation of acid production.

Rebamipide is another agent used for ulcer therapy. Its cytoprotective effect is related to the augmentation of prostaglandin synthesis in gastric mucosa, and antioxidant capacity. Another agent, ecabet (GASTROM), increases PGE₂ and PGI₂ (prostacyclin) formation and used for ulcer therapy. Bismuth containing agents bind to the site of the ulcer and stimulate mucine and bicarbonate production, and possess significant antibacterial effects. Bismuth compounds are used as cytoprotective agents against helicobacter infections.

Therapy for Helicobacter pylori infection: Helicobacter pylori related infection is associated with gastritis and the development of gastric and duodenal ulcers, gastric adenocarcinoma, and gastric B-cell lymphoma. Elimination of Helicobacter pylori is a key therapeutic strategy in patients afflicted with gastric or duodenal ulcers. Elimination of Helicobacter pylori is also indicated in the treatment of mucosa-related lymphomas of the stomach. Combination therapy with various antibiotics (amoxicillin, clarithromycin) and acid suppressive therapy are currently the most effective approaches to Helicobacter pylori eradication. Additionally, treatment with proton pump inhibitors or H₂ receptor antagonists significantly increases the effectiveness of the pharmacotherapy. Two week combined treatment is typically used.

(ii) The bowel motility, laxatives, antinauseant and antiemetic agents, biliary and pancreatic diseases

Bowel motility

Gastrointestinal motility is controlled by the central nervous system, local nerves (i.e., enteric nervous system, ENS), and humoral systems. The ENS is a collection of nerves located in the wall of gastrointestinal (GI) tract consisting of the myenteric (Auerbach) plexus and the submucosal (Meissner) plexus. The myenteric plexus is responsible for motor control, and the submucosal plexus regulates vascular flow, fluid transport, and secretion. The primary neurotransmitter in the excitatory motor neurons is ACh, however, tachykinins also play a role in these neurons. Nitric oxide (NO) is the principal inhibitory neurotransmitter in the inhibitory motor neurons, but vasoactive intestinal peptide (VIP), pituitary adenylyl cyclase activating peptide (PACAP), and ATP are also important contributors as inhibitory neurotransmitters.

The control of contraction in GI smooth muscle cells (SMC), as in many other tissues, depends on the intracellular Ca²⁺ concentration. Inhibitory receptors also exist in GI SMC and act via kinases (PKA and PKG) leading to hyperpolarization, decreased cytosolic Ca²⁺ concentration and smooth muscle relaxation. NO induces smooth muscle relaxation via the
activation of guanylyl cyclase system leading to increased cGMP level, and opening of K⁺
channels.

GI motility disorders include dysfunctions of the esophagus and myopathic-neuropathic forms of intestinal dysmotilities. Treatments of these disorders remain symptom-
based and empirical.

Acetylcholinesterase inhibitors, inhibiting the degradation of ACh (e.g., neostigmine), allows accumulation of ACh at sites of release and can improve the motility and contractility of the gut. The normal dose of neostigmine is about 2.5 mg as a single bonus injection, and may be repeated until bowel motility is normalized.

Dopamine receptor antagonists such as metoclopramide and domperidone (MOTILIIUM) can suppress the release of ACh from motor neurons mediated by D₂ dopaminergic receptors, thereby improving gastrointestinal motility. These dopamine receptor antagonists are effective prokinetic agents which offer an additional advantage by antagonizing dopamine receptors leading to the suppression of nausea and vomiting. Dopamine receptor antagonists are used for the treatment of patients afflicted with gastroparesis (e.g., postoperative ileus) and hiccups. Doses of these agents range from 10 to 40 mg/day. Domperidone is able clearly to antagonize D₂ receptors without influencing ACh receptors. Another D₂ receptor antagonist that acts as a prokinetic agent is levosulpiride.

Serotonin (5-HT) and serotonin receptor modulators play an important role in the regulation and control of the GI tract. Serotonin receptor modulators include tegaserod (ZELNORM), cisapride (PROPULSID), and mosapride. More than 90% of the total serotonin content of the body exists in the GI system. Serotonin stimulates peristaltic reflexes via the intrinsic neurons and 5-HT4 receptors, and the extrinsic vagal and spinal neurons along with the 5-HT3 receptors. In addition, stimulation of 5-HT₁a receptor leads to an inhibitory effect in the GI tract. Stimulation of 5-HT₁ receptors facilitates the release of nitric oxide and diminishes the tone of smooth muscle. These drugs stimulate the motility of the esophagus, stomach, small bowel, and ascending colon via 5-HT4 receptors. The daily dose of serotonin receptor modulators ranges between 2 mg and 6 mg.

Laxatives

Water content of stool is about 75%, and fluid content reflects the balance between ingestion (water and electrolytes) and output in the GI tract. Under physiological circumstances, water and fluid absorption capacities of the small intestine and colon are 16 liters and 5 liters per day, respectively. Many mechanisms, such as drugs, pathogens, neuronal and hormonal, can alter physiological processes leading to changes in absorption and secretion in epithelial cells of the GI tract. With reduced bowel motility and excess fluid removal, constipation will occur. Constipation results in many secondary changes in drug absorption and elimination, hormonal disturbances, autonomic and central neuronal functions, and de development in many illnesses. Constipation could be balanced by adherence to fiber rich diet, appropriate fluid intake, and suspension of the administration of constipating drugs. In the lack of the success of the aforementioned nonpharmacological measures, bulk forming and osmotic agents can be used to counteract constipative influences. In the case of surgical intervention, radiological and endoscopic examinations are necessary, an empty colon is desirable.

Use of laxatives may mediate the following outcomes:
(i) Increased retention of intraluminal water by osmotic and hydrophilic mechanisms,
(ii) Decreased absorption of fluid by alteration of electrolyte transports in small and large intestine; and 
(iii) Alteration of bowel motility via autonomic and intestinal nervous system.

Laxatives may therefore be grouped into three major functional categories:
(a) Luminal-active agents: These include: hydrophilic colloids (e.g., bran, psyllium); Osmotic agents (e.g., inorganic salts and sugars); and stool wetting (surfactants) and emollients (docusate, mineral oil).
(b) Stimulators of fluid secretion and motility (bisacodyl, senna and cascara, and Castor oil).
(c) Prokinetic drugs which primarily affect motility (dopamin receptor antagonista, 5-HT4 receptor agonists, and motilides such as erythromycin).

(a) The hydration of stool depends on its fiber content. Fibers resist enzymatic digestion and reach the colon unchanged. Colonic bacteria ferment fiber producing short-chain fatty acids and increasing bacterial mass. Short-chain fatty acids have prokinetic effects, and increase bacterial mass along with stool volume. Unfermented fiber absorbs water and enhances stool bulk. For instance, lignin, an insoluble fiber, is highly effective in enhancing stool bulk and transit rate. Wheat bran and its lignin content is also very effective in increasing stool weight. Psyllium, derived from Plantago ovata, is a component of many commercial products (e.g., METAMUCIL) for constipation. Doses of psyllium are typically 2.5 gram/day to 5.0 gram/day. Other luminally active agents are methylcellulose (CITRUCEL) and malt soup extract (MALSTUPEX).

Osmotic agents, also called saline laxatives, contain magnesium and/or phosphate ions. Their laxative action is based on osmotically-mediated water retention leading to peristaltic stimulation and intestinal motility. Saline laxatives produce 400-500 ml of stool within 7 hours. The bitter taste of saline laxatives may induce nausea as an adverse side effect.

Nondigestible sugars (e.g., lactulose) resist intestinal disaccharidase enzyme activity. Lactulose, mannitol, and sorbitol are hydrolyzed in the colon and stimulate its motility by drawing water into the lumen. These sugar laxatives are used for the treatment of constipation induced by opioids. The laxative effect typically occurs after 30 to 40 hours following oral administration of these sugars.

Stool-wetting agents and emollients facilitate mixing of fatty and aqueous components in the gut enabling easier defecation. These agents stimulate electrolyte and intestinal fluid secretion and increase mucosal permeability. Docusate calcium (SURFAK) and docusate sodium (DOXINATE) are frequently effective in the treatment of constipation. Mineral oil obtained from petrolatum is indigestible and taken orally for 2 days. This agent interferes with the resorption of water in the intestine. Mineral oil also decreases the absorption of fat-soluble vitamins in the intestinal mucosa.

(b) Stimulators of fluid secretion and motility (bisacodyl, senna and cascara, and Castor oil).

The action mechanisms of these laxative stimulators is related to the activation of prostaglandin-cAMP and NO-cGMP signaling. Such agents include diphenylmethane (bisacodyl: DULCOLAX, phenolphthalein, sodium picosulfate: LUBRILAX) and anthraquinone (extracts of alooe, cascara, and senna) derivatives.

The daily oral dose of bisacodyl (DULCOLAX) ranges from 11 mg/day to 15 mg/day with an effect typically observed after 8 hours. The effect of suppositories develops after about 60 min, and is excreted in the stool. Overdosage can cause electrolyte imbalance.
Phenolphthalein is a dastric laxative and was withdrawn because its carcinogenic effect. Sodium picosulfate (LUBRILAX) is hydrolyzed by colonic bacteria, thus it acts locally in the colon.

Anthraquinone derivatives (aloe, cascara, senna) are derived from plants, but anthraquinone derivatives may be synthesized. Anthraquinones induce colonic contractions and electrolyte secretion. The laxative effect is typically observed 12 hours following oral administration. Anthraquinones are excreted via the bile, milk, and urine. Anthraquinone laxatives are not recommended for long-term use.

Castor oil (NEOLOID) is derived from the bean of the castor plant (Ricinus communis). The effective component of castrol oil is ricin, a highly toxic protein; and the triglyceride-ricinoleic acid. Glycerol and ricinoleic acid are the active components of castrol oil, which are hydrolyzed from triglyceride-ricinoleic acid in the intestine. Castor oil is used orally in a dose of 10-20 ml.

(c) Prokinetic drugs which primarily affect motility (5-HT4 receptor agonists, dopamin receptor antagonist, and motilides such as erythromycin).

Opioids, the main group of analgesics, and postoperative ileus cause constipation after abdominal and non-abdominal surgery.

5-HT receptors play an important role in secretory function of the bowel. Serotonin and stimulation of serotonin receptors both result in release of nitric oxide (NO) and reduction in smooth muscle tone. Prucalopride (RESOROL) and cisapride (PROPULSID), potent 5-HT4 receptor agonists, are under clinical investigation and effective for the treatment of reflux and chronic constipation.

Dopamine (DA) has many inhibitory effects on GI motility, which are mediated via D2 dopaminergic receptors. Thus, by antagonizing the inhibitory effect of DA, DA receptor antagonists (metoclopramide, domperidone) are effective prokinetic agents. In addition, DA receptor antagonists such as metoclopramide and domperidone are able to relieve nausea and vomiting.

Metoclopramide (REGLAN) and domperidone, beside their DA antagonizing effect, have a potent 5-HT4 receptor agonist effect in addition to their ability to antagonize DA. Both drugs antagonize the D2 receptors. Their effects are mainly localized in the upper digestive tract, and the drugs have no significant effects on large bowel motility. Metoclopramide and domperidone are well absorbed after oral administration, subsequently undergoing glucuronide conjugation by the liver and excretion in the urine. Metoclopramide and domperidone are used for the treatment of gastroesophageal reflux, and reflux induced by esophagitis. These drugs are also used for the treatment of postoperative ileus. However, most common application of metoclopramide and domperidone is to ameliorate nausea and vomiting that often accompany GI dysmotility complications. Maximal dosage of metoclopramide and domperidone is 20 mg/day. Side effects include dystonias, parkinson-like symptoms, tardive dyskinesia, and galactorrhea.

Motilides (macrolides and erythromycin) are potent contractile agents of the upper GI tract. Motilin, an amino acid peptide hormone found in M cells of the upper small bowel, is also a potent contractile agent. The effects of motilin can be mimicked by erythromycin, a macrolide antibiotic. The motilin-like effect of erythromycin is most pronounced at higher doses of 300 mg - 500 mg. Erythromycin stimulates gastric and and small bowel contractility, and at higher doses, it induces spastic constriction, cramps, and vomiting. The typical dose of
Erythromycin for GI tract stimulation is 3 mg/kg intravenously or 250 mg orally every 8 hours.

Other motilides such as sinalide (KINEVAC) and dexloxiglumide (cholecystokinin receptor antagonists) increase gastric emptying and motility. Octreotide acetate (SANDOSTATIN), a somatostatin analog, is also used for the treatment of intestinal dysmotility in patients.

Botulinum toxin (a blocker of motility, BOTOX, MYOBLOC) directly injected in esophageal sphincter suppresses gastric motility. Botulinum toxin inhibits acetylcholine release from nerve endings leading to partial paralysis of sphincter muscle with significant improvement of the treatment of esophageal reflux. This agent is used for blocking GI tract motility dysfunction of the Oddi sphincter and anal fissures.

**Antinauseant and antiemetic agents**

Sensations of nausea are generally protective reflexes to rid the GI tract of toxic chemicals and prevent their further absorption. Vomiting is a very complex process consisting of three major processes occurring in sequence (1) gastric and relaxation, (2) rhythmic contraction of respiratory muscles and diaphragm, and (3) ejection, including abdominal muscle contractions and relaxation of the upper esophageal sphincter. This complex process is coordinated by the emetic center (Figure 20) consisting of the chemoreceptor trigger zone (CTZ) in the area postrema (AP), and the solitary tract nucleus (STN).

![Figure 20. The emetic center and stimuli.](image)

The emetic center receives stimuli by the vagus nerve via the STN. Other inputs to the emetic center come from the cerebellum and the vestibular apparatus (inner ear). Cells of the CTZ express receptors for serotonin (5-HT3), dopamin (D2), muscarine (M1), and
endo
cannabinoid (CB1). Cells of the STN express 5-HT3, D2, M1, CB1, H1, and substance P (NK1) receptors, while the cerebellum has only H1 and M1 receptors. Thus, all of the aforementioned neurotransmitters are involved to different degrees and at different central stimulation sites in nausea and vomiting. Thus, an understanding of their nature may allow a rational approach to pharmacological intervention in nausea and vomiting. Antiemetic drugs are classified according to their receptors on which they act. For the prevention and treatment of nausea and vomiting, several antiemetic drugs acting at various receptors can be used in combination.

Six major classes of antiemetic agents are currently in use, broadly classified as follows:

a). 5-HT3 receptor antagonists
b). Dopamine (D2) receptor antagonists
c). Histamine (H1) receptor antagonists
d). Anticholinergic agents: muscarinic receptor antagonists (M1R)
e). Neurokinin receptor antagonists (Substance P, NK1 antagonists)
f). Cannabinoid receptor (CB1) agonists

a). 5-HT3 receptor antagonists

A prototype of 5-HT3 receptor antagonist drug is ondansetron (ZOFRAN). Ondansetron was introduced for management of nausea and vomiting in the early 1990s. Other agents of the 5-HT3 receptor antagonist category include granisetron (KYTRIL), dolasetron (ANZEMET), palonosetron (ALOXI), and tropisetron. The antiemetic effects of 5-HT3 receptor antagonists persist long after their elimination from the circulation. These drugs are typically used once daily by oral administration. These drugs are effective for the treatment of chemotherapy- and upper abdominal radiation-induced nausea and vomiting. They also may be used for treatment of postoperative nausea and hyperemesis of pregnancy. The 5-HT3 receptor antagonists are very well tolerated by patients with constipation and headache as common adverse effects.

b). Dopamine (D2) receptor antagonists

Phenothiazine drugs including chlorpromazine (THORAZINE), fluphenazine (PROLIXIN), perphenazine (TRILAFON), trifluoperazine (STELAZINE), and prochlorperazine are among the commonly used antiemetics and antinauseants. Their pharmacological effects are very complex, but their principal antemetic and antinauseant action mechanisms are known to occur via D2 receptor antagonism at CTZ and STN. These agents also possess anticholinergic (antimuscarinic at M1 receptors) and antihistaminic (at H1 receptors) activities, which are of value in nausea due to movement (motion sickness) through mechanisms in the cerebellum. These drugs have also been used as antipsychotic and antischizophrenic agents as discussed in the chapter of the central nervous system (CNS), which describes pharmacotherapy of CNS diseases. Antipsychotic and antischizophrenic effects related to D2 receptors target the limbic, mesolimbic and mesocortical systems of the CNS where antipsychotic and antischizophrenic effects are mediated. The behavioral effects of these drugs parallel D2 receptor occupancy causing psychomotor agitation, decreased social isolation, and less interference by disorganized and delusional thoughts and hallucinations.
c). Histamine (H1) receptor antagonists

H1 receptor antagonists are inverse agonists that decrease constitutive activity of histamine receptors and compete with histamine. Histamine receptor antagonists are mainly useful for the treatment of nausea and emesis induced by motion sickness and operations. These drugs include promethazine (PHENERGAN), cyclizine (MAREZINE), dimenhydrinate (DRAMAMINE), diphenhydramine (BENADRYL), and hydroxyzine (ATARAX). Beside their antihistaminic effects, these drugs possess antidopaminergic (D2 receptor-specific) and antimuscarinergic (M1 receptor-specific) effects. H1 receptor antagonists are also used for treatment of allergies, urticaria, and insomnia. H1 antagonists inhibit the vasoconstrictor effects of histamine, and a rapid vasodilator effect is mediated by activation of H1 receptors on endothelial cells leading to the release of nitric oxide (NO), a potent vasodilator molecule.

d). Anticholinergic agents: muscarinic receptor antagonists (M1R)

Muscarine receptor antagonists block the effects of acetylcholine by preventing its binding to muscarine receptors at parasympathetic and sympathetic cholinergic neuroeffector junctions, in peripheral ganglia, and in the central nervous system. Atropine and scopolamine (TRANSDERM-SCOP) are the most commonly used muscarinic receptor antagonists. Both drugs are typically administered by intravenous injection as sulfate and hydrobromide derivatives, respectively. Their application is mainly in prevention and treatment of postoperative nausea, vomiting, and motion sickness. Other important therapeutic uses of muscarine receptor antagonists include the decrease of intestinal tone and motility, and reduction of gastric and salivary gland secretion. Vagal effects on heart rate are also inhibited, thus the heart rate is increased by M1R antagonists. M1R antagonists in clinical use are are nonselective, and their effects vary little from those of atropine and scopolamine. Variations in clinical efficacy of muscarinic receptor antagonists arises from a balance of antagonistic effects on two or more muscarinic receptor subtypes. The standard doses of atropine and scopolamine range between 1-2 mg/day, but in certain conditions (e.g., organophosphate-induced toxicity) it can be over 30 mg/day.

e). Neurokinin receptor antagonists (Substance P, NK1 antagonists)

NK1 receptors are expressed by cells of the solitary tract nucleus. The drugs, Aprepitant and fosaprepitant (EMEND), bind to NK1 receptors resulting in antiemetic effects, especially in cancer patients who have received extensive chemotherapy. Aprepitant and fosaprepitant are bound to plasma proteins, and metabolized by hepatic cytochrome oxidase enzymes (CYP) and excreted in stool. The main indication for use of these two drugs is occurrence of nausea and vomiting in cancer patients. Undergoing chemotherapy, the standard dose of these drugs is 125 mg/day in combination with 5-HT3 receptor antagonists.

f). Cannabinoid receptor (CB1) agonists

Dronabinol (delta-9-tetrahydrocannabinol) is a naturally occurring cannabinoid extracted from Cannabis sativa, and nabilone (CESAMET) is a syntethic cannabinoid with the same action of those of dronabinol. The action mechanism of both agents is related to the stimulation of cannabinoid (CB) receptors on neurons in the vomiting center (chemoreceptor trigger zone and solitary tract nucleus). Dronabinol and nabilone are lipid soluble structures and well absorbed after oral administration. Both drugs are used prophylactically in patients undergoing cancer chemotherapy. Typically they are used when other antiemetic agents are
ineffective. Both drugs also can stimulate appetite and are used in patients afflicted with immunodeficiency syndrome (AIDS) and anorexia. Dronabinol and nabilone have central sympathomimetic activity on the CNS. Adverse effects include include palpitations, vasodilation, hypotension, and cardiac arrhythmias. Supervision of patients receiving them is necessary since dronabinol and nabilone cause psychotropic effects, which include euphoria and panic reaction.

**Biliary and pancreatic diseases**

The bile produces various acids that are synthesized from cholesterol in the liver. The major bile acids include cholic acid, chenodeoxycholic acid, deoxycholic acid, lithocholic acid, and ursodeoxycholic acid. Functions of bile acids include (1) feedback-inhibit cholesterol synthesis, (2) intestinal cholesterol excretion, (3) absorption of fat-soluble vitamins and lipids. Bile acids are reabsorbed in the terminal ileum, return to the liver, and then are secreted again in the bile, participating in the enterohepatic circulation. Ursodeoxycholic acid (ACTIGALL) is a dehydroxylated bile acid that is converted by intestinal bacteria to chenodeoxycholic acid, a functional component of bile acids. Bile acids and their diols, such as ursodiol, are used for the treatment of biliary cirrhosis and cystic fibrosis at a concentration of 15 mg/kg/day.

**Pancreatitis** results from the loss of exocrine and endocrine glandular function, and the development of inflammation and pain. Therapies for this disorder target the malabsorption of pancreatic enzymes and mediate palliation of pain and inflammation. Pancrelipase (CREON) contains various amounts of protease, amylase, and lipase. It may reduce the progress of chronic pancreatitis.

Malabsorption of fats (steatorrhea) and protein digestion occur, if the pancreas fails to produce adequate levels of digestive enzymes. Malabsorption and diarrhea associated with pancreatitis is typically treated with 30,000 units of pancreatic lipase. The preparation of pancreatic enzymes contains 20,000 units of lipase and 76,000 units of protease. Pancreatic amylase associated with this treatment loss is not a major problem since the salivary glands produce sufficient amount of amilase. Pain is another symptom of chronic pancreatitis and its treatment with pancreatic enzymes is based on negative feedback inhibition by doudenal proteases in the pancreas. The release of cholecystokinin (CCK) is triggered by CCK-releasing peptide in the duodenum, which is denatured by pancreatic trypsin. Trypsin insufficiency leads to the activation of this peptide and increases the release of CCK, which causes pancreatic pain. Delivery of proteases into the duodenum may lead to interruption of this process. Adverse effects of protease therapy include hyperuricosuria, cystic fibrosis, and folate and iron absorption.

**(iii) Treatment of intestinal bowel disease**

Intestinal bowel disease (IBD) also known as inflammatory bowel disease is a chronic intestinal illness. IBD gastrointestinal symptoms include abdominal pain, diarrhea, bleeding, anemia and loss of weight. IBD may contribute to development of spondylitis, arthritis, iritis, uveitis, erythema nodosum, and pyoderma gangrenosum. IBD can be classified into two subtypes including (1) ulcerative colitis and (2) Crohn’s disease. Ulcerative colitis consists of inflammation of the colon mucosa starting at the anal segment, and extending proximally. Crohn’s disease is a transmural inflammation of any segment of the gastrointestinal tract, but usually is close to the ileocecal valve. Inflammation associated with this disorder may lead to fibrosis and fistula formation.

The pathogenesis of IBD is very complex, and is related to hyperactivation of a network of immune cells, including monocytes, dendritic cells; neutrofils; Helper T cells;
CD4+ lymphocytes secreting cytokines such as interleukin (IL)-4, IL-6, IL-12, and IL-18; transforming growth factor beta, interferon gamma; and tumor necrosis factor alpha. Pharmacological interventions include the inhibition of the function of the aforementioned agents and molecules.

At the time of this writing, specific pharmacotherapies capable of including remission of IBD and other severe inflammatory pathologies are not available to the general public. However, a highly promising approach developed at the University of Debrecen, in Hungary, and approved for use in patient treatment at a major U.S. Hospital (New York Eye and Ear Infirmary, in New York City) shows enormous treatment in IBD. This treatment, known as “Tolovax” is a two-phase therapeutic approach, which first reduces systemic oxidative stress in a patient by appregulating activity of heme oxygenase-1 (HO-1) using dermaly delivered sour cherry biosour cherry seed biflavones, which include HO-1 induces. Such reduction in oxidative stress allows natural immunoregulatory mechanisms to function more effectively. The second phase of Tolovax therapy involves subcutaneous vaccination of an IBD patient with a preparation of heat shock proteins and other stress-response antigens. These agents catalyze conversion of pathogenic activated T lymphocytes to T-regulatory immunophenotypes (T-reg). Activity of Tolovax-induce T-reg in the gastric mucosa downregulates pathological inflammation. Tolovax is a particularly attractive management strategy for IBD and all other forms pathologically dysregulated inflammation based on three major features: (1) No adverse effects, (2) very low cost, and (3) easily administered.

Thus, the aims of the IBD treatment include prevention of the exacerbation of the disease and supression of fistulas. Although specific treatment for IBD is not available, (a) 5-aminosalicylic acid (5-ASA), (b) glucocorticoids, (c) immunosuppressives, e.g., 6-mercaptopurine and methotrexate, (d) biological response modifiers, e.g., infliximab, and (e) antibiotics.

(a) 5-aminosalicylic acid (5-ASA)

Mesalamine (5-aminosalicylic acid, 5-ASA) is used for the treatment of moderate and mild ulcerative colitis. Beside The drug was initially introduced for the therapy of rheumatoid arthritis. Although mesalamine is a salicylate derivative, its action mechanism is not related to the inhibition of cyclooxygenase enzyme in patients afflicted with IBD. The action mechanism of mesalamine is complex, and can be explained by the inhibition of NF-kappaB, scavenging of reactive oxygen species, and influence on the lipoxygenase pathway. Other derivatives of 5-ASA which are used for the treatment of IBD include olsalazine (DIPENTUM) and balsalazide (COLAZIDE). The delayed release formulations of these drugs are named PENTASA and ASACOL, which are commercially available. The typical dose of mesalamine, olsalazine, and balsalazide is between 1 g/day and 6 g/day in Crohn’s disease. These drugs are useful in preventing relapses once remission has been achieved.

About 20 % of orally administered mesalamine, olsalazine, and balsalazide are absorbed in the small intestine and the remaining 80% reaches the colon. Once absorbed, the drugs follow various metabolic pathways including hydroxylation and acetylation, conjugation with glucuronic acid in the liver, and excretion via the urine. Side effects may be manifested as ulcerative colitis, headache, fatigue, nausea, allergic reactions, fever, dyspepsia, hepatitis, pneumonitis, nephrotoxicity, and bone marrow suppression.

(b) Glucocorticoids

The application of glucocorticoids in either ulcerative colitis or Crohn’s disease is indicated for moderate to severe IBD. Patient reaction to to these drugs may be responsive,
unresponsive, or dependent. About 35% of patients are glucocorticoid responsive, 35% have partial response, and 30% are refractory to this therapy. Failure to respond to steroids requires alternative therapies such as anti-TNF-alpha and/or immunosuppressive therapies. Initial doses of methylprednisolone and hydrocortisone or their equivalents are typically 20 mg/day to 50 mg/day, and these may be slowly tapered over months. Responses to glucocorticoids may develop within two weeks and persist during their application in glucocorticoid responsive patients. Glucocorticoid enemas are effective in patients whose diseases are localized in the left colon or rectum. Budesonide (ENTOCORT ER) is used for ileocecal Crohn’s disease localized to the left side of the colon. The optimal initial dose of budesonide is 8 mg/day followed by 6 mg/day for 3 months. Complications of glucocorticoids include multidrug resistance, abscesses, sepsis, and infections with organisms such as cytomegalovirus and Clostridium difficile.

(c) Immunosuppressives

Many therapeutic agents initially developed for tumor chemotherapy and immunosuppression have been adapted for IBD treatment. Mercaptopurine (PURINETHOL) and azathioprine (IMURAN) are used in patients afflicted with severe IBD which is resistant to steroid treatments. Azathioprine is converted to mercaptopurine which is metabolized to thioguanine nucleotides that are effective components. Both mercaptopurine and azathioprine are effective in Crohn’s disease and ulcerative colitis at doses of between 1 and 3 mg/kg. Adverse effects involve idiosyncratic reactions (the most serious is pancreatitis), fever, rash, nausea, vomiting, and bone marrow suppression. Blood counts and liver function must be monitored during therapies. The risk of infections is a significant concern with immunosuppressive and glucocorticoid therapies. These therapies are also associated with an increased incidence of non-Hodgkin’s lymphoma. The enzymes, which are responsible for the metabolism of mercaptopurine, include xanthine oxidase, thiopurine methyltransferase, and hypoxanthine-guanine phosphoribosyl transferase.

Methotrexate inhibits dihydrofolate reductase, therefore blocks DNA synthesis leading to cell death. Other than its role in tumor therapy, methotrexate has beneficial effects in the treatment of autoimmune diseases such as rheumatoid arthritis and psoriasis. Methotrexate is used also, as mercaptopurine and azathioprine, for the treatment of steroid-resistant Crohn’s disease at a dose of 25 mg/week. The application of methotrexate for IBD is frequently supplanted by biological therapy including anti-TNFalpha antibodies.

(d) Biological response modifiers, e.g., infliximab

Infliximab (REMICADE) is a combined immunoglobulin (75% human and 25% mouse) that neutralizes and binds to TNF-alpha. TNF-alpha is one of the cytokines mediating T_h1 (type 1 Helper T cells) immune response characteristic of Crohn’s disease. Infliximab at doses of 5 mg to 10 mg decrease the frequency of acute flares in Crohn’s disease and facilitate the closing of enterocutaneous fistulas. Infliximab is frequently combined with azathioprine in steroid-resistant patients.

Acute and subacute reactions of infliximab such as urticaria, fever, chills, anaphylaxis, and lupus-like syndrome occur as adverse effects. Infliximab treatment is also associated with elevated incidence of respiratory infections and reactivation of tuberculosis. The drug is contraindicated in congestive heart failure.

Other biological response modifiers, including recombinant human monoclonal antibodies, against TNF-alpha (anti TNF-alpha agents) in Crohn’s disease include adalimumab (HUMIRA), etanercept (ENBREL), and natalizumab (TYSABRI). The
importance of anti-TNF therapy is less clear in ulcerative colitis. However, it is clear that elevated levels of TNF-alpha were detected in patients suffered from ulcerative colitis.

(e) Antibiotics

The physiological functions of the GI tract are distributed among tissues of the mucosal epithelium, immune cells, and the natural gut flora. Many bacterial strains e.g., Bacteroides, Lactobacillus), may manipulate the normal colonic flora in IBD patients. Thus, antibiotics are used for the latter reason in patients afflicted with Crohn’s disease. Thus, antibiotics can be used as (1) adjunctive treatment with other drugs in IBD patient, (2) specific therapy, and (3) prevention of the recurrence of Crohn’s disease.

Metronidazole, clarithromycin, and ciprofloxacin are most frequently used antibiotics in Crohn’s disease. The indication of these antibiotics, in Crohn’s disease, includes fistulas and perirectal abscesses in the perianal region, bacterial overgrowth due to small bowel obstruction, secondary infection caused by C. difficile, and various postoperative infections. Crohn’s disease may also be managed by probiotic mixtures of lyophilized bacteria given orally. In supplementary therapy, loperamide or diphenoxylate can be used to decrease the frequency of bowel motility. Beneficial effects of probiotics are proven in ulcerative colitis and pouchitis. Up to now, however, the application of probiotics as a primary or adjunctive therapy for the treatment of IBD remains unclear.

In summary, strategies for treatment of IBD may have several desired outcomes including the relief of symptoms, prevention of relapse, and healing of fistulas. Acute ulcerative colitis related to inflammatory processes may be treated with 5-ASA (mesalamine), glucocorticoids or tolovax. Purine metabolites (azathioprine, mercaptopurine) and probiotic bacteria may be also used. Crohn’s disease can be pharmacologically managed by azathioprine, mercaptopurine, methotrexate, and corticosteroids. Antibiotics, especially metronidazole, are useful adjuncets for the treatment of acute Crohn’s disease.
ASTHMA AND PULMONARY PHARMACOLOGY

Pulmonary pharmacology is an area of medical practice focused on use of drugs for therapy of airway obstruction. Including prominently among these disorders are asthma and chronic obstructive pulmonary disease (COPD), which are among the most common chronic diseases in the world. Asthma and COPD are both characterized by chronic inflammation of airways, although there are substantial differences in mechanisms of inflammation and responses to pharmacotherapy between these two diseases. In the present chapter, pharmacotherapy for asthma and COPD, using beta-2 agonist and corticosteroid treatments is explored. The present chapter also describes other drugs used for obstructive airway diseases including mucolytics, respiratory stimulants, therapies for cough, which is the most common respiratory symptom, and drugs used for the treatment of pulmonary hypertension.

Asthma is a chronic inflammatory disease characterized by activation of mast cells, infiltration of eosinophils, and T helper 2 (T\(\text{H}2\)) lymphocytes (Figure 21).

![Diagram of asthma and pulmonary pharmacology](image-url)

Figure 21. The release of inflammatory mediators leads to bronchoconstriction and asthmatic attack.
The activation of mast cells by physical stimuli and allergens (e.g., pollen, dust) releases bronchoconstrictor mediators including histamine, prostaglandin D2, and leukotriene D4, which produce bronchoconstriction, vascular leakage, and plasma exudation. Other mediators such as cytokines, chemokines, and growth factors also play important role in the development of asthma. The accumulation of mast cells in airway smooth muscle is a characteristic of asthma. Asthmatic inflammation may also be mediated by dendritic cells, which stimulate the activities of eosinophils, aggravating the severity of asthmatic attacks. Chronic asthmatic inflammation leads to subepithelial fibrosis, airway smooth muscle hypertrophy, angiogenesis, and hyperplasia of mucus-secreting cells. A histological feature of asthma is collagen deposition (fibrosis) under the basement membrane of the airway epithelium. Symptoms of asthma in most cases can be well managed by corticosteroids and beta-2 adrenoreceptor stimulators. Inflammation in patients with severe asthma is similar to COPD and may lead to reduced responsiveness to corticosteroid treatments.

Chronic obstructive pulmonary disease (COPD) differs from asthma, because in the development of COPD, neutrophils, macrophages, and cytotoxic T-lymphocytes (Tc1 cells) play a primary role. COPD leads to small airway narrowing, chronic obstructive bronchiolitis (fibrosis), destruction of alveolar walls, and emphysema (Figure 22). These changes result in airway closure on expiration and account for shortness of breath on exertion and characteristic symptoms of COPD.

![Figure 22. Pathways of chronic obstructive pulmonary disease (COPD) leading to fibrosis, emphysema, and mucus hypersecretion.](image-url)

Bronchodilators increase interface between air and the pulmonary vascular bed by dilatation of peripheral airways. These drugs are currently the major pharmacological tools in COPD treatment. Inflammation in COPD is a very complex process. In the peripheral lung-airway system, tissue damage is mediated by multiple inflammatory mediators and metabolites, and differs from that of asthma. In contrast to asthma, the majority of COPD patients are resistant to corticosteroid therapy. In addition, COPD patients exhibit a wide
range of comorbidities, including skeletal muscle wasting, weight loss, osteoporosis, anemia, depression, and other comorbid diseases such as diabetes, congestive heart failure, angina, and hypertension. Drugs can be delivered to the lung by oral or parenteral routes, and by inhalation. The selection of drug administration route depends on COPD severity. Generally, inhalation is the preferred route of delivery into airways for the treatment of asthma and COPD. The major advantage to inhalation of a drug is lower occurrence of systemic side effects. Additionally, inhaled bronchodilators have a more rapid onset of action than do those taken orally. For most therapeutic regimens, the optimum size of inhaled particles is between 2 and 5 microns. Drug inhalation for treatment of asthma and COPD can be done by pressurized metered-dose inhalers, spacer chambers, dry powder inhalers, and nebulizers.

The main classes of bronchodilators include the following drug categories: (a) beta adrenergic agonists (beta sympathomimetics), (b) methylxanthine (e.g., theophylline), (c) muscarin receptor antagonists, (d) corticosteroids, (e) other asthma and COPD mediator antagonists, (f) immunomodulators, (g) emerging novel pharmacological strategies in management of asthma and related disorders, and (h) therapy of pulmonary arterial hypertension.

(a) Beta adrenergic agonists (beta sympathomimetics)

Inhaled beta2 adrenergic receptor agonists are the most effective bronchodilators in the treatment of acute asthmatic attacks. Systemic and nonselective beta adrenergic receptor agonists should be only used as the measure of final resort. The chemical structure of beta2 adrenergic receptor agonists derives from substitutions to the rings of epinephrine and norepinephrine. Thus, changes in epinephrine and norepinephrine structures resulted in beta2 adrenergic receptor selectivity and led to albuterol (salbutamol) and terbutaline.

Salbutamol and terbutaline stimulate beta2 adrenergic receptors resulting in the activation of Gs adenyl cyclase - cAMP - PKA - cascade and the relaxation of bronchial smooth muscle. The mechanisms by which beta2 adrenergic receptor agonists lead to relaxation of bronchial smooth muscle are complex and include:

- Lowering of intracellular calcium concentration.
- Inhibition of PLC (phospholipase C) – IP3 (inositol triphosphate) pathway.
- Activation of myosin light chain phosphatase.
- Opening of Ca-activated K channels.
- Increase cAMP levels by the activation cAMP-regulated proteins.

Beta2 adrenergic receptor agonists may induce bronchodilation by direct action via beta2 adrenergic receptor stimulation, and also indirectly by suppressing the release of bronchoconstrictor mediators from inflammatory cells and bronchoconstrictor neurotransmitters from bronchial nerves. The aforementioned indirect mechanisms include:

- Inhibition of mediator release from mast cells via beta2 adrenergic receptors.
- Prevention of microvascular leakage and edema formation by inhibiting activity of histamine and leukotrien D4.
- Increasing of mucus secretion from submucosal glands, thus enhancing mucociliary clearance and reversing the defective clearance in asthma.
- Decreasing neurotransmitter release in airway cholinergic nerves by inhibiting of acetylcholine release at presynaptically located beta2 receptors.

Short acting and inhaled beta2 adrenergic receptor agonists: These drugs are the most effective bronchodilators in the treatment of acute severe asthmatic attacks. As inhalants, they provide rapid onset relief, are easy to use, and cause no significant systemic side effects. The
use of oral and intravenous routes of beta2 adrenergic receptor agonists produces more severe side effects in comparison with those administered by inhalation. Short-acting beta2 adrenergic receptor agonists available in clinical use include salbutamol levalbuterol, metaproterenol, terbutaline, fenoterol, tulobuterol, pirbuterol, and rimiterol.

**Long-acting inhaled beta2 adrenergic receptor agonists (LABA):** This class of drugs, which includes salmeterol, formoterol, and arformoterol have a prolonged (longer than 12 hours) protective effect in the treatment of asthma and COPD. LABAs are frequently combined with glucocorticoids (ADVAIR and SYMPLICORT (fluticasone and salmeterol, budesonide and formoterol), are widely used for both the treatment of asthma and COPD. These combinations are more effective in COPD treatment than LABA or glucocorticoid treatment alone.

Major side effects of orally and intravenously administered short acting beta2 adrenergic receptor agonists and LABAs are due to stimulation of extrapulmonary beta adrenergic receptors. These side effects include (1) muscle tremor due to the stimulation of beta2 adrenergic receptors in skeletal muscles, (2) ventricular tachycardia and palpitation due to peripheral vasodilation and the direct stimulation of atrial beta2 adrenergic receptors, (3) and hypokalemia due to beta2 adrenergic receptor stimulation of K⁺ entry into skeletal muscle, which is related to insulin secretion in the pancreas, (4) ventilation perfusion, which is related to vasodilation in pulmonary vessels, and (5) metabolic effects related to fatty acid, glucose, and insulin utilities and consumption.

Additional side effects: Continuous, long-term application of beta2 adrenergic receptor agonists can lead to desensitization and subsensitivity, which may occur due to downregulation of beta2 adrenergic receptors. Moreover, a marked increase was reported in the risk of death in asthmatic patients treated with high doses of beta2 adrenergic receptor agonists, but when doses were adjusted and reduced no significant difference in the risk of death was observed. In some cases, inhaled beta2 adrenergic receptor antagonists may increase allergen-induced asthma and sputum eosinophilia. A possible mechanistic explanation for this phenomenon is that beta2 adrenergic receptor antagonists may upregulate the expression of PLC (phospholipase C)-beta1 receptors, resulting in an increase of bronchoconstrictor responses to cholinergic agonists. Beta2 adrenergic receptor agonists are the first choice for the treatment of asthma because they are effective in all patients and have a low to negligible incidence of side effects when applied in low doses. Other beta2 adrenergic receptor antagonists used for asthma therapy include indacaterol and carmoterol.

(b) Methylxanthine (e.g., theophylline)

Methylxanthines, such as theophylline, have been used for the treatment of asthma since 1930s. Theophylline is still frequently used for the treatment of asthma, although its effectiveness is much less in comparison with beta2 adrenergic receptor agonists. Nevertheless, for patients afflicted with severe asthma and/or COPD, theophylline remains a very useful drug. The structure of theophylline is very similar to theobromine and caffeine. Several salts of theophylline are marketed, and the most common of which is aminophylline, which is the ethylenediamine salt of theophylline. Theophylline is the major methylxanthine in clinical therapy. The action mechanisms of theophylline are complex and include:

- Inhibition of various phosphodiesterease (PDE) enzymes leading to the increase of cellular cAMP and cGMP levels and bronchodilation. Several isoenzymes of PDE have been discovered, and the inhibition of PDE3, PDE4, and PDE5 are responsible for smooth muscle relaxation in the bronchi.
- Blockade of adenosine receptors. Adenosine causes bronchoconstriction by stimulation of A1 receptors in airway smooth muscles.
- Increase IL-10 expression, which also may lead to bronchodilation.
- Inhibition of translocation of the proinflammatory transcription factor NF-kappaB into the nucleus, resulting in blockade of COPD- and asthma-associated gene expression.
- Promotion of apoptosis (program cell death) in eosinophils and neutrophils, thus, reducing inflammation in the lung.
- Activation of histone deacetylase-2, thereby increasing the antiinflammatory effects of corticosteroids.
- Theophylline inhibits the late response to inhaled allergen and reduces infiltration of eosinophils and CD4+ lymphocytes into the airways after allergene challenge.

Therapeutic concentrations of theophylline for the treatment of asthma are between 10-20 mg/liter in plasma. The dose of theophylline given intravenously is typically 6 mg/kg. Theophylline is frequently given with beta2 adrenergic receptor agonists for the treatment of asthma and COPD. Theophylline is administered as aminophylline composition in acute asthma. Theophylline is completely absorbed after oral application and metabolized in the liver by CYP1A2 enzyme. Side effects of the drug, if concentrations are higher than 20 mg/liter in the plasma, include nausea and vomiting, headaches, gastric discomfort, cardiac arrhythmias, diuresis, and epileptic seizures.

(c) Muscarin receptor antagonists

Blockade of the effects of acetylcholine (Ach) at the muscarinic receptor is a powerful intervention for the relief of asthma in the lung. Datura stramonium, Hyoscyamus niger and related species contain a mixture of muscarinic antagonists such as atropine, hyoscyamine, and scopolamine, which have been used as a smoked inhalant for the relief of asthma for hundreds of years. As a consequence, atropine, a purified alkaloid was introduced for the treatment of asthma. Due to the inhibition of critical endocrine activity, less soluble quaternary compounds e.g., atropine methylnitrate and ipratropium bromide have been developed and applied in asthma therapy.

This class of drugs competitively antagonize the effects of (Ach) at muscarinic cholinergic receptors, leading to the prevention of the acetylcholine-induced direct smooth muscle constriction via the M3-PLC-IP3-Ca2+ mechanism in airways and the lung. Ach promotes bronchoconstriction, augments secretion by tracheobronchial tract tissue and stimulates chemoreceptors in the carotic and aortic bodies. Therefore, the prevention of bronchial smooth muscle constriction by antagonizing of the function of muscarinergic receptors is an important therapeutic target in asthma and COPD. In asthmatic subjects, anticholinergic drugs are less effective bronchodilators than beta2 adrenergic receptor agonists. However, anticholinergic drugs are used as additional bronchodilators in asthmatic subjects not under treatment with long-acting inhaled beta2 adrenergic (LABA) receptor agonists. In COPD patients, anticholinergic drugs may be as effective or even superior to beta2 adrenergic receptor agonists. The greater effectiveness of anticholinergic drugs in COPD patients than in asthmatics can be explained by an inhibitory effect on vagal tone. Anticholinergics reduce air trapping and increase exercise tolerance in COPD patients. Combination of an anticholinergic and B2 adrenergic receptor agonist, e.g., ipratropium and albuterol (DOUNEBO, COMBIVENT) is very effective in the treatment of COPD.

Adverse effects of anticholinergic agents include reduction of gland secretion leading to more viscous mucus, unpleasant bitter taste, glaucoma in elderly patients, and urinary retention. New anticholinergic bronchodilators such as glycopyrrolate and aclidinium are under clinical development.
(d) Corticosteroids

Glucocorticoid therapies are a basic tool in the treatment of several inflammatory lung diseases and remain the most effective pharmacotherapy available for asthmatic patients. However, the often severe side effects of these drugs led to the investigation of new related agents, which retain beneficial effects of glucocorticoids on airway tracts without significant adverse effects. Asthma is a chronic inflammatory disease, therefore, inhaled corticosteroids (ICS) are first line drugs for its treatment. ICS drugs are less effective in the management of COPD and may be used by patients afflicted with severe diseases who experience frequent exacerbations. Thus, oral glucocorticoids may be used for the treatment of sarcoidosis, pulmonary eosinophilic syndromes, and interstitial lung diseases.

The adrenal cortex produces cortisol (hydrocortisone), which is an endogenous steroid antiinflammatory compound. Modification of its structure has resulted in synthetic glucocorticoid derivatives such as prednisolone, prednisone, bethametasone, and dexamethasone. These compounds exhibit amplified corticosteroid effects but with reduced mineralocorticoid activities. Glucocorticoids enter target cells (Fig. 23) and bind to glucocorticoid receptors (GRs) in the cytoplasm. Subsequently, the GRs-steroid complex translocates into the nucleus and binds to certain target genes causing an increased transcription of these genes resulting in increased or reduced synthesis of gene products (Fig. 23). GRs may also interact with various protein transcription factors in the nucleus and affect synthesis of certain proteins independently any direct effects on DNA. The repression of various transcription factors, such as NF-kappaB and activator protein-1 (AP-1), is responsible for the antiinflammatory effects of glucocorticoids in asthma. In addition corticosteroids possess inhibitory effects on MAP kinase signaling pathways through the induction of MKP-1, which inhibits the expression of various inflammatory genes.
Figure 23. Antiinflammatory action mechanism of glucocorticoids in asthma. Inflammatory stimuli (IL-1Beta, TNF-alpha) results in activation of NF-kappaB in the cytoplasm inducing formation of the NF-kappaB p65 and p50 protein complex. This protein complex translocates into the nucleus where it promotes histone acetylation. Glucocorticoids prevent histone acetylation and gene transcription or repression.

The complex action mechanism of glucocorticoids potentially inhibits the expression of cytokines such as IL-1, IL-3, IL-4, IL-5, IL-9, IL-13, TNFalpha, and granulocyte-macrophage colony stimulating factor (GM-CSF), which are secreted by macrophages, mast cells, and T-lymphocytes in asthma. In addition, glucocorticoids also decrease the number of eosinophils by inducing apoptosis.

Systemic adverse effects of glucocorticoids include (1) inhibition of ACTH and cortisol secretion by a negative feedback mechanism in the pituitary gland, (2) fluid retention, (3) hypertension, (4) increased appetite and weight gain, (5) peptic ulceration, (6) diabetes, (7) cataracts and glaucoma, and (8) psychosis. Local side effects (9) in the respiratory tract involve the development of oropharyngeal candidiasis, cough, and dysphonia.

Many inhaled corticosteroids (ICS) are available for the pharmacotherapy of asthma, such as beclomethasone (QVAR), fluticasone (AEROSPAN, FLOVENT), ciclesonide (ALVESCO), mometasone (ASMANEX), and budesonide (PULMICORT). Doses of these ICS are between 800-1000 micrograms. A new direction in the development of antiastmatic
agents includes the „dissociated steroids” and/or selective glucocorticoid receptor agonists (SEGRAs). Theoretically, the „dissociated steroids” or SEGRAs retain their antiinflammatory activity but have significantly reduced adverse effects. The action mechanism of these drugs involves dissociation of glucocorticoid DNA-binding activity from NF-kappaB antiinflammatory effects. As discussed above, NF-kappaB plays a critical role in the development of asthma.

(e). Other asthma and COPD mediator antagonists

Several inflammatory mediators have been implicated in asthma and COPD mechanisms, indicating that inhibition their synthesis may be beneficial in pharmacotherapy. Within this category of drugs, H1 antihistamines and antileukotrienes have been used to treat airway diseases, however their advantage versus glucocorticoids and beta2 adrenergic receptor agonists is minimal. There is also little evidence that histamine H1 receptor antagonists provide significant clinical benefit. The new generation of antihistamines, such as azelastine and cetirizine, has some beneficial effects in the treatment of asthma, but these may be unrelated to H1 receptor antagonism. Thus, antihistamines are not recommended for the treatment of asthma.

There is evidence that leukotrienes (LT) are produced in asthma and they affect airway function including bronchoconstriction, mucus secretion, plasma exudation, and eosinophil infiltration. Thus, it is reasonable to believe that blocking of LTs synthesis may be a useful pharmacological tool in the treatment of asthma. LT antagonists inhibit to some extent the bronchoconstrictor effect of inhaled LT-D4, and bronchoconstriction induced by allergens, cold air, and excercise. The same effect has been noted with zileuton, a 5-LO inhibitor (lipoxygenase inhibitor). In patients with moderate asthma, antileukotrienes produce a moderate improvement in lung function and reduce asthma-induced symptoms. In addition, leukotriene antagonists reduce the amount of eosinophils in sputum. Leukotriene antagonists are significantly less effective in asthmatic patients than inhaled glucocorticoids and B2 adrenergic receptor agonists. Thus, leukotriene antagonists cannot be considered as first choice in asthma therapy. 5-LO inhibitors, that inhibit LTB4 synthesis may have some beneficial effect by reducing neutrophil-induced inflammation.

Adverse effects of leukotriene antagonists (zileuton, zafirlukast, montelukast) include hepatic dysfunction, vasculitis (Churg-Strauss syndrome), and peripheral nerve stimulation.

(f) Immunomodulators

Immunosuppressants are typically not the primary drugs of choice for management of asthma due to their adverse effects. However, immunosuppressive therapy may be used in asthma for patients who either cannot tolerate or are refractory to glucocorticoids. Immunosuppressives include methotrexate, cyclosporine A, auruin (a gold-based drug), and intravenous immunoglobulin. However, immunosuppressive therapy in asthma is less effective than oral or inhaled glucocorticoid or beta2 receptor agonist treatment, therefore, cannot be routinely recommended in clinical practice.

Anti-IgE therapy is a major strategy for treatment of allergic asthma. One representative drug in this class is omalizumab a human monoclonal antibody that inhibits the binding of IgE to high affinity IgE receptors (Fc-epsilon-R1) in mast cells, thus prevents the activation of receptors by antigens. Omalizumab interferes with the binding of IgE to low affinity IgE receptors (Fc-epsilon-R2, CD23) located on T and B lymphocytes, eosinophils, and macrophages, preventing the chronic inflammation. This drug is administered to patients
with severe asthma by subcutaneous injection every 3 weeks. Omalizumab reduces dosage requirements for glucocorticoids in asthma, and also effective in the treatment of allergic rhinitis.

**Specific immunotherapy** should also be effective in the prevention of asthma. Although specific immunotherapy is effective in allergic rhinitis, there is no evidence that desensitizing injection to allergens is effective in asthma. More specific immunotherapies may be developed with cloned allergen epitopes, vaccines of conjugated allergens, CpG oligonucleotides, and T-cell peptide fragments of allergens.

(g) Emerging novel pharmacological strategies in management of asthma and related disorders: Role of "Phytochemical Synergy"

At the time of this writing intensive efforts are being made to identify compounds capable of preventing inflammatory tissue damage without the debilitating side effects associated with corticosteroids and other antiinflammatory drugs currently in use.

Disregulated inflammation is a common mechanism leading to symptoms or pathology of many illnesses including asthma, COPD and other pulmonary disease. Pathological inflammation is currently treated with small molecule drugs that are typically designed to act at single critical checkpoints in the inflammatory cascade. This strategy may be effective for suppressing major symptoms of many diseases. However severe inflammatory disease is rarely cured by anti-inflammatory drugs and long-term treatments are often limited by drug cost and toxicity. Many phytochemicals widely distributed in human diet, particularly in common spices and in medicinal herbs such as *Ginkgo biloba*, have anti-inflammatory properties, but are individually non- or marginally therapeutic. It has been shown that multiple phytochemicals may interact collectively to achieve efficacy similar to pharmaceutical drugs. A major limitation to use of phytochemicals in healthcare is that most of compounds individually have very low potencies and require high doses to achieve even modest efficacy. These limitations can however be overcome by use of formulations more reflective of a healthy diet, containing multiple phytochemicals that interact collectively. It was demonstrated that ginkgolides, the component phytochemicals of *Ginkgo biloba*, interact additively and in some cases synergistically with NSAIDS, major immunosuppressants and other phytochemicals to inhibit inflammatory tissue damage and biomarkers of inflammation in asthma, cardiovascular disease and rheumatoid arthritis. These effects were demonstrated in cultured human cells and in allergen-induced asthmatic animal models.

Seven classes of pharmacological agents have shown particular promise in management of asthma, allergic disease and COPD while avoiding seriously adverse side effects. These are summarized briefly below:

i. *Ginkgolides*: These compounds derived from leaves of *Ginkgo biloba* include polyphenolic compounds which mediate several processes know to diminish the toxic effects of oxidative stress and contribute to strengthening of normal homeostatic control of inflammation. Of particular interest are the terpene lactone ginkgolides, notably Ginkgolide B (GB, BN52021), which is strongly antagonizes the platelet activating factor receptor. GB-mediated PAF inhibition, in pulmonary CD3+ T lymphocytes, significantly downregulates pro-inflammatory signaling in these cells. This effect in human T cells has been extensively characterized, in work that has served as a basis for development of a very promising approach to management of asthma, COPD and many other chronic inflammatory disorders.
ii. *Antioxidants*: Oxidative stress plays a role in the development of many diseases including asthma and COPD. Although antioxidants alone are only marginally effective in treatment of pulmonary diseases, their use in combination with glucocorticoids and beta2 adrenergic agonists has proven beneficial in some treatment regimens.

iii. *Endothelin antagonists*: Endothelin (ET) is a major mediator of pathological remodeling of airway tissue architecture in asthma and COPD. ET antagonists, which are currently used for treatment of pulmonary hypertension may prove be a useful tool in suppression of asthma- and COPD-induced remodeling.

iv. *Chemokine inhibitors*: Several chemokines implicated in the pathogenesis of asthma and COPD also play an important role in recovery by influencing the function of eosinophils, neutrophils, macrophages, and lymphocytes in pathological processes. Thus, the blockade of chemokine receptors (CCR3 receptors), which may result in reduced eosinophil migration in the lung may be an important strategy in the treatment of asthma and COPD.

v. *NF-kappaB inhibitors*: NF-kappaB is a transcription factor that enables expression of a diverse range of protein mediators which contribute to inflammatory pathologies including asthma and COPD. Therefore, inhibition of NF-kappaB and downstream metabolites is likely to emerge as a valuable tool in therapy for asthma and COPD.

vi. *Mitogen-activated protein kinase (MAPK) inhibitors*: Blockade of MAPK activity, especially by p38 MAPK blockers may reduce severity of inflammatory tissue damage in asthma and COPD by interfering with cellular signaling leading to symptoms of these diseases.

vii. *Miscellaneous compounds with potential in pulmonary medicine*: Ongoing research has identified an expanding repertoire of classes of agent with potential for treatment of asthma, COPD and related pulmonary diseases with low incidence of adverse side effects. Included are the followings: Phosphodiesterase inhibitors, mucolitics, expectorants, and antitussive agents.

(h) Therapy of pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) may develop as a consequence of asthma and COPD. The syndrome is characterized by vascular proliferation and remodeling of small pulmonary arteries as a result of progressive elevation in pulmonary vascular resistance, which may lead to right heart failure and sudden cardiac death by left ventricular fibrillation. PAH includes pulmonary endothelial and smooth muscle cell dysfunction via the formation of several endogenous vasoconstrictor and vasodilator mediators. Vasodilator pharmacotherapy is the main choice of the treatment of PAH. These pharmacotherapies aim to antagonize the effects of vasoconstrictor mediators and increase vasoconstriction. Therefore, combination therapy is recommended in the treatment of PAH. Most cases of pulmonary hypertension is associated with other organ disorders such as hypoxic lung disease, general vascular sclerosis leading to venous thrombosis, and right heart failure.

Treatment of PAH: PAH may be treated with prostacyclin (PGI2, epoprostenol, FLOLAN), which vasodilation effect opposes to the effects of vasoconstrictor effect of TXA2.
Figure 24. Function of endothelin 1 (ET-1), nitric monoxide (NO), and prostacyclin (PGI2) in pulmonary artery arterial hypertension (PAH).

Endothelin (ET-1) receptor antagonists also lead to vasodilation caused by endothelin (Figure 24). Bosentan (TRACLEER) was the first ET-1 receptor antagonist brought into clinical use. Bosentan exerts its effects by blocking both ET-A and ET-B receptors. Ambrisentan (LETAIRIS) is a selective ET-A receptor antagonist, and given orally once at a daily dose of maximum 10 mg, resulting in a reduction in intracellular Ca$^{2+}$ level and vasodilation. The ET-1 receptor antagonist also may stimulate the release of PGI2 and nitric oxide giving an additional vasodilation in the vascular system (Figure 24).

Phosphodiesterase 5 inhibitors activate soluble guanylate cyclase activity, leading to increased cGMP levels and smooth muscle relaxation in endothelial cells. These drugs include various compositions of theophylline.
ENDOCRINOLOGY, HORMONES, AND HORMONE ANTAGONISTS

Endocrinology is a field of study which describes hormones in the context of their production sites and interaction with receptors and other physiologic targets to mediate a wide range of homeostatic mechanisms in cells, tissues and organs. The term of hormone refers to soluble mediators in body fluids or nerve synapses producing specific effects via various receptors in target organs from a distant point of origin. Initially hormones were defined as products of ductless glands. It is not known that several organs that are not defined „endocrine” e.g., brain, kidneys, heart, and gastrointestinal tract, synthesize and secrete various hormones that affect basic physiological functions. Many of these hormones are used therapeutically and diagnostically in clinical medicine.

The scope of endocrinology has been expanded to include the actions of growth factors exerting influences via autocrine and paracrine mechanisms, and influencing neurological activity, especially those of the hypothalamus, which regulate and control endocrine functions and various components of immune system. Conceptually, hormones may be divided in two main classes: (I) those that act predominantly on nuclear receptors and modulate transcription in target cells and tissues (steroid and thyroid hormones, vitamin D), and (II) those that directly act on membrane receptors, producing immediate effects via signal transduction pathways (peptides and amino acids). Regardless of action mechanisms, physiological regulation of hormones can be perturbed, if a given hormone in disease states is either over or underproduced if its signaling mechanism is impaired.

The hypothalamic-pituitary endocrine system

Several endocrine hormones are regulated and controlled by complex interactions between the hypothalamus/pituitary and endocrine glands. The function of the hypothalamic-pituitary-endocrine axis is depicted in Figure 25. Certain hypothalamic neurons produce various releasing hormones, which are axonally transported into the median eminence. These neurons secrete hypothalamic releasing hormones into the hypothalamic plexus, which connects to the anterior pituitary gland. Hypothalamic releasing hormones bind to specific receptors of pituitary cells and stimulate the secretion of the corresponding pituitary hormones. Pituitary hormones circulate to the target endocrine glands, activating specific receptors to stimulate the synthesis and secretion of the targeted endocrine hormones.

Knowledge of the levels of pituitary signal hormones and target hormones allow clinicians to identify various endocrine disorders. Peptide hormones of the anterior pituitary are essential for the regulation and control of growth and development, reproduction, and intermediary metabolisms (Figure 25). Various diseases affect their release and secretion. The elucidation of structures of pituitary hormones and hypothalamic releasing hormones has made it possible to synthetize peptide hormone agonists and antagonists, which have basic diagnostic and therapeutic applications. The synthesis and release of anterior pituitary hormones are controlled by the central nervous system. The posterior pituitary, known as neurohypophysis, includes the endings of nerve axons originating from supraoptic and paraventricular nuclei of the hypothalamus, synthesizing arginine vasopressin (AVP) and oxytocin (OXT) (Figure 25). AVP has a basic function in water homeostasis and OXT has a key role in the regulation of uterus contraction in parturition and milk letdown.
The anterior pituitary hormones are classified based on their structures into three groups: (i) Corticotropin (ACTH, adrenocorticotropic hormone) and alpha-melanocyte stimulating hormone (alpha-MSH). These are peptides derived from proopiomelanocortin by proteolysis. (ii) Growth hormone (GH) and prolactin (PR) belong to somatotropic hormone family, which also includes lactogen in human placenta. (iii) Thyroid stimulating hormone (TSH, thyrotropin), luteinizing hormone (LH, lutropin), and follicle stimulating hormone (FSH, follitropin) are glycoproteins with beta-subunits that determine their biological activities.

**Somatotrophic hormones: growth hormone (GH) and prolactin (PR)**

GH and PR belong to the somatotrophic hormone family and possess several common biological features. Pituitary cells produce both GH and PR and consistent with their common origin, certain transcription factors affect both cell lineages. GH and PR act on membrane receptors, which belong to the cytokine receptor family and modulate cell functions via very similar signal transduction mechanisms. In addition, for PR, the negative dopaminergic input is the predominant regulator for its secretion.
The gene encoding human GH is located on the chromosome 17 (17q22). GH is secreted by somatotropes as a heterogeneous mixture of peptides. Significantly, obesity increases circulating levels of GH binding proteins. Recombinant human GH is a 22 kDa molecule approved for therapeutic use. GH secretion changes throughout life. It is elevated in children, peaks during puberty, and decreases in an age-related manner in adulthood.

GHRH (growth hormone releasing hormone), produced by hypothalamic neurons, stimulates GH secretion (Figure 26). Upon binding to GHRH, the GHRH receptor couples to Gs protein, raising intracellular levels of cAMP and calcium, thereby stimulating GH synthesis and secretion. Insulin-like growth factor 1 (IGF-1) acts via a negative feedback mechanism to suppress GH secretion. Somatostatin (SST), by contrast, mediates the negative feedback action of GH. Ghrelin, a 28-amino acid peptide, also stimulates GH secretion (Figure 26). Ghrelin is synthesized predominantly in endocrine cells in the fundus of the stomach. Both fasting and hypoglycemia stimulate circulating ghrelin levels.

![Figure 26. Growth hormone-releasing hormone stimulates GHRH), while somatostatin (SST) inhibits the release of growth hormone (GH) in the pituitary. Ghrelin, produced by the stomach, stimulates the release of GH. (-): inhibition; (+) stimulation.](image)

Human prolactin is a 23 kDa protein with three intramolecular disulfide bounds, predominately synthesized by lactotropes. Prolactin secretion is predominantly inhibitory and regulated by dopamine (DA), which interacts with D2 receptors to inhibit prolactin secretion. During human pregnancy, the maternal serum prolactin level increases at 8 weeks of gestation of 250 ng/ml, and declines thereafter to prepregnancy levels unless mothers breast-feed infants.

The effects of both GH and prolactin are related to their interactions with specific membrane receptors on target tissues. GH and prolactin receptors belong to the cytokine receptor family, thus share structural similarity with receptors for leptin, erythropoietin granulocyte macrophage colony stimulating factor, and many of interleukins. The GH-receptor complex activates JAK2 (Janus kinase), and this leads to tyrosine phosphorylation of cytoplasmic proteins, and the activation of insulin receptor substrate-1 (IRS-1), which mediates the expression of glucose transporters in the cell membrane (Figure 27) and glucose
uptake by cells. JAK2 also activates MAPK, which results in gene expression including insulin-like growth factor-1 (IGF-1) in the nucleus (Figure 27).

Figure 27. Action mechanisms of GH and prolactin. GH: growth hormone; GHR: growth hormone-receptor complex; JAK2: Janus kinase; IRS-1: Insulin receptor substrate-1; MAPK: mitogen activated protein kinase; IGF-1: Insulin-like growth factor 1.

Increased secretion of GH and prolactin promotes somatotrope or lactotrope adenomas. Clinical symptoms of these adenomas include longitudinal growth resulting in gigantism, acromegaly, and often death from cardiovascular complications.

Hyperprolactinemia is an endocrine abnormality that develops as a consequence of hypothalamic or pituitary diseases, due to interference with (i) the delivery of inhibitory dopaminergic signals, (ii) renal failure, (iii) increased TRH levels, or (iv) treatment with dopaminergic receptor antagonists. Most frequently, hyperprolactinemia is caused by prolactin-secreting pituitary adenomas. Clinical symptoms of hyperprolactinemia include galactorrhea, amenorrhea, and infertility. Prolactin deficiency results from pituitary damage.

Pharmacotherapy of increased growth hormone production may be used in conjunction with surgery or drugs that inhibit GH secretion or its action. The favored pharmacotherapy is application of somatostatin (SST) analogs (a), GH receptor antagonists (b), and dopamin agonists (c).

SST analogs (a) are used for the treatment of acromegaly. The aim of the treatment is to reduce GH levels below 2.5 ng/ml. Currently, two SST analogs, octreotide (SANDOSTATIN) and lanreotide (SOMATULINE), are used. These drugs bind to SST2 and SST5 receptors. Side effects include diarrhea, nausea, abdominal pain, gallstones, bile secretion. The inhibitory effects of octreotide and lanreotide on TSH secretion results in hypothyroidism. SST block not only GH secretion but also the secretion of other hormones, cytokines, and growth factors. Therefore, octreotide and lanreotide are also used to treat symptoms of various carcinoid tumors and thyrotrope adenomas that oversecrete TSH.
GH receptor antagonists (b) effectively bind to GH receptors without activating JAK-STAT signaling or IGF-1 secretion. Pegvisomat (SOMAVERT) is subcutaneously administered at a loading dose of 40 mg/day followed by self administration of a dose of 10 mg/day for the treatment of acromegaly. In higher doses, pegvisomat decreases IGF-1 in the serum and significantly reduced the clinical symptoms such as fatigue, tissue swelling, and perspiration. The clinical use of pregvisomat is highly effective treatment in patients refractory to SST analog therapy.

Dopamin agonists (c) suppress prolactin production via D2 receptor activation are widely used for the treatment of prolactinomas. These agents decrease both prolactin secretion and the size of adenomas, thus improving physiological endocrine function and decreasing neurological symptoms caused by adenomas. Quinagolide (NORPROLAC), cabergoline (DOSTINEX), bromocriptine (PARLODEL), and pergolide (PERMAX) are the members of this family and used for the treatment in patients afflicted with prolactinomas. These dopamine agonists relieve the inhibitory effect of prolactin in ovulation, and help most prolactinoma patients to become pregnant. Bromocriptine is especially recommended for fertility induction in patients with hyperprolactinemia.

Adverse effects of dopamine agonists include headache, nausea, vomiting, hypotension, psychosis, hallucinations, nightmares, and insomnia. Quinagolide and cabergoline have lower incidence of side effects in comparison with bromocriptine. Pergolide is, an ergot alkaloid derivative, predominantly used for the treatment of Parkinson disease, however, it is used for the treatment of hyperprolactinemia. In 2008, pergolide was withdrawn from the market.

Pharmacotherapy of growth hormone (somatotropic) deficiency is based on (1) GH replacement and (2) IGF-1 treatment in GH-deficient children and adults.

(1) In the past, GH replacement for therapeutic use was prepared from human cadaver pituitaries. Currently, human GH is produced by recombinant DNA technology providing unlimited amounts of the hormone and eliminating the risk of disease transmission associated with the pituitary derived preparations. Somatropin (GENOTROPIN, HUMATROPE, NUTROPIN, OMNITROPE, VALTROPIN, ZORBTIVE) is intramuscularly used monthly in a dose of 1.5 mg/kg body weight. GH therapy has been applied from the 1950s to treat children with short stature caused by Turner’s syndrome and idiopathic short stature, and additional diseases including Noonan’s syndrome and chronic renal insufficiency. GH therapy is also used for AIDS-related wasting and malabsorption associated with the short bowel syndrome.

Adverse effects of GH therapy include hypertension, papilla and peripheral edema, nausea, vomiting, and headache. Somatropin could be subcutaneously administered in a daily dose of 25-50 microgram/kg in children, and 200 microgram/kg/day in adults. Drug interaction could occur with estrogen and glucocorticoids.

(2) IGF-1 treatment is based on the fact that GH acts enhances of IGF-1 production. Thus, recombinant human IGF-1 (mecasermin, INCRELEX), and the combination of recombinant human IGF-1 with its binding protein, IGFBP3 (mecasermin-rinfabate, IPLEX) are used for treatment of insulin resistance, muscular dystrophy, and HIV-related adipose redistribution syndrome. IGF-1 therapy is used for impaired growth and mutations in GH receptors. Adverse effects of mecasermin and mecasermin rinfabate include hypoglycemia, lipohypertrophy, enlarged tonsils, and hypertension. Maximal daily dose of these drugs is 120 microgram/kg, respectively.

Glycoprotein hormones: TSH and gonadotropins
The gonadotropins include LH (luteinizing hormone), FSH (follicle-stimulating hormone), and hCG (human chorionic gonadotropin). They are termed gonadotropins based on their activity in gonadal tissue. These include LH, FSH, and hCG together with TSH (thyroid-stimulating hormone), they constitute the glycoprotein group of pituitary hormones (Figure 28). LH and FSH are synthesized in the anterior pituitary, while hCG is produced by syncytiotrophoblast in the placenta. Pituitary gonadotropin production is stimulated by GnRH (gonadotropin-releasing hormone). Although the role of TSH is different, TSH is also produced in the anterior pituitary and used for treatment of differentiated thyroid cancers.

Figure 28. The hypothalamic-pituitary system. GnRH (gonadotropin-releasing hormone) regulates the synthesis of LH (luteinizing hormone) and FSH (follicle-stimulating hormone) in both males and females. Gonads produce steroid hormones (estrogens, progesterone, and androgens), which exert feedback inhibition on the hypothalamus and pituitary. Sex steroids produced by gonads also control and regulate hormone productions in the hypothalamus and pituitary. (-): inhibition; (+) stimulation.

The primary regulator of gonadotropin synthesis and secretion is the GnRH in the hypothalamus (Figure 28). GnRH production is gradually increased with age until the adult pattern is established. GnRH binds to GPCR (G protein-coupled receptors) that activates $G_{q/11}$ protein synthesis and stimulates the PLC-IP3-Calcium pathway, leading to an increased synthesis and secretion of LH and FSH in the anterior pituitary. In females, low levels of estradiol and progesterone inhibit the production of gonadotropin production, while higher levels of estradiol exert positive feedback, triggering ovulation. In males, testosterone inhibits gonadotropin production. Gonadotropin expression is also regulated by inhibins (A and B). Inhibins act directly in the pituitary and inhibit FSH secretion with no effect on LH production and secretion.

Puberty, in humans, is a process occurring during several years as a major outcome of GnRH-mediated upregulation of gonadal steroids, leading to the development of gender-specific secondary sexual characteristics. Disorders of the hypothalamus-pituitary-gonad system manifest as hyper- or hypogonadism, resulting in impaired sex steroid production, as a result of deficiency in the hypothalamus or pituitary. Hypogonadotrophic hypogonadism may result from GnRH receptor mutations and results in impaired gonadotropin secretion, resulting in pituitary tumors, sarcoidosis, and exercise-induced amenorrhea. If fertility augmentation is desired, therapy with GnRH or gonadotropins may be used to stimulate germ
cell maturation. GnRH and its synthetic analogs are used both diagnostically and therapeutically in human reproductive disorders and treatment of various tumors.

**Synthetic GnRH agonists**, leuprolide (LUPRON), goserelin (ZOLADEX), histrelin (VANTAS), nafarelin (SYNAREL), and triptorelin (TRELSTAR DEPO), have longer half-lives than native GnRH. Following transient stimulation of gonadotropin secretion, these agents downregulate GnRH receptors and inhibit gonadotropin secretion. Clinical use of synthetic GnRH agonists is made fore endometriosis, advanced prostate cancer, breast cancer, and central precocious puberty. Additionally, these drugs are used to achieve pharmacological castration in diseases that respond to reduction in gonadal steroids.

Adverse effects of synthetic GnRH agonists include hot flashes, decreased bone density, headache, various neurological manifestations, vaginal dryness and atrophy in women, and erectile dysfunction in men. The use of GnRH agonists is well tolerated by patients.

**GnRH antagonists** are synthetic peptides with modifications of some amino acid residues in the sequence of the native GnRH. The GnRH antagonists, ganirelix (ANTAGON), cetrorelix (CETROTIDE), and abarelix (PLENAXIS), are used to suppress the LH surge, preventing premature ovulation in ovarian stimulation programs as part of assisted reproduction programs. These drugs are also used off label for endometriosis and uterine fibrosis, both of which are estrogen dependent. The „depot” product of abarelix is used for adrogen suppression with advanced prostate cancer in humans. GnRH antagonists are formulated for subcutaneous injections used in a daily dose.

**FSH, LH, and hCG (natural and recombinant gonadotropins):** The menotropin (REPRONEX) formulation contains about equal amounts of FSH and LH and is administered intramuscularly. Urofollitropin (MENOPUR), an FSH preparation with monoclonal antibodies, is pure enough to be used subcutaneously. The amount of LH in this preparation is substantially diminished. The recombinant FSH (rFSH) preparations include follitropin alpha (GONAL-F) and follitropin beta (FOLLISTIM) are used for substitution therapy in hypogonadism and to promote follicle maturation. The hCG (human chorionic gonadotropin) preparation is used for the diagnosis of pregnancy after a woman’s first missed menstrual period. The hCG assay can also be used to follow the malignance of germ cell tumors that secret hCG. The application of hCG is suggested to stimulate testosterone production, and thus to assess Leydig cell function in males having hypogonadism. Intramuscular injection of hCG (2000 IU/m² body surface area) is indicated in cryptorchidism, the failure of one or both testes to descend into the scrotum.

**Oxytocin and vasopressin (posterior pituitary hormones)**

The structures of oxytocin and arginine vasopressin (also called antidiuretic hormone, ADH) are peptides, and each consists of 9 amino acids in length with unique sequences. Both hormones are synthesized in the supraoptic nucleus and paraventricular nucleus and stored in the posterior pituitary.

Arginine vasopressin is the main hormone that regulates fluid osmolality in the body. Various diseases of water homeostasis and many pharmacological therapies for treating such disorders involve arginine vasopressin. Vasopressin effects are mediated via V1 (V1a and V1b) and V2 receptors. The V1a receptor is the most widespread subtype of the V1 receptor subclass. It is found vascular smooth muscle, adrenal gland, bladder, myometrium, platelets, myometrium, adipocytes, hepatocytes, renal medullary interstitial cells, epithelial cells in the
renal cortical collecting duct, testis, and various CNS structures. V1b receptors are present in the anterior pituitary, various regions of the brain, pancreas, and adrenal medulla. V2 receptors are predominantly found in the renal collecting duct and vascular endothelial cells.

Vasopressin, via V1 receptors, activates Gq-PLC-IP3 pathway by mobilizing intracellular calcium, and leading to immediate responses, which include vasoconstriction, glycogenolysis, platelet aggregation, and ACTH release.

The V2-receptor stimulating effect of vasopressin is related to the triggering of functional water channels (aquaporin 2) in the collecting duct, resulting in increased water permeability of the apical membrane, and reduced urine volume and diuresis. Thus, the collecting duct, in the kidney, is critical for water conversation. For this reason, vasopressin agonists are used for reducing the volume of urine, while vasopressin antagonists stimulate increased urine volume.

Oxytocin (PITOCIN, SYNTOCINON) is a nonapeptide that differs from vasopressin by two amino acids. It is produced by the nucleus paraventricularis and the nucleus supraopticus in the hypotalamus. Oxytocin secretion is stimulated by dilation of the cervix and vagina, and suckling of the breast. Estradiol also stimulates oxytocin secretion, whereas the ovarian polypeptide relaxin inhibits release of this hormone.

Oxytocin stimulates the frequency and force of uterine contractions. In addition, it plays a physiological role in milk ejection. Stimulation of the breast produces oxytocin secretion, resulting in constriction of the myoepithelium that surrounds alveolar channels in the mammary gland. Oxytocin deficiency is associated with disorders of the posterior pituitary impair milk letdown after delivery. Oxytocin is therapeutically used to induce (a) labor (40 IU/min) in infusion, and to treat or prevent postpartum hemorrhage at a low dose of 10 ml/min of infusion. At low concentration (10 ml/min) of oxytocin can be infused until the uterus is contracted. Ergot alkaloids such as ergonovine (ERGOTRATE) and methylergonovine (METHERGINE) applied intramuscularly or intravenously are used for the treatment of postpartum hemorrhage in normotensive women. In hypertensive patients, the application of ergot alkaloids is contraindicated.

Thyroid and antithyroid drugs

Thyroid hormons maintain metabolic homeostasis and influences the function of all organs. The thyroid gland produces and and sequestrates large stores of thyroid hormone in the form of thyroglobulin. This hormone contains iodine that must be supplied by nutritional intake. Thyroidal secretion predominantly consists of the prohormone thyroxine, which is converted in the liver and other tissues to an active molecule, triiodothyronine. Serum levels of thyroid hormones are regulated by the pituitary hormone, thyrotropin (TSH) and regulated by negative feedback inhibition. Major activities of thyroid hormones are mediated through binding to nuclear thyroid hormone recepors (TRs) and modulate transcription of specific genes. In addition, thyroid hormones share a common action mechanism with steroid and steroid-like hormones, such as vitamin D and retinoids, whose receptors are members of a superfamiy of nuclear receptors. Although the major action mechanisms of thyroid hormones are not precisely clear at the time of this writing, some actions of these hormones outside the nucleus have been characterized.

Thyroid nodules, goiter, and thyroid enlargement, are the most common thyroid abnormalities and may be either benign or malignant. Maternal and neonatal hypothyroidism due to iodine deficiency remains the major cause of mental retardation worldwide. Treatment of hypothyroid patients typically involves thyroid hormone replacement. While treatment options for hyperthyroid patients include antithyroid drugs to reduce hormone synthesis and secretion, destruction of the gland by radioactive iodine, or surgical removal is also used.
Metastatic disease frequently responds radioiodide therapy but may become highly aggressive and unresponsive to conventional therapy.

The thyroid gland is the source of two fundamentally different types of hormones. The thyroid follicle produces iodothyronine hormones including thyroxine (T4), and triiodothyronine (T3). These hormones are essential for physiological growth and development, and play a basic role in energy metabolism. The thyroid gland also contains parafollicular cells (C-cells) that produce calcitonin.

Structural features of thyroid hormones which relate to their biological activities have been characterized. The 3-monosubstituted compound is more active than the 3,5-disubstituted molecules, and triiodothyronine is five times more potent than thyroxine. The thyroid hormones are synthesized and stored as amino acid residues of thyroglobulin in the thyroid gland. The major processes involving synthesis and release of thyroid hormones may be summarized as follows:

- Iodide (I) uptake by the gland.
- Iodide oxidation and iodination of tyrosyl groups of thyroglobulin.
- Coupling of iodothyrosine residues to generate iodothyronines.
- Resorption of thyroglobulin colloid by cells.
- Proteolysis of thyroglobulin and release of thyroxine and triiodothyronine into the blood.
- Recycling of iodine within thyroid cells and reuse of I.
- Conversion of thyroxine (T4) to triiodothyronine (T3) in tissues and in the thyroid gland.

Iodine in the circulation is present in various forms, with 95% as organic iodine and 5% as iodide. The physiological daily production of thyroxine is about between 80 to 100 micrograms. Thyroxine-binding globulin is a major carrier of thyroid hormones. Binding of thyroid hormones to plasma proteins protects the hormones from metabolism and excretion, resulting in extended half-life in the circulation. Only the unbound hormone has metabolic activity. Certain drugs (e.g., estrogens) and different pathological (e.g., HIV infection, liver diseases) and physiological (e.g., pregnancy) conditions can alter the binding of thyroid hormones to plasma proteins. The liver is the major site of non-deiodinative degradation of thyroid hormones via conjugation with glucuronic and sulfuric acids, and excreted in the bile.

Thyrotropin or TSH (thyroid-stimulating hormone) is a glucoprotein hormone consists of alpha and beta subunits. TSH is secreted in a pulsatile manner with expression circadian patterns. Its level is highest in the circulation during sleep at night. TSH secretion is controlled by the hypothalamic peptide, thyrotropin-releasing hormone (TRH). The regulation of thyroid hormone secretion (T4 and T3) is depicted in Figure 29. External applied thyroid hormone (T4 or T3) inhibits transcription of both the TRH gene and the genes encoding the alpha and beta subunits of thyrotropin, which suppress the secretion of TSH and causes the thyroid gland to become inactive and regress. TRH stimulates the release of TSH from hypothalamic neurons and synthesis of alpha and beta subunits of TSH. Elevated T4 and T3 levels in the circulation inhibits TRH release from hypothalamic neurons, leading to a reduced TSH release from the pituitary. Dopamine, somatostatine (SST), and glucocorticoids inhibit the release of TRH, and as a consequence, block TSH release from the pituitary. TRH is also localized in the cerebral cortex, pineal gland, and spinal cord. The localization of TRH in nerve endings, suggest that TRH may act as a neurotransmitter or neuromodulator outside of the hypothalamus-pituitary axis.

Physiological thyroid gland function requires adequate iodine intake. With inadequate intake of iodine, the thyroid gland becomes hypertrophic. In cases of severe iodine deficiency, adult hypothyroidism and cretinism develop. Goiter is also consequence of
insufficient iodine intake. The recommended doses of iodine range from 100 to 200 microgram/day. Dairy products and fish are relatively rich in iodine.

Figure 29. Regulation of $T_4$ and $T_3$ secretion. TSH: thyroid stimulating hormone, TRH: thyrotropin releasing hormone, GH: Growth hormone, LH: luteinizing hormone, FSH: follicle stimulating hormone, ACTH: adrenocorticotropic hormone, AVP: arginine vasopressin, OXT: oxytocin, SST: somatostatin. (-): inhibition; (+) stimulation.

The metabolic activities of thyroid hormones are mediated by the binding of $T_3$ to thyroid hormone receptors (TRs). $T_3$ binds to TR with about 10-fold higher affinity than $T_4$ does. Moreover, $T_4$ is not thought to be active under physiological conditions. TRs bind to specific DNA sequences, called thyroid hormone response elements in the promoter/regulatory regions of target genes. TRs associate with the p85α subunit of phosphatidyl inositol 3-kinase (PI3K), which results in phosphorylation and activation of PI3K/Akt, affecting cellular metabolism. This phosphorylation stimulates nitric oxide
production by endothelial cells, which leads to vasodilatation. Vasodilation is thus a major therapeutic effect of T₃ administration.

Thyroid hormones play a major role in brain development. Underproduction of thyroid hormones during the initial period of neurogenesis leads to irreversible mental retardation (cretinism) and is accompanied by multiple morphological pathological changes in the brain such as deranged axonal projection and reduced synaptogenesis. Decreased expression of myelin-associated proteins impairs myelinization in the hypothyroid brain. Supplementation with exogenously administered thyroid hormones in the first two weeks of postnatal life prevents the development of these pathological changes. The action of thyroid hormones on protein synthesis and enzyme activity affects the function of all tissues. Thyroid hormones regulate thermogenesis, cardiac function, and vascular resistance. Hyperthyroid patients exhibit ventricular tachycardia, cardiac hypertrophy, and increased heart rate. By contrast, hypothyroid patients exhibit ventricular bradycardia, increased peripheral vascular resistance, and reduced heart rate. Thyroid hormones upregulate expression of LDL receptors and metabolism of cholesterol in the liver. Carbohydrate metabolism is also regulated by thyroid hormones. Blockade of thyroid hormone receptors results in depleted glycogen stores and enhanced gluconeogenesis.

**Hypothyroidism:** Hypothyroidism, also called myxedema if severe, is the most common disorder of thyroid gland. Its main cause is iodine deficiency. This disorder is characterized by high levels of circulating antibodies directed against thyroid peroxidase and thyroglobulin. The primary symptom of hypothyroidism is failure of thyroid gland function. Secondary hypothyroidism (central hypothyroidism) is another commonly occurring symptom resulting from diminished stimulation of the thyroid gland by TSH due to failure of the pituitary and/or hypothalamus. If hypothyroidism is present at birth, the disease is considered to be congenital hypothyroidism. Congenital hypothyroidism is the most preventable cause of mental retardation since thyroid hormone replacement prevents development of cretinism. Symptoms of hypothyroidism include lethargy, fatigue, mental slowness, depression, cold intolerance, dry skin, weight gain, fluid retention, facial puffiness, edema, muscle stiffness, infertility, irregular menses, goiter, bradycardia, constipation, sleepiness, and hypertension.

**Hyperthyroidism (thyrotoxicosis):** Hyperthyroidism is caused by elevated concentrations of circulating free thyroid hormones. This disease is caused by increased TSH receptor stimulation and iodine uptake by the thyroid gland. TSH receptor stimulation occurs either as a result of TSH receptor stimulating antibody (Graves’ disease), or TSH receptor mutations in autonomously functioning nodules or toxic goiter. This syndrome is the most common cause of thyrotoxicosis. Graves’ disease is an autoimmune disorder characterized by increased thyroid hormone production, diffuse goiter, and immunoglobulin (IgG) antibodies that activate TSH receptors. Graves’ disease is commonly associated with other autoimmune diseases. Exophthalmos associated with the disorder is manifested as an autoimmune-mediated inflammation of periorbital connective tissues and extraocular muscles. Symptoms of thyrotoxicosis include increased motor activity, excessive heat production, increased sensitivity to catecholamines (sympathomimetic activity), warm and moist skin, fast heart rate, weight loss, insomnia, anxiety, increased bowel movements, arrhythmias and cardiac failure.

**Thyroid hormone therapy**

The major indications for thyroid hormone therapy are for hormone replacement in patients afflicted with hypothyroidism and suppression therapy in patients with thyroid
cancer. Levothyroxine (L-T₄, LEVOTHROID, LEVOXYL), liothyronine (L-T₃), and their mixture (THYLORAL, L-T₄, L-T₃) are available in tablets and lyophilized powder for injection. Levothyroxine is the hormone of choice for thyroid hormone replacement due to its consistent potency and prolonged action duration. The average daily dose of levothyroxine is about 1.7 microgram/kg body weight. The major therapeutic objectives are to normalize serum TSH levels and relieve the symptoms of hypothyroidism.

Myxedema is a rare syndrome that represents the extreme expression of severe and long-standing hypothyroidism. Clinical features of myxedema include respiratory depression, hypothermia, bradycardia, delayed reflexes, and decreased consciousness. Therapeutic management of myxedema coma includes the correction of hyponatremia. Due to the coexisting decreased adrenal reserve in patients, intravenous steroids are indicated before initiation of tyroxine therapy and may be continued until adrenal function is normalized. Therapy with levothyroxine is in the range of 250-500 microgram/day.

Treatment of congenital hypothyroidism depends on age of the patient. If therapy is initiated within the first two weeks of life, normal physical and mental development can be maintained. Recommended daily dose of levothyroxine is 10-15 microgram/kg for 3 years until the end of physical growth, neuronal development, bone maturation, and developmental progress.

Nodular thyroid disease is the most common endocrinopathy, and nodules are more frequent in females. Approximately 5% of thyroid nodules are malignant. Nodules cause neck discomfort, dysphagia, and choking sensation. Most patients with thyroid nodules are euthyroid, which can be confirmed by TSH measurement.

Therapy for papillary and follicular thyroid tumors includes surgical thyroidectomy, radioiodine, and levothyroxine to suppress TSH production, in cases where TSH is the growth factor for a particular tumor. These interventions may be of benefit for those patients diagnosed with stage 2 or higher category of thyroid cancer. For most low-risk patients with stage 1 or 2 cancer, maintaining the TSH level just below the reference range for not more than 5 years is a reasonable approach for successful therapy. Adverse effects of thyroid hormone treatments include atrial fibrillation and osteoporosis in postmenopausal women.

Novel thyroid hormone analogs include (i) TR-beta expressed by the liver, (ii) thyromimetics such as monocarboxylate transporter 8 (MCT8) expressed by the brain, which transports T₃ into cells, (iii) thyroid hormone receptor antagonists, which may be useful therapeutics in the management of cardiac arrhythmias and cholesterol lowering, and (iv) thyroamines, which are thyroid hormone metabolites. All of these agents are under clinical investigations at the time of this writing.

Antithyroid drugs and thyroid inhibitors

Many drugs are capable of interfering with the synthesis and release of thyroid hormones. Inhibitors of thyroid function can be classified in five major categories:

1). Antithyroid drugs, which directly inhibit the synthesis of thyroid hormones (T₄ and T₃) in the thyroid gland.
2). Ionic inhibitors, which block iodide transport mechanisms.
3). High concentrations of iodide, which decrease the release of thyroid hormones in the thyroid gland, and may decrease hormone synthesis.
4). Radioactive iodine, which kills cancer cells, but also damages thyroid tissue with ionizing radiation.
5). Adjuvant therapy with drugs, which have no specific effects on hormone synthesis, but effective in controlling peripheral manifestations of thyrotoxicosis. These drugs, which
include beta adrenergic receptor blockers, and calcium channel blockers inhibit deiodination of thyroxine to the active hormone.

1). Antithyroid drugs

The antithyroid drugs can be further classified into three major groups, which include: (i) thioureylenrs or thiamides (e.g., propylthiouracil, methimazole, and carbimazole), (ii) aniline derivatives (e.g., sulfonamides), and (iii) polyhydric phenols (e.g., resorcinol). In this subchapter, only (i) thioureylenrs or thiamides (e.g., propylthiouracil, methimazole, and carbimazole) are discussed in detail.

(i) Propylthiouracil, a thionamide molecule, is considered as the prototype of antithyroid drugs. Therapy for hyperthyroidism with thiamides has proven effective, and the substances used became known as antithyroid drugs. This group of drugs inhibits the formation of thyroid hormones by blocking the incorporation of iodine into tyrosil residues of thyroglobulin, and prevents the oxidation of iodotyrosyl groups. If Graves’ disease is treated with antithyroid drugs, concentrations of immunoglobulins are reduced in the circulation, indicating that these agents act as immunosuppressants.

Propylthiouracil, metimazole (TAPAZOLE), and carbimazole are available in the USA and EU. Propylthiouracil and metimazol cross the placenta and extrete in milk. Side effects of these drugs are relatively low, but agranulocytosis was recorded in some cases. Therefore, peripheral blood leukocyte counts are monitored monthly. Notably, agranulocytosis is reversible upon discontinuation of this class of drugs. Urticarial papular rash may also occur, therefore antihistamine and corticosteroid treatments are necessary. Other adverse effects include nausea, headache, skin pigmentation, and loss of hair.

Propylthiouracil, metimazole (TAPAZOLE), and carbimazole are used for primarily according to 3 major considerations; (a) definitive treatment of hyperthyreoidism and the remission of Graves’ disease; (b) to control the disorder in preparation for surgical treatment; and (c) in conjunction with radioactive iodine. Treatment of hyperthyreoidism includes antithyroid drug therapy, radioactive iodine treatment, and subtotal thyroidectomy. The thyrotoxic state typically improves in 4-5 weeks after the onset of treatment, and clinical response is related to the size of the goiter and may allow reduction in effective dosage of antithyroid drugs. A major positive indicator of drug-induced remission is reduced size of the goiter. The dosages of antithyroid drugs are in a range of 15-300 mg/day.

Before surgery, the aim of preoperative preparation is to reduce operative morbidity and mortality. Thus, an euthyroid state should be induced in patients before subtotal thyroidectomy. The operative mortality in these patients is extremely low. For this purpose, iodide is administered to patients for 8-9 days before surgery to decrease vascular circulation and vascularity of the thyroid gland, making it less friable during surgery.

2). Ionic inhibitors, which block iodide transport mechanisms

Ionic inhibitors include substances that interfere with the accumulation (uptake) of iodide by the thyroid gland. These agents are monovalent hydrated anions such as thiocyanate, perchlorate, fluoroborate, and lithium. Such drugs also inhibit the organification of iodine by the thyroid gland. Perchlorate activity is 10 times higher than thiocyanate. Application of perchlorate may be used to control hyperthyroidism, but it may also cause fatal aplastic anemia if given in excessive amounts (2-3 gram day). Fluoroborate is as effective as perchlorate. Lithium, which is also an antimanic agent, decreases thyroxine and triiodothyronine secretion int he thyroid gland.
3. High concentrations of iodide

High doses of iodide affect all aspects of iodine metabolism in the thyroid gland. The most important clinical effect of high iodide concentrations is the inhibition of the release of thyroid hormones (T4 and T3) from the thyroid gland. This action is fast and efficacious in severe thyrotoxicosis. Therapeutic effects are detectable within 24 hours. Another effect is decreased thyroid hormone synthesis and vascular circularity of the thyroid gland. Maximal iodide effects typically develop after two weeks with improvement in signs and symptoms of hyperthyroidism. The use of iodide in hyperthyroidism is in the preoperative period as preparation for thyroidectomy in combination with antithyroid and beta adrenergic receptor blocker drugs in order to avoid thyrotoxic crisis. Another use of iodide is to protect the thyroid gland from radioactive iodine fallout following a nuclear plant accident, military exposure, or large radioiodination in laboratories. The daily administration of 30-100 mg of iodide decreases the thyroid uptake of radioisotope iodine.

Lugol’s solution consisting of 5% iodine and 10% of KI is widely used. This preparation contains a dosage of 8 mg/kg of iodine per drop. Lugol’s solution is used 3 times/day, 2-4 drops each time. Iodine is reduced to iodide in the gut before absorption. Adverse reactions include allergic response, diarrhea, anorexia, sneezing, cough, frontal headache, depression, angio and pulmonary edema, inflammation (pharynx, larynx, and tonsils), cutaneous hemorrhages, lymph node enlargement, fever, eosinophilia, and thrombocytopenia.

4). Radioactive iodine

Iodine has several radioactive isotopes including $^{123}$I and $^{131}$I, which are most frequently used in medicine. $^{123}$I is a gamma-emitter and used for diagnostics to measure iodine uptake and thyroid gland imaging. $^{131}$I is gamma- and beta-emitter and used therapeutically in thyroid gland destruction of overactive or enlarged thyroid tissue and metastatic cancers. Treatment of metastatic cancers with radioiodine relies on rapid uptake of $^{131}$I, which is quickly and effectively trapped by the thyroid gland, incorporated into iodoamino acids, and stored as a colloid of the follicles from which it is slowly liberated. Pycnosis and necrosis of the follicular cells are followed by disappearance of colloids and fibrosis of the thyroid gland. Sodium iodide $^{131}$I (HICON) is available in solution and capsules for oral administration.

In hyperthyroidism, $^{131}$I is administered orally at concentrations of 7,000-10,000 rads per gram of thyroid tissue. After a few weeks of treatment, symptoms of hyperthyroidism gradually abate over a period of 2-3 months. $^{131}$I is used for the treatment of Graves’ disease and toxic nodular goiter. Surgery remains the main intervention for patients with multinodular goiters, radioactive iodine therapy may benefit in elderly patients, especially with those are having cardiovascular diseases. The consequence of the use of radioactive iodine is the high incidence of the development of hypothyroidism, and salivary gland dysfunction may develop. Radiactive iodine therapy may aggravate ophthalmopathy. The main contraindication of $^{131}$I is pregnancy.

5). Adjuvant therapy

Drugs used for adjuvant therapy have no specific effects on thyroid hormone synthesis, but are effective in controlling peripheral manifestations and symptoms of thyrotoxicosis. These drugs, such as beta adrenergic receptor blockers and calcium channel
blockers, are discussed in detail in the chapters of „Therapy of myocardial ischemia” and “Antiarrhythmic drugs” of the CARDIOVASCULAR SYSTEM.

ESTROGENS AND PROGESTINS

Females physiology on estrogens and progestins as major mediators of (a) developmental effects, (b) neuroendocrine function in control of ovulation, (c) cyclical preparation of the reproductive tract for fertilization and implantation, and (d) actions on mineral, carbohydrate, protein, and lipid metabolism. Estrogens also influence male physiology through such activities as regulation of bone function, spermatogenesis, and behavior. Estrogen receptors are present in the body for each hormone and receptor-mediated biological actions are present in both non-ligand mediated processes and steroid hormone ligand-dependent mechanisms.

The most common clinical use of estrogens and progestins are for menopausal hormone therapy and contraception in women. Antagonists of estrogen and progesteron are also available and used for treatment of hormone-responsive breast cancer and infertility.

Some cancer chemotherapeutic strategies are based on the blockade of estrogen- and progesterone-receptor functions. Selective estrogen receptor modulators (SERMs) including agonists and antagonists are used to prevent breast cancer and the development of osteoporosis. The main application of antiprogestin treatments is medical abortion.

Estrogens

Steroid estrogens (a) including estradiol, estradiol valerate, ethinyl estradiol, estriol, estrone, mestranol, and (b) nonsteroidal agents such as diethylstilbestrol, bisphenol, and genistein possess estrogenic activity. The most potent natural estrogens are 17-beta estradiol, estrone, and estriol. Nonsteroid agents with estrogen activity include flavones (e.g., genistein) and other derivatives present in fungi and plants. Steroid estrogens are derived from testosterone or androstenedione by ring-aromatization, which is catalized by the aromatase enzyme (CYP19). The ovaries are the principal source of circulating estrogen in premenopausal women, with estradiol the main secretory molecule. In postmenopausal women, the primary source of circulating estrogen is adipose tissue stroma, which is the source material for estrone synthesis. Specifically, dehydroepiandrosterone secreted by adrenals. In males, estrogens are produced by the testes is converted to estrone.

Estrogens are responsible for pubertal changes and secondary sexual characteristics in females. These hormones cause the development of vagina, uterus, fallopian tubes, and contribute to breast enlargement, growth of axillary and pubic hair, shaping the skeleton, and body contours. In males, estrogen deficiency diminishes pubertal growth spurt, delays skeletal maturation and epiphyseal closure.

The menstrual cycle is controled by the hypothalamus, pituitary, and ovaries. Gonadotropin releasing hormone (GnRH) causes the release of luteizining hormone (LH) and follicle stimulating hormone (FSH) in the pituitary. The frequency of GnRH pulses, which varies in the different interwalls of the menstrual cycle, regulates the synthesis of FSH and LH.

Gonadotropins (LH and FSH) regulate the growth and maturation in the ovary and the ovarian production of estrogen and progesterone, which exert feedback regulation with pituitary/hypothalamus axis. LH and FSH secretion is pulsatile and regulated by the intermittent release of GnRH (gonadotropin-releasing hormone). However, gonadotropin release is controlled by the action of estrogens and progesterone on the pituitary.
In the menstrual cycle, the average LH levels are similar throughout the early (follicular) and late (luteal) phases of the cycle, but the frequency and amplitude of LH pulses are different in the two phases. These changes in hormone secretions result from complex positive and negative feedback mechanisms. In the early follicular phase, GnRH secretion occurs as a burst and results in the release of LH and FSH. In the mid-cycle, serum estradiol level rises and exerts a brief positive feedback effect on the pituitary to trigger the preovulatory surge of LH and FSH, following which follicle rupture and ovulation develop within 1-2 days. The ruptured follicle then develops into the corpus luteum, which produces large amounts of progesterone and lesser amounts of estrogen under the influence of LH during the second half of the cycle. If the ovaries are surgically removed or cease to function, overproduction of FSH and LH may occur, with surplus quantities of these hormones eliminate via urine.

Estrogens affect the function of many tissues and organs and have a plethora metabolic actions. Estrogens influence and control mineral, lipid, carbohydrate, and protein metabolism. Nonreproductive tissues such as bone, gastrointestinal tract, central nervous system, liver, vascular endothelium, heart, and immune system express estrogen receptors (ER), and the ratio of ERalpha and ERbeta varies in cell specific manner.

Estrogens participate the follow major activities: (a) in „bone-remodeling” by the resorptive action of osteoclasts and the bone-forming action of osteoblasts. Osteoclasts and osteoblasts express both ER-alpha and ER-beta, and the action of ER-alpha predominate in bone. Estrogens directly regulate osteoblasts, and increase the synthesis of osteocalcin, osteopontin, osteonectin, and alkaline phosphatase. In addition, estrogens increase osteocyte survival by inhibiting apoptosis. The major effect of estrogens in bone is to reduce the activity and number of osteoclasts. Estrogens decrease osteoblast production via osteoclast-stimulating interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-alpha); and increase the production of IGF-1 and transforming growth factor (TGFbeta), which are antiresorptive mediators.

Estrogens affect (b) lipid metabolism including serum lipoprotein and triglyceride levels. Estrogens elevate serum triglycerides and reduce total serum cholesterol levels. In addition, estrogens increase high density lipoprotein HDL levels and decrease low density lipoprotein (LDL) and lipoprotein-A (LPA) levels. This change in the ratio of HDL and LDL is an important effect of estrogen therapy in postmenopausal women.

Estrogens have (c) antioxidant activity and inhibit the oxidation of LDL by affecting the function of superoxide dismutase. Long term use of estrogens (d) results in a reduction of plasma renin, angiotensin-converting enzyme, endothelin-1, and an increase in NO and prostacycline (PGI2) production. All of these changes promote vasodilation leading to the prevention of the development of hypertension.

Systemic effects of estrogens (d) include the hepatic production of plasma proteins and the clotting cascade. Estrogens increase the activity of coagulation factors (II, VII, IX, X, and XII) and decrease the activity of anticoagulation factors (protein C, protein S, and antithrombin III).

The two estrogen receptor genes are located on separate chromosomes; ESR1 encodes ER-alpha, and ESR2 encodes ER-beta. The estrogen receptor is divided into six different domains; the NH2-terminal A/B domain contains the activation function-1 (AF-1) portion, which can activate transcription independently of ligand; the C domain comprises the DNA-binding domain; the D domain includes the nuclear localization signal; the E/F domain has multiple function including ligand binding, dimerization, and ligand dependent transactivation. ER-alpha is expressed in the uterus, vagina, ovaries, mammary gland, hypothalamus, and vascular smooth muscle. ER-beta is expressed in the prostate, ovaries,
lung, brain, and vasculature. Both ER-alpha and ER-beta are expressed in patients afflicted with breast cancers.

Estrogen receptors (ERs) are ligand-activated transcription factors that increase or decrease the transcription of target genes. After entering the cell, estrogens bind to ERs in the nucleus. ERs are present as inactive monomers bound to heat shock protein-90 (HSP90), and upon binding estrogens, a change in ERs conformation following dimerization dissociates HSP90 by increasing the affinity and the rate of receptor binding to DNA. Interactions of ERs with receptor antagonists also promotes dimerization and DNA binding. Estrogen receptor antagonist-induced conformational changes facilitate binding of co-repressors, e.g., nuclear hormone receptor co-repressor/silencing mediator of retinoid and thyroid receptors (NCoR/SMRT). Co-repressor/ER complexes further recruit various proteins with histone deacetylase activity. Histone deacetylases are major regulators of gene expression through their modification or gene promoter sequences.

Estrogens are available for oral, transdermal, parenteral, or topical administration. Oil-based estrogen esters are available for intramuscular administration typically in once per month. For a variety of therapeutic uses, estrogens are available in combination with progestins. Oral estrogen preparations are marketed under the trademarks of PREMARIN, MENEST, CENESTÍN, OGEN, and ENJUVIA. ALORA, CLIMARA, ESTRADERM are used in transdermal patches, providing slow and sustained release of estrogens allowing more stable serum levels than oral delivery. Transdermal patches are typically applied once daily on the arm. Estradiol valerate (DELESTROGEN) and estradiol cypionate (DEPO-ESTRADIOL) as oil preparations are used for intramuscularly once per month. Estrogens undergo hepatic biotransformation and are excreted via the urine.

Adverse effects of estrogen include the risk of various cancers, thromboembolic and gallbladder diseases. A major concern is risk of developing breast, endometrial, cervical, and vaginal tumors especially in postmenopausal women. This increased risk can be substantially diminished, if progestins are coadministered with estrogens. Oral estrogen applications increase the risk of thromboembolic diseases in both healthy and preexisting cardiovascular diseased women. Women treated with estrogen also exhibit decreased cognitive function.

The major therapeutic uses of estrogens are for hormone therapy, and in combinations, for oral contraceptives. In postmenopausal hormone therapies, 0.625 mg/day of estrogens is most often used. For oral contraceptives, 20-35 microgram/day of ethinyl estradiol are used. It is important to note that 0.625 mg of conjugated estrogens is considered equivalent to 5-10 microgram of ethinyl estradiol. The benefits of estrogen therapy in postmenopausal women include the amelioration of vasomotor symptoms, and the prevention of bone fractures and urogenital atrophy. Osteoporosis is a disorder of the loss of bone mass including the thinning and weakening of bones and and increased incidence of fractures especially in the hip and wrist. Estrogen therapy for osteoporosis significantly reduces the incidence of bone fractures. In addition to other drugs, such as bisphosphonate treatment, estrogens are the most efficacious agents available for prevention of fractures at all sites in postmenopausal women.

The risk of cardiovascular diseases is lower in women than in males as a consequence of estrogen bioactivity. Additionally, estrogens mediate a beneficial lipoprotein profile, promote vasodilation, and reduce atherosclerosis. Estrogen replacement therapy in postmenopausal women is primarily to reduce vasomotor symptoms, vaginitis, and osteoporosis. The risk of endometrial carcinoma is nevertheless increased in estrogen replacement therapy. However, the application of progesterone can reduce incidence of estrogen-induced hyperplasia and carcinoma in postmenopausal women.

Selective estrogen receptor modulators and antiestrogens
Tamoxifen (TAMOXIFEN), raloxifene (EVISTA), and toremifene (FARESTON) are selective estrogen receptor modulators (SERMs). These SERMs mediate beneficial estrogen activity in some tissues including bone, brain, and liver in postmenopausal hormone therapy. However, adverse effects on breast and endometrium can be deleterious and carcinogenic. Tamoxifen and toremifene are preliminary used for the therapy of breast cancer, and raloxifene is used for the treatment and prevention of osteoporosis. These drugs cause antiresorptive effects in bone leading to reduction of vertebral fractures by 50% in dose-dependent manner. In addition, these agents decrease total cholesterol, LDL, and LPA levels in the serum.

The antiestrogen family includes clomiphene (CLOMID, SEROPHENE) and fulvestrant (FASLODEX), which are pure estrogen antagonists in all tissues and organs. Clomiphene is used for therapy of infertility in anovulatory women, while fulvestrant is used for therapy in progressive breast cancer. These agents are used to develop the male reproductive system based on testosterone feedback on the pituitary and hypothalamus, which is mediated by estrogens derived from aromatization of androgen hormones.

The antiestrogen family also includes agents, which are able to block the biosynthesis of estrogens. Thus, long-term administration of GnRH agonists prevents ovarian synthesis of estrogens. These drugs include exemestane (AROMASIN), anastrozole (ARIMIDEX), and letrozole (FEMARA), which are selective blockers of estrogen production.

**Progestins (gestogens, progestogens)**

Hormones with biological activities similar to those of progesterone are referred to in the literature as progestins, progestogens, or gestogens, and all of them complex with progesterone (PR) receptors. Progestins include the naturally occurring progesterone, 17alpha-acetoxyprogesterone derivatives, 19-nortestosterone derivatives (estranes), and norgestrel related compounds. Medroxyprogesterone acetate (MPA) and orally administered micronized progesterone are used as oral and injectable contraceptives. Some synthetic progestins also bind to glucocorticoid, androgen, and mineralocorticoid receptors that account for some of their nonprogestin activities.

Progesterone is secreted by the ovary from the corpus luteum during the second half of the menstrual cycle. LH stimulates progesterone secretion during the normal cycle. After fertilization, the trophoblast secretes human chorionic gonadotropin (hCG) into the maternal circulation, which stimulates LH receptors to sustain the corpus luteum, thus maintaining progesterone production. During the first trimester of pregnancy, the developing placenta begins to secrete estrogen and progesterone in cooperation with the fetal adrenal glands, thus thereafter, the corpus luteum is not essential for continuation of gestation. Secretion of estrogens and progesterone continues at high levels by the placenta until delivery.

Physiological and pharmacological effects of progesterone include: (a) decrease of frequency in pulses of GnRH release. GnRH-mediated suppression is the major mechanism of progestin-containing contraceptives. Progesterone (b) decreases estrogen-dependent endometrial proliferation and leads to development of the secretory endometrium. The abrupt decline in progesterone levels at the end of the cycle is the main cause of the menstruation onset. Under physiological conditions, estrogen accompanies progesterone’s action in the endometrium, and is essential for the development of the physiological menstrual process. Progesterone (c) is a basic hormone for the maintenance of pregnancy, and suppresses menstruation and uterus contractility. Both (d) progesterone and estrogen are required for the development of mammary gland. These hormones cause a proliferation of the acini of the mammary gland by regulating lactation during pregnancy. Progestins including progesterone
(e) increase basal insulin levels after carbohydrate ingestion, but do not alter glucose tolerance. Finally, (f) progesterone and its derivatives increase LDL levels in the serum.

The action mechanisms of progesterone (PR) and its derivatives include binding of these hormones to both PR-A and PR-B receptors in the PR gene region in the nucleus. Since the ligand-binding domains of the two PR isoforms are identical, therefore, there is no difference in ligand-binding activities. The biological activities of PR-A and PR-B receptors are different. PR-B receptors mediate the stimulatory activity of progesterone, while PR-A receptors inhibit PR-B receptor-mediated stimulatory effects.

Progesterone and its derivatives undergo rapid first-pass metabolism in the liver, but high doses of micronized progesterone preparations are available for oral application. However, the bioavailability of micronized progesterone derivatives is low. Progesterone is also available for injection in oil solution, vaginal application and as a component of intrauterine devices for contraception. In the plasma, progesterone binds extensively to albumins and globulins. The elimination (half-time) of progesterone is about 5 min. The hormone is metabolized in the liver in hydroxylated and glucuronidated forms, and eliminated in the urine. Synthetic progestins have longer half lives (7-10 hours) than progesterone, but the way of elimination is the same.

Anti-progestins and progesterone receptor modulators

Mifepristone (MIFEPREX) was the first antiprogestin agent and used for the termination of pregnancy. Mifepristone eventually supplanted onapristone as antiprogestin agent. These antiprogestins act as competitive progesterone receptor antagonists on both progesterone receptors (A and B), and also have several other applications including the prevention of conception, to induce labor, to treat uterine leiomyomas, meningiomas, endometriosis, and breast cancer. Mifepristone and onapristone are orally active agents with good bioavailability. Mifepristone in combination with prostaglandins is primarily used for the termination of pregnancy.

Ulipristal (ELLA) is a selective progesteron receptor modulator (SPRM) and has antiproliferative effects in the uterus, however its most relevant action is to inhibit ovulation. Antiovulatory action of ulipristal is related to progesterone regulation including inhibition of LH release and LH-induced follicular rupture in the ovary. Ulipristal at a dose of 30 mg inhibits ovulation up to five days after intercourse. Headache and abdominal pain may develop as side effects.

Contraceptives

A variety of contraceptive formulations are available including pills, skin patches, subdermal implants, vaginal rings, injections, and intrauterine devices. The most frequently used agents are oral hormonal contraceptives containing both estrogen and progestin combinations. Monophasic, biphasic, and triphasic pills are provided in 21-day packs. Monophasic pills contain fixed amounts of estrogen and progestin. Each pill, which is taken daily once for 21 days is followed by 7-day pill-free period. Biphasic and triphasic pills include two or three different pills containing various amounts of estrogen and progestin. Combinations reduce the doses of steroids and more closely approximate the ratio of estrogen and progestin normally occurring during menstrual cycle. Estrogen dosage in pills range from 20 to 50 micrograms, while progestin contentents are between 0.1 and 0.5 mg. Many formulations are available for „progestin-only” contraception with efficacies of 99%. Their mechanism of action includes effects on the pituitary along with thickening of cervical mucus, which decreases sperm penetration.
Combinations of oral contraceptives act by preventing ovulation. Measurements of plasma hormone levels show that LH and FSH levels are suppressed or absent, and endogenous steroid levels are diminished as a result of drug effects. Although each component alone mediates these effects, combinations synergistically decrease serum gonadotropin levels and suppresses ovulation more consistently than either alone. The proper frequency of LH pulses is essential for ovulation, this effect of progesterone plays a major role in the contraceptive action. In addition, the multiple pituitary effects of estrogens and progestins contribute to oral contraceptive action.

Adverse effects of oral contraceptive combinations include disorders of the cardiovascular system such as myocardial infarction, hypertension, ischemic or hemorrhagic stroke, and thrombosis/embolism. Breast, hepatic, and cervical cancers may also develop. Combinations of oral contraceptives do not increase the incidence of endometrial cancer but actually correlate with a 50 % decrease in the incidence of this disease. Clinical data also show that oral contraceptive use decreases the risk of colorectal cancer. However, the ethinyl estradiol use in oral contraceptive pills appears to cause a dose-dependent increase in several known serum factors that increase blood coagulation. Withdrawal bleeding occurs after approximately one week following discontinuation of contraceptive use, during which time pregnancy status may be uncertain.

Uses of 'modern' contraceptives are considered safe in healthy women, but these agents may contribute to the increased incidence and severity of cardiovascular and thromboembolic events, and occasionally development of malignant tumors particularly if other risk factors (e.g., smoking, chronic alcohol intake) are present. The following conditions are considered to be absolute contraindications for use of combined contraceptives: thromboembolic diseases, myocardial infarction, stroke, congenital hyperlipidemia, breast carcinoma, vaginal bleeding, and impaired liver function.

Testosterone and other androgens

Testosterone is the principal secreted androgen in men. This hormone is synthesized by the Leydig cells of the testes from cellular cholesterol. Testosterone also is the principal androgen synthesized by the corpus luteum and adrenal cortex in women, and its levels change during pregnancy. During puberty, serum testosterone concentration in males increases to a greater degree, at a range of 5000 to 7000 ng/liter; and 300 to 500 ng/liter in females. The increased testosterone concentration in males is responsible for pubertal changes. With age, testosterone levels gradually decrease resulting in exacerbation of many effects of aging in men. LH, a pituitary hormone, is the principal stimulus for testosterone secretion, which is potentiated by FSH in men. In females, LH stimulates corpus luteum, which is formed from the follicle after the release of ovum, to secrete progesterone.

Testosterone is metabolized to two active steroid metabolites: dihydrotestosterone and estradiol. Thus, the effects of testosterone are mediated by testosterone itself, by dihydrotestosterone and estradiol. Testosterone-dihydrotestosterone conversation is catalyzed by 5alpha-reductase, while aromatase catalyzes the conversion of testosterone to estradiol. Testosterone is metabolized in the liver to androsterone and etiocholanolone, which are biologically inactive molecules. Dihydrotestosterone is metabolized to androsterone and androstanediol.

Testosterone acts directly as an androgen by binding to androgen receptors, and indirectly by conversion to dihydrotestosterone, which binds also to androgen receptors. In addition, testosterone acts as an estrogen by conversion to estradiol, which binds to estrogen receptors. Androgen receptors (designated NR3A) are members of a nuclear receptor superfamily, which includes steroid hormone receptors and thyroid hormone receptors. Figure
Figure 30 shows the biological effects of testosterone after conversion to dihydrotestosterone and estradiol via binding to androgen and estrogen receptors.

Prostate cancer is generally androgen selective, and this sensitivity is the basis for the initial treatment of metastatic prostate cancer by androgen deprivation. Metastatic prostate cancer is initially responsive to androgen treatment, but then becomes refractory to continued androgen deprivation. Some patients are resistant to androgen deprivation therapy, in such cases, adrenal androgen synthesis inhibitors such as abiraterone can be used.

Serum testosterone levels are maintained during early adulthood and midlife in men. With age, serum testosterone levels gradually declines. One medical significance of the major changes in decline of testosterone level is the manifestation of benign prostatic hyperplasia. Other changes that occur during adulthood with increasing age are the development of prostate cancer, decreasing energy, libido, muscle mass, and bone mineral density.

There are two major therapeutic uses for androgens: (i) as treatment for male hypogonadism related to testosterone deficiency; and (ii) at low concentration in female hypogonadism, in which testosterone increases mineral density of bone, fat free-mass, and sexual function in comparison with placebo application.

Antiandrogens

Under certain circumstances, the effects of androgens are undesirable, therefore various agents have been developed to inhibit their effects and synthesis. For example, testosterone secretion is inhibited by GnRH (gonadotropin releasing hormone) analogs via inhibition of LH secretion in the pituitary. GnRH analogs are used for treatment of prostate cancer.
Androgen receptor antagonists such as flutamide, bicalutamide, and nilutamide are used in combination with GnRH analogs for treatment of metastatic prostate cancer. Androgen receptor antagonists are also used for treatment of hirsutism in women.

Finasteride (PROSCAR) and dutasteride (AVODART) are inhibitors of 5alpha-reductase enzyme, which blocks the conversion of testosterone to dihydrotestosterone especially in males. These drugs are used to treat benign prostatic hyperplasia. Finasteride and dutasteride increase urine flow rate by reducing concentration of dihydrotestosterone and prostatic mass volume. Side effect of these drugs are not severe.

ACTH (adrenocorticotropic hormone) and adrenal steroids

Glucocorticoids and mineralocorticoids are the products of the adrenal cortex. These agents are typically used for hormone replacement therapy. Furthermore, glucocorticoids suppress inflammation, and are therefore used for treatment of inflammatory conditions such as asthma and autoimmune diseases. Adrenocortical steroids also play an important role in mediating endocrine functions of the anterior pituitary.

Human ACTH is a 39 amino acid peptide. The effects of ACTH (adrenocorticotropic hormone) and other melanocortines derived from POMC (proopiomelanocortin) are mediated by their interactions with five different melanocortin receptor (MC) subtypes comprising a distinct subfamily of G protein-coupled receptors. For instance, the well known effects of MSH (melanocyte-stimulating hormone) on pigmentation result from interaction of the hormone with MC1 receptors on melanocytes. ACTH, which is identical to alpha-MSH in its first 13 amino acids, exerts its effects on the adrenal cortex through MC2 receptors. Beta-MSH acts via MC3 and MC4 receptors on the hypothalamic regulation of appetite and body weight. Therefore, these proteins are subjects of investigation as targets for drugs affecting appetite. MC5 receptors also play a role in the development of aggressive behavior.

ACTH, via MC2 receptors, stimulates the adrenal cortex to secrete mineralocorticoids, glucocorticoids and the androgen precursor dehydroepiandrosterone (DHEA), which can be converted into more potent adrogens in peripheral tissues. The adrenal cortex is separated into three functionally distinct zones that produce various steroids. The outer zona glomerulosa secretes mineralocorticoids (e.g., aldosterone); the middle zona fasciculata secretes glucocorticoids (e.g., cortisol); and the inner zona reticularis secretes DHEA and its sulfate-derived molecule DHEA-S, which circulates at concentration of 1000 times higher than DHEA. In the absence of the anterior pituitary and atrophy of the cortex inner zone, production of glucocorticoids and adrenal androgens is markedly reduced and impaired.

At high concentrations, ACTH induces metabolic changes including ketosis, lipolysis, hypoglycemia, and insulin resistance. Arginine-vasopressin also stimulates corticotropin releasing hormone (CRH), thus liberating ACTH via PLC-IP$_3$-Ca$^{2+}$ pathway. Glucocorticoids inhibit ACTH secretion via direct and indirect actions on CRH neurons. In the pituitary gland, glucocorticoids act through glucocorticoid receptors and inhibit the release of ACTH.

Adrenocortical steroids in humans: Cortisol (hydrocortisone) is the main glucocorticoid, and aldosterone is the main mineralocorticoid in humans. Patients with adrenal insufficiency can be restored to normal health by replacement therapy with mineralocorticoids and glucocorticoids. Adrenal androgens are not necessary for survival.

Physiological effects of corticosteroids include lipid, carbohydrate, and protein metabolism; maintenance of electrolyte and fluid balance; contributing to and preservation of physiological function of the central nervous system, endocrine, kidney, skeletal muscle, immune, and cardiovascular systems. Immunosuppressive and antiinflammatory effects of steroids also provide protective mechanisms under physiological conditions. Effects of corticosteroids based on their potencies in Na$^+$ retention and antiinflammatory actions. The
effects of corticosteroids on Na\(^+\) retention and antiinflammatory actions are not related to each other, and reflect selective actions at different receptors.

Corticosteroids bind to specific receptor proteins in target cells to regulate expression of corticosteroid-responsive genes in changing the levels and array of proteins synthesized by various target tissues. Corticoid-mediated gene expression and protein synthesis is not immediate, but becomes apparent after several hours. Corticosteroids act predominantly via increasing gene transcription, there are some cases in which corticosteroids (glucocorticoids) decrease gene transcription by inhibiting protein-protein interactions. The gene encoding glucocorticoid receptors (GR) is located on human chromosome 5, and gives rise to various receptor isoforms (e.g., GR-alpha, GR-beta) as a result of alternative RNA splicing, leading to production of heat-shock proteins (HSP) including HSP-70 and HSP-90.

Mineralocorticoid receptor (MR) activity is also associated with HSP-90 expression. Furthermore, aldosterone as the main mineralocorticoid hormone exerts its effects on Na\(^+\)/K\(^+\)/H\(^+\) homeostasis and exchange via its action on principal cells in the distal renal tubules and collecting ducts. Aldosterone enhances reabsorption of Na\(^+\) from the tubular fluid and increases urinary excretion of K\(^+\) and H\(^+\), although this does not involve a symple 1:1 ratio of cation exchange in the renal tubule. The imbalance of Na\(^+\)/K\(^+\)/H\(^+\) homeostasis leads to abnormalities of Ca\(^{2+}\) homeostasis in the heart, and may lead to development of atrial and ventricular arrhythmias. Mineralocorticoid and aldosterone deficiency, by contrast, lead to Na\(^+\) wasting, hyponatremia, and metabolic acidosis. When present as a chronic condition, hyperaldosteronism induces hypertension, whereas aldosterone deficiency leads to hypotension and vascular collapse. Hypertension is also registered in patients with Cushing’s syndrome, which is related to endogenous secretion of cortisol.

Antiinflammatory and immunosuppressive actions of glucocorticoids are related to their effects on lymphocytes by altering the immune responses of these cells. Multiple cellular mechanisms are involved in the inflammatory suppression of glucocorticoids. They decrease the release of vasoactive and chemotaxtective factors, diminish secretion of proteolytic enzymes and decrease extravasation of leukocytes and fibrosis. Glucocorticoids also reduce expression of proinflammatory cytokines, IL-1, IL6, TNFalpha, enzymes of COX2 and NOS.

Only the fraction of glucocorticoids that is unbound is active and can enter cells. Two major effects result from the therapeutic use of corticosteroids. One of them is withdrawal of steroid therapy leading to acute adrenal insufficiency, and the other one is the fluid and electrolyte abnormalities causing hypertension, hyperglycemia, osteoporosis, osteonecrosis, and increased susceptibility to infections, myopathy, cataracts, peptic ulcers, and growth arrest.

The following adrenocortical steroids are in medical use: alclometasone (ACLOVATE), metamethasone (CELESTONE), budesonide (PULMICORT), ciclesonide (ALVESCO), desonide (DESONATE), dexamethasone (MAXIDEY), flunisolide (AEROBID), hydrocortisone (TEXACORT), hydroxycortisone (LOCOID), methylprednisolone (MEDROL), prednisolone (FLO-PRED), triamcinolone (AZMACORT).

Therapeutic uses of corticosteroids include (i) replacement therapy in acute and chronic adrenal insufficiency, (ii) congenital adrenal hyperplasia, rheumatic and inflammatory diseases such as systemic lupus erythematosus vasculitis, polyarteritis nodosa, and Wawener’s granulomatosis, (iii) renal diseases, (iv) allergic diseases, (v) asthma bronchiale, (vi) skin diseases in treatment of varety of inflammatory dermatoses, (vii) chronic bowel diseases such as chronic ulcerative colitis and Crohn’s disease, (viii) cerebral edema, (ix) hepatic diseases, (x) ocular diseases, (xi) thrombocytopenia, (xii) autoimmune disease, and (xiii) organ transplantation. Although, glucocorticoid therapies are contraindicated in
infectious diseases, there are a limited number of settings, in which they are indicated for therapy of specific infectious pathogens. Two such examples (xiv) for beneficial effects of glucocorticoids in AIDS patients are (1) Pneumocystis carinii caused pneumonia, and (2) decreased incidence of long term neurological impairment associated with Haemophilus influenzae type B meningitis in infants.

Inhibitors of the biosynthesis of adrenocortical steroids

Hypercortisolism is most frequently caused by corticotrophic adenomas that overproduce ACTH (Cushing’s disease) or by adrenocortical tumors and bilateral hyperplasias that overproduce cortisol (Cushing’s syndrome). Surgery is the primary treatment of choice in the aforementioned diseases, although it is not always effective, and adjuvant therapy with steroid inhibitors is also necessary. This group of agents includes etomidate (AMIDATE), mitotane (LYSODREN), metyrapone (METOPIRONE), and ketoconazole (NIZORAL).

Metyrapone is a selective inhibitor of 11-beta-hydroxylase (CYP11B1) which converts 11-deoxycortisol to cortisol in the terminal reaction of glucocorticoid biosynthesis. Thus, ACTH production and adrenal biosynthetic capacity are inhibited by this drug. Metyrapone is used to treat hypercorticism resulting from adrenal neoplasms and tumors producing ACTH ectopically.

Ketoconazole is primarily an antifungal agent and inhibits the activity of 17-alpha-hydroxylase (CYP17) enzyme by blocking steriodogenesis. Ketoconazole is well tolerated by patients and the most effective inhibitor of steroid hormone biosynthesis in hypercortisolism.

Etomidate and mitotane have sedative and anaesthetic activity, and are able to inhibit cortisol secretion by inhibiting CYP11B1 enzyme activity.