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Wrocław University of Technology

Medicinal Chemistry

Roman Gancarz

SYNTHETIC ORGANIC DRUGS
Lecture

Wrocław 2011

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Preface

Every book which covers the description of the major drugs used in the modern pharmacological therapy consists of many pages. Due to the limited space of this study guide, it is not possible to cover all pharmacologically important drugs with the mechanism of their action. The aim of this study guide is not to present all of them, since the reader may find much better and more detailed information in the literature which is suggested for further study.

In addition, this study guide is not addressed to pharmacy students but to students of chemistry attending the lectures "Synthetic organic drugs". The major goal in their education is preparation for the design of new drugs so the major intention of this study guide is to get an idea about the strategies of pharmaceutical therapy and drug action.

Since it is not possible to cover all drugs, we will focus only on a more detailed description of a few selected drug classes from the point of view of their mechanism of action. The presented examples were selected in order to present various possible strategies of drug action.

Two drug categories were chosen as examples for a more detailed description. One group of drugs are chemotherapeutic drugs whose action is to kill the growing cell (killing the organism or cell or stopping the action of the enzyme). The other type presented in this manuscript are drugs acting on the nervous system which acts on receptors and modulates their response (neurotransmitter synthesis, release, action, reuptake, degradation).

For the rest of the most important drugs there is only basic information about their action. The reader should extend their knowledge based on the suggested further reading. In the additional materials the reader will find the examples of the strategies of treatment in ten states of sickness.

In order to follow that main topic, the reader is provided with basic information on the biological system, its function and also basic information about the mechanisms and forces governing the interaction between molecules.

Such information is necessary to understand why and how the system is functioning and how it can be regulated by external compounds (drugs). The guide is addressed to chemistry students so the major aim is to present chosen examples of how chemical knowledge can be applied in understanding the drug activity and especially to get an idea for a new drug design.

<u>In the preparation of the presented study guide the following materials were taken advantage:</u>

M. Lieberman, Marks' Basic Medical Biochemistry a Clinical Approach, Wolters Kluwer Health/Lippincott Wiliams & Wilkins, 2009

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Wikipedia, http://en.wikipedia.org/

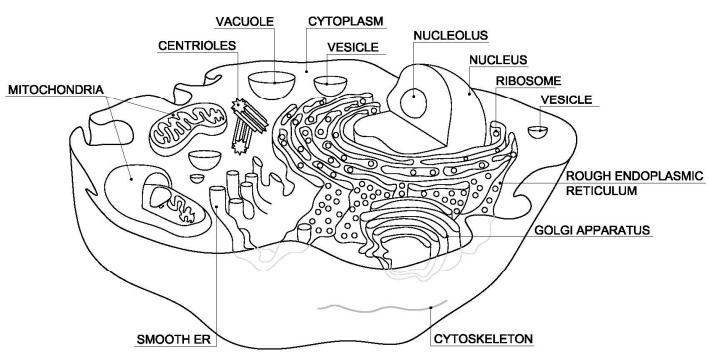
1.Fundamentals of Cell Biology

The **action of drugs** on the human body is called pharmacodynamics, and what the **body does with the drug** is called pharmacokinetics. The drug is addressed to enter a cell of a human body or a cell of an unwanted organism. Then its role is to stimulate certain receptors, ion channels, enzymes or transporter proteins in order to return back the pathological state to normal physiological state. Thus to understand the drug action it is necessary to have basic knowledge about the cell structure and basic processes taking place in it. In order to help to follow the topic of the subsequent chapters some basic structures and processes taking place in the cell are outlined in the following chapter.

1.1.Cell

A cell is a basic unit of a living organism. Each tissue in human body is composed of similar cell types and different from those in other tissues. The structural feature of the cell reflects its function. The cell is composed from plasma membrane which forms a selective barrier between interior and exterior of the cell. Inside the cell there are organelles forming separate compartments, each surrounded by their own membranes and each having a unique function.

1.1.1.Compartments in a cell



Schematic figure showing the major components of a typical animal cell (organelles).The components are given below:

(1) nucleolus
(2) nucleus
(3) ribosomes (little dots)
(4) vesicle
(5) rough endoplasmic reticulum (ER)
(6) Golgi apparatus
(7) Cytoskeleton
(8) smooth ER
(9) mitochondria
(10) vacuole
(11) cytosol
(12) lysosome
(13) centrioles within centrosome

1.1.1.1.Cytoplasm

Cytoplasm is the part of a cell that is enclosed within the cell membrane. It contains organelles, seperated from each other by biological membrans. Most of the cellular activities, metabolic pathways and cell divisions occur in cytoplasm. Cytoplasm has three major elements: the cytosol, organelles and inclusions.

1.1.1.2.Cytosol

The part of the cytoplasm outside organelles which makes up 70% of cell volume is called cytosol. It is a complex mixture of dissolved molecules, and water. Cytosol is a gel containing the proteins that make up the cytoskeleton.

1.1.1.3.Organelles

Organelles are membrane-bound compartments within the cell each with specific functions The major organelles are**: lysosyme, mitochondria, ribosomes, peroxisomes, nucleus, endoplasmic reticulum, Golgi complex.** Organelles contain various amounts of different enzymes consistent with the function of the organelle.

(endocytosis) or out of the cell (exocytossis).

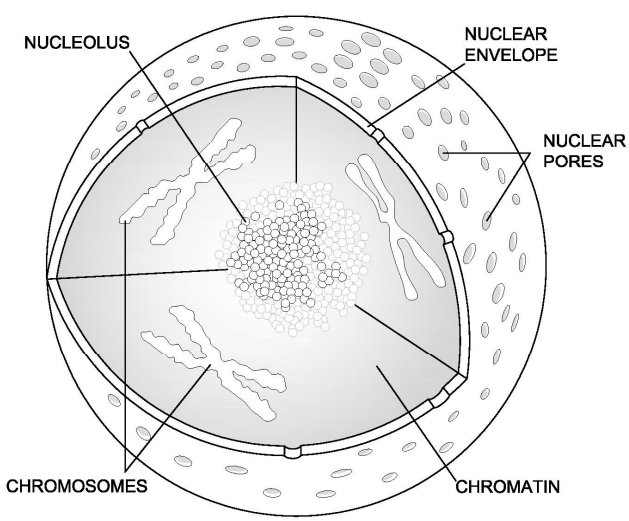
Lysosyme

Lysosyme contains enzymes degrading proteins and other large molecules. They are inside the cell surrounded by their own membrane, so their digestive enzymes are not released into cytosol. Their role is to eliminate unwanted material, foreign cells (phagocytosis), and making use of their components.

Peroxisomes

They are cytoplasmic organelles, similar to lysosomes, involved in oxidative oxidation using molecular oxygen. Peroxisomes oxidate very long fatty acids, convert cholesterol to bile acids, they synthesise the ether lipids (plasmalogens).

Nucleus and Nucleolus



The largest animal organelle nucleus, separated from the rest of cell contains genetic material located in the chromosomes which are composed of DNA. It contains proteins called histones playing a role in gene regulation and also a variable amount of other proteins. The

nucleolus, substructure of the nucleus is a non-membrane bound structure composed of proteins and nucleic acids and is the site of rRNA transcription. Ribosomes are generated in nucleolus and must travel into the cytoplasm through nuclear pores. Proteins required for replication, transcription and other processes are moving through these pores into the nucleus.

mRNA when transcribed from DNA moves through the nuclear pores into the cytoplasm and is translated into the sequence of aminoacids.

Ribosome

This is the place where the final step of protein synthesis takes place. They are generated in nucleolus and must travel to cytoplasm.

Endoplasmic reticulum

Some proteins are synthesized in endoplasmic reticulum which is the complex of ribosome and complex membrane system. Endoplasmic reticulum is also the place of lipid synthesis and transport of molecules to the Golgi.

Mitochondria

Mitochondria play the role of a cell power station where most of the ATP is synthesized.

Golgi complex

Golgi complex is responsible for transport of molecules to the plasma membrane and other membrane systems and also for secretion. It also participates in posttranslational modification of proteins like carbohydrate addition, sulfation, phosphorylation.

Centrioles and centrosomes

Centrioles are a very important part of centrosomes, which are involved in organizing microtubules in the cytoplasm.

Vesicle

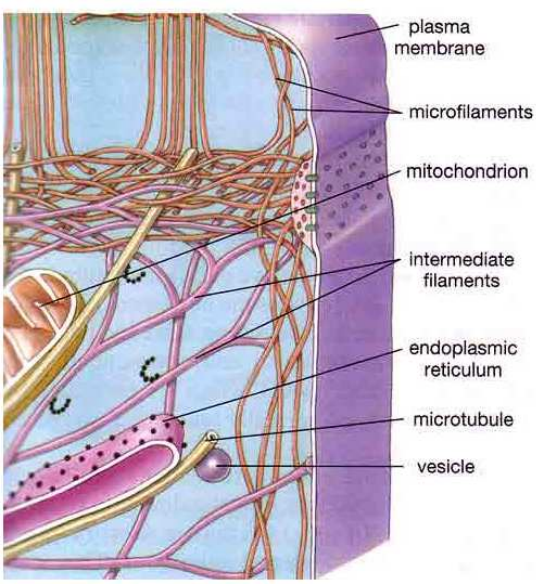
Vesicle is a small bubble separated from cytosol by at least one phospholipid bilayer. Vesicles have specialized functions depending on what materials they contain. They can store or transport the material.

Inclusions

The inclusions are small particles of insoluble substances suspended in cytosol (crystals of calcium oxalate or silicon dioxide granules of starch, glycogen, or polyhydroxybutyrate, lipid droplets storing fatty acids and sterols.

1.1.1.4.Cytoskeleton

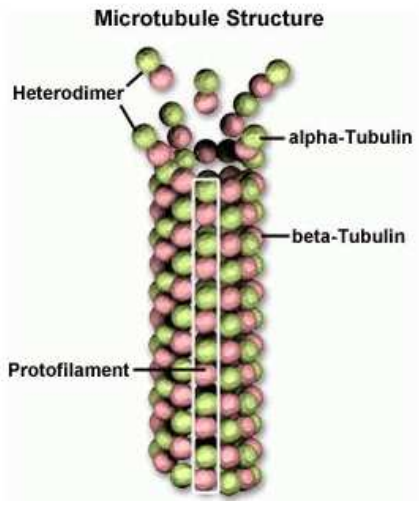
This is the flexible fibrous complex network of protein system maintaining the position of organelles and responsible for moving the compounds and organelles within the cell. It is important to know that cytoskeleton is not only a passive internal support but also plays a dynamic regulatory function in the cell. It contains: microfilaments, myofilament**,** intermediate filaments, microtubules, catenins and other.



http://liquidbio.pbworks.com/f/1194728224/cytoskeletonn.jpg

Microfilaments (or **actin filaments**) are flexible and relatively strong linear polymers of actin subunits, they are the thinnest filaments of the cytoskeleton found in the cytoplasm of all eukaryotic cells. Microfilaments function in cell is crawling, amoeboid movement, and changes in cell shape.

Microtubules, cylindrical tubes composed of tubulin subunits with a diameter of 25 nm and length from 200 nanometres to 25 micrometers, are the components of the cytoskeleton. They are responsible for the positioning of the organelles in the cytoplasm and movement of the vesicles and vesicular transport. They are very important in the process of cell division as they form a spindle. They consist of polymerized α and β tubulin dimers.



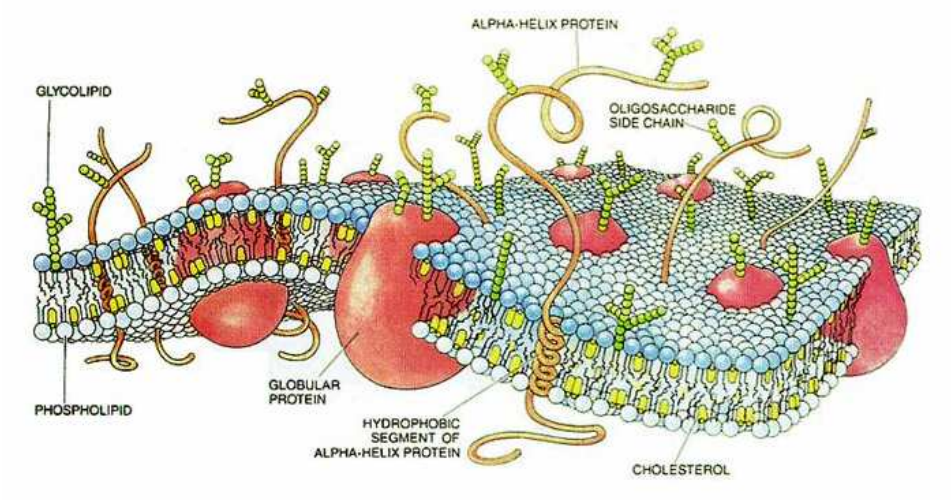
http://vbaulin.front.ru/research/images/microtubule.gif

Intermediate filaments are made from fibrous protein polymers which have an average diameter of 10 nanometers, i.e. the size which is between that of actin (microfilaments and microtubules). They provide the support for the membrane and other cellular components.

1.2.Membrane

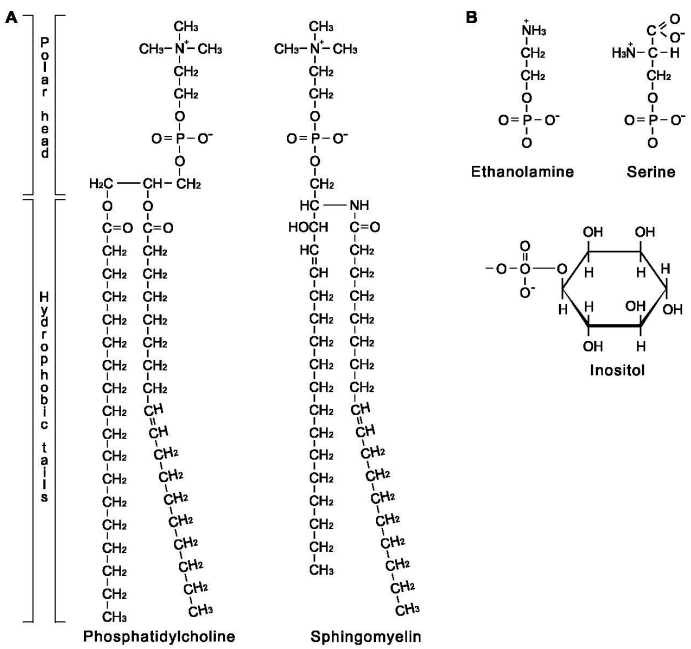
Membrane is a fluid mosaic composed of a lipid bilayer and the mosaic of proteins able to move laterally. Proteins are spanning the cell membrane, **integral proteins**, or are attached to the surface of membrane (lipid or protein part), **peripheral proteins**. Some proteins are

glycoproteins as they have carbohydrate chains attached to them. The carbohydrate component function in many cases serves as cell recognition markers.



http://www.ncnr.nist.gov/programs/reflect/rp/biology/cell_membrane_p2.jpg

1.2.1.Phospholipids.



1.2.2. Proteins in the membrane

Transmembrane proteins

Transmembrane proteins posses hydrophobic fragments interacting with the membrane lipid portion and thus sealing the membrane while hydrophilic fragments are on both aqueous sides of the membrane. Many of such proteins are either structural proteins, channels or transporters for ions and molecules, others are receptors for neurotransmitters or hormones.

Peripheral proteins

Peripheral proteins are bound through weak electrostatic interactions with the head group of lipids or with integral proteins.

Lipid anchored proteins

Lipid anchored proteins are proteins attached via covelent bonds to the inner or outer surface of membrane. A great number of such proteins are involved in hormonal regulations.

Glycosylated proteins and lipids

Some of the membrane proteins and lipids are glycosylated with short oligosaccharides. Some of those residues serve as the cell recognition elements, others form a hydrophilic carbohydrate layer which protects a cell against digestion, for example. The last one is called glycocalyx

1.3.Transport across membrane

Membranes form a barrier around the cell and control the exchange of the molecules between the the exterior and interior. So the transport system is required. Transport is passive if no energy is required or active if the process requires energy supply (in most cases provided by the ATP hydrolysis).

For small molecules transport falls into four categories:

-simple diffusion

Gases like oxygen, nitrogen, lipid soluble compound like steroid hormones can cross the membrane by simple diffusion. The process is controlled by the concentration gradient so energy is not required.

-facilitative diffusion

This process requires that the transported molecule is bounded to a specific carrier (transport protein). The changes in the conformation of such complex allow the transported molecule to be released on the other side of the membrane. The process does not require energy supply so it is considered as diffusion and the compound is transported down an electrochemical gradient usually from a high concentration to a low concentration, to equilibrate between both sides of the membrane.

-gated channels

In such transport the transmembrane proteins form a pore which is opened on a stimulus, for example a voltage change, or phosporylation of the regulatory domain. Transport requires energy supply.

-active transport

Active transport similarly to facilitative transport is mediated by protein transporters in the membrane, but energy is required in order to concentrate the compound on one side of the membrane so it works against the gradient. It could be classified as primary or secondary.

Primary active transport, also called direct active transport, if the energy is supplied directly to transporter molecule.

In **secondary active transport**, in contrast there is no direct coupling of ATP. In this case energy is used to establish the ion gradient which is then used to concentrate another compound.

For example in the transport of glucose, first a sodium ion binds to carrier protein, stimulating binding of glucose. After conformational change the protein releases the sodium ion and glucose on the other side of the membrane.

Three main forms of active transport are; antiport (if two species are moved in opposite directions across a membrane), symport (if two species are moved in the same directions across a membrane) and uniport (if single molecule is transported at a time).

-vesicular transport

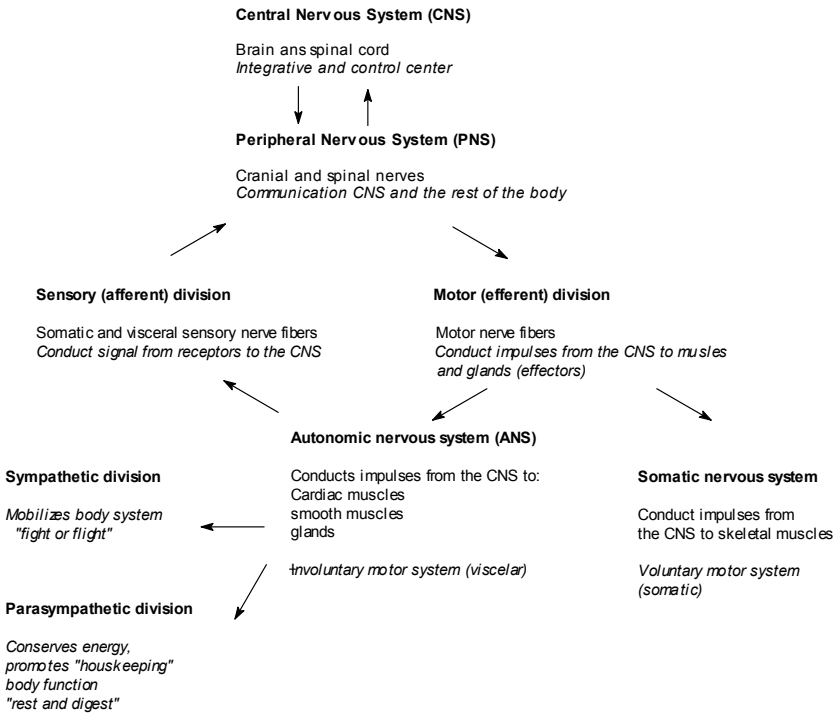
Vesicular transport occurs when a membrane completelely surrounds the compound or other individuum, and after that the fusion with another membrane system occurs (for example cell). The effect of the process is moving the transported idividuum into the cell

2.Systems in the Body

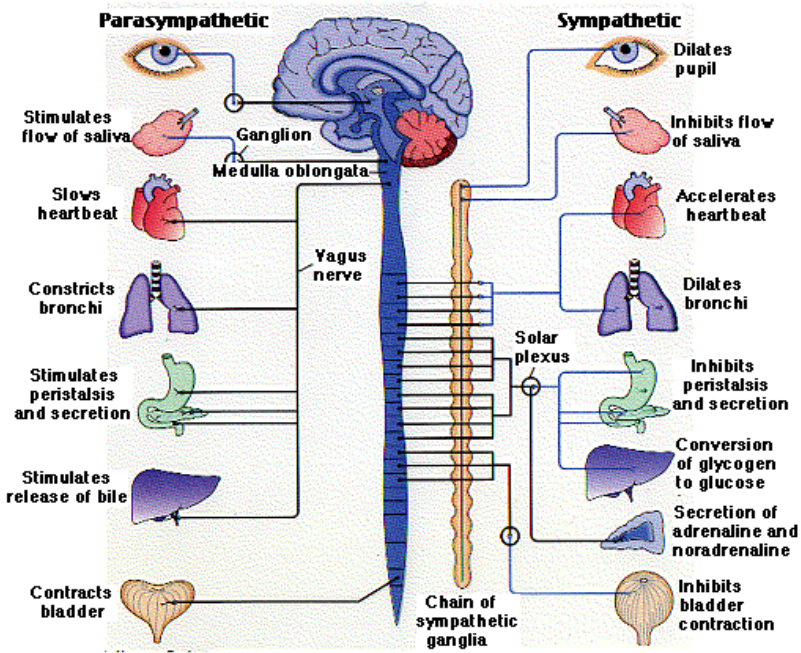
Cells and tissues do not exist in isolation. They compose anatomically and functionally different structures called systems. Processes performed by organelles account for the processes in cells, which in turn create an effect in tissues and organs in the body. The interaction between systems provide for almost all if not all aspects of the life. Such knowledge helps define the biochemistry underlying good health and disturbances leading to disease. It is possible to separate disease into classes that loosely correlate with the different systems.

2.1.Nervous system

Anatomically there are two parts of the nervous system – CNS (central nervous system) which consist of a brain and a spinal cord and the rest called peripheral nervous system. Part of the peripheral nervous system is the autonomic nervous system which controls the glands and non skeletal muscles and is not under conscious control.



The control in the autonomic nervous system is provided by two parts antagonistic to each other: sympathetic and parasympathetic nervous systems



Wikipedia, http://en.wikipedia.org/

In addition to the brain and spinal cord, the principal organs of the nervous system are:

- eyes
- ears
- sensory organs of taste
- sensory organs of smell
- sensory receptors located in the skin, joints, muscles, and other parts of the body

The nervous system can be damaged by:

- injuries
- infections
- degeneration
- structural defects
- tumours
-

Main disorders of the nervous system may involve:

vascular disorders - such as stroke, transient ischemic attack (TIA), subarachnoid hemorrhage, subdural hemorrhage and hematoma, and extradural hemorrhage

infections - such as meningitis, encephalitis, polio, and epidural abscess

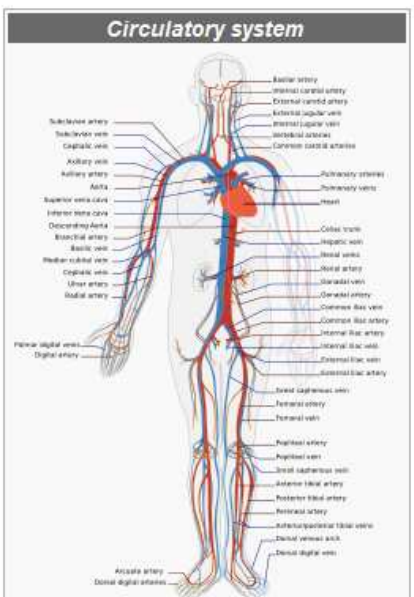
structural disorders - such as brain or spinal cord injury, Bell's palsy, cervical spondylosis, carpal tunnel syndrome, brain or spinal cord tumors, peripheral neuropathy, and Guillain-Barre syndrome

functional disorders - such as headache, epilepsy, dizziness, and neuralgia

degeneration - such as Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis (ALS), Huntington's chorea, and Alzheimer's disease

2.2.Cardiovascular system

The circulatory system consist of heart, arteries, capillaries, veins and is responsible for material and heat transfer.



The human circulatory system. Red indicates oxygenated blood, blue indicates deoxygenated.

Latin *systema cardiovasculare*

Wikipedia, http://en.wikipedia.org/

Main disorders of the cardiovascular system may involve:

Some of the most common cardiovascular diseases include "heart disease," "hypertension," "atherosclerosis," "diabetes" and "peripheral artery disease" or "PAD."

2.3.*Integumental system*

The integumentary system (skin, hair, nails) is the organ system that protects the body from damage, it may serve to waterproof, cushion and protect the deeper tissues, excrete wastes, regulate temperature and is the place for sensory receptors to detect pain, sensation, pressure and temperature. In humans it accounts for about 16 percent of total body weight and as such is one of the largest system.

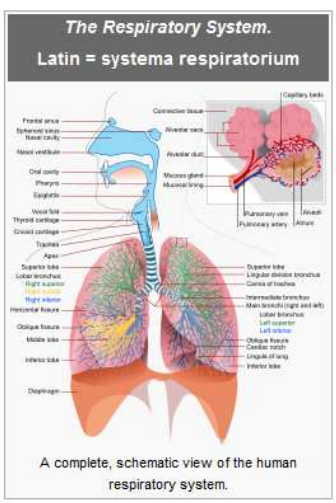
Main disorders of the integumental system may involve:

Possible diseases and injuries to the human integumentary system include:

rash, blister, athlete's foot, infection, sunburn, skin cancer, albinism, acne, herpes, cold sores

2.4.Respiratory system

The main role of the respiratory system is to provide about 360 liters of oxygen every day and elimination carbon dioxide.



A complete, schematic view of the human respiratory system.

Wikipedia, http://en.wikipedia.org/

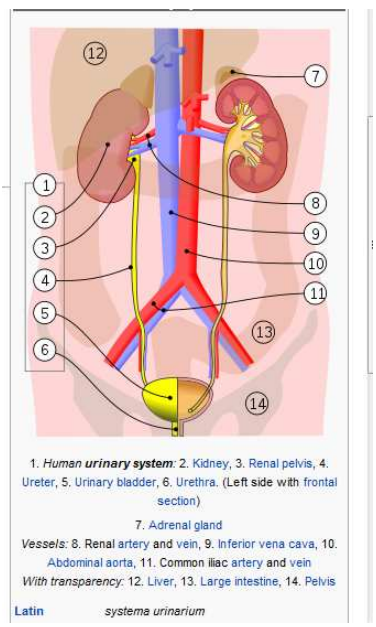
The respiratory tract is constantly exposed to microbes. One of the mechanisms to defend it and prevent pathogens from entering the body is coughing.

Main disorders of the respiratory system may involve:

Disorders of the respiratory system can be classified into four general areas: obstructive conditions (e.g., emphysema, bronchitis, asthma attacks), restrictive conditions (e.g., fibrosis, sarcoidosis, alveolar damage, pleural effusion), vascular diseases (e.g., pulmonary edema, pulmonary embolism, pulmonary hypertension), Infectious, environmental and other (e.g., pneumonia, tuberculosis, asbestosis).

2.5.Urinary system

The urinary system is responsible for the elimination of soluble waste product from blood. The separation takes place in the kidneys.



1. *Human **urinary system**:* 2. Kidney, 3. Renal pelvis, 4. Ureter, 5. Urinary bladder, 6. Urethra. (Left side with frontal section)

7. Adrenal gland

Vessels: 8. Renal artery and vein, 9. Inferior vena cava, 10. Abdominal aorta, 11. Common iliac artery and vein

With transparency: 12. Liver, 13. Large intestine, 14. Pelvis

Latin *systema urinarium*

Wikipedia, http://en.wikipedia.org/

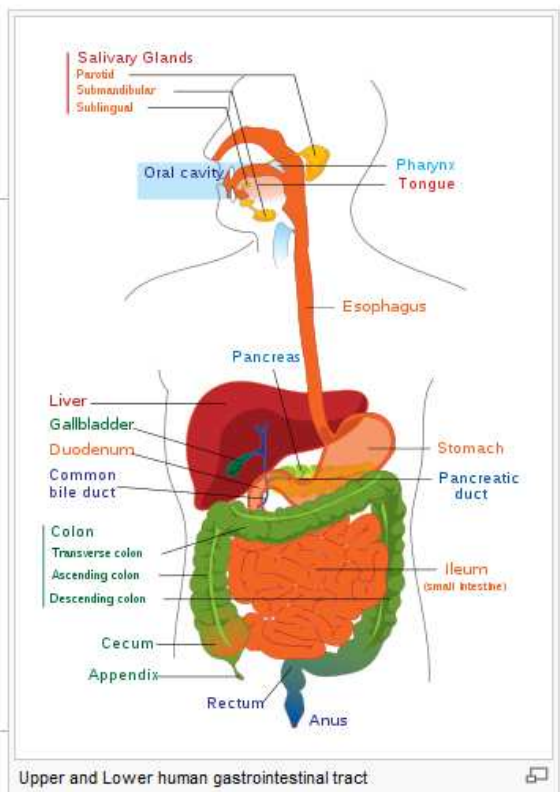
Main disorders of the urinary system may involve:

Kidney disease

Renal failure is defined by functional impairment of the kidney and can be acute or chronic.

It may require medication, change of dietary habits, change of lifestyle and dialysis. Kidney can be affected by primary renal cell carcinomas as well as metastatic cancers - renal cell carcinoma (kidney cancer). The term used for the disease of the kidney is "nephropathy".
The term "uropathy" refers to a disease of the urinary tract: hemorrhage, functional blockage, inflammation infection (bacteria, protozoa or fungi), uncontrolled cell growth (can cause neoplasia), urinary tract infections (UTIs), interstitial cystitis, involuntary loss of urine, benign prostatic hyperplasia (where the prostate overgrows), prostatitis (inflammation of the prostate), bladder cancer, prostate cancer.

2.6.Digestive system



Upper and Lower human gastrointestinal tract

Wikipedia, http://en.wikipedia.org/

This is a tract from the mouth to anus associated with liver, glands, pancreas, gall bladder. This is a system in which enzymatic digestion and absorption of products of digestion takes

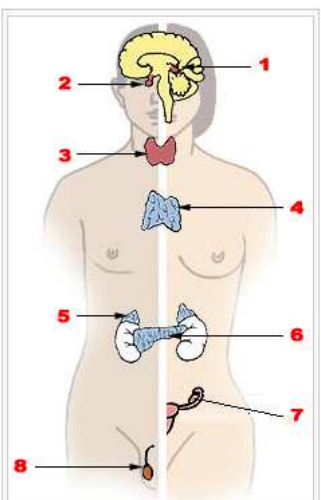
place. The main function of the liver is to modify, and store them as well as detoxify and inactivate those which may be dangerous to health.

Main disorders of the digestive system may involve:

There are a number of diseases and conditions affecting the gastrointestinal system, including: cholera, colorectal cancer, diverticulitis, enteric duplication cyst, gastroenteritis, ("stomach flu" an inflammation of the stomach and intestines), giardiasis, inflammatory bowel disease (including Crohn's disease and ulcerative colitis), irritable bowel syndrome, pancreatitis, peptic ulcer disease, appendicitis, celiac disease,

2.7.Endocrine system

The **endocrine system** is a system of glands, each of which secretes a type of hormone into the bloodstream to regulate the body functions. Hormones regulate many functions of an organism, like mood, growth and development, tissue function, and metabolism. Some organs like liver, kidney and intestine also secrete hormones and they also are part of endocrine system.



Major endocrine glands. (Male on the left, female on the right.) ***1.*** *Pineal gland* ***2.*** *Pituitary gland* ***3.*** *Thyroid gland* ***5.*** *Adrenal gland* ***6.*** *Pancreas* ***7.*** *Ovary* ***8.*** *Testis.* Note: the Thymus (labelled 4.) is not an endocrine gland.

Wikipedia, http://en.wikipedia.org/

Endocrine disorders may be divided into three groups:
Endocrine gland hyposecretion (leading to hormone deficiency)
Endocrine gland hypersecretion (leading to hormone excess)
Tumors (benign or malignant) of endocrine glands

Main disorders of the endocrine system may involve:
The list of the endocrine system diseases is long. The most common ones are: diabetes mellitus, thyroid disease, and obesity, productive pituitary adenoma, lack of a gland diabetes mellitus, adrenal hormone excess, sex hormone disorders, menstrual function or fertility disorders, tumours of the endocrine

2.8.Reproductive system

The **reproductive system** is a system within an organism the role of which is reproduction. The major organs of the human reproductive system include testes in a male and ovaries in a female and genitalia (penis and vulva). Both the ovary and testes produce hormones so they overlap with endocrine system.

The main disorders of the reproductive system may involve:
A **reproductive system disease** is a disease that impairs the ability to reproduce. They can be:
1. genetic or congenital abnormalities, (hermaphroditism), 2.cancers, 3. infections, 4. functional problems (impotence, physical damage, physiological issues or infertility).
The most typical reproductive tract infections, (sexually transmitted diseases) are for female (fallopian tubes, ovary and uterus vagina, cervix and vulva) and for males penis, testicles, urethra or the sperm tube. The infections are endogenous infections, iatrogenic infections and sexually transmitted infections and can be caused by a bacterium, virus, fungus or other organism. Some can be cured easily but some are incurable such as AIDS and herpes.
Specific reproductive diseases are Peyronie's disease in males and endometriosis in females. Turner syndrome, Klinefelter's syndrome, cystic fibrosis, and bloom syndrome. Some chemicals may have influence on reproductive tract disorders: lead, dioxin, styrene, toluene.

2.9.Musculoskeletal system

Bones constitute the framework and support for the attachment of the muscles. The latter ones are responsible for the locomotion. In the long bones there are cavities in which bone marrow is present, there blood red cells and immune white cells are produced for the blood and lymph.

The main disorders of the muscoskeletal system may involve:

Back pain, repetitive strain injury (chronic), osteoarthritis, rheumatoid arthritis systemic lupus erythematosus, fibromyalgia (chronic)

2.10.Immune system

Immune system has no cell and is anatomically diffuse. It consists of cells which mediate immune response and tissues which produce and store them (bone marrow, lymph nods, thymus splin)

The main disorders of the immune system may involve:

Failures can be classified into three broad categories: immunodeficiencies, autoimmunity, and hypersensitivities.

Immunodeficiencies occur when one or more of the components of the immune system are inactive. The reasons are age, obesity, alcoholism, deficiency of nutrients such as iron; copper; zinc; selenium; vitamins A, C, E, and B_6; and folic acid (vitamin $B_{9)}$, loss of the thymus. AIDS and some types of cancer cause acquired immunodeficiency.

Autoimmunity when immune system fails to properly distinguish between self and non-self, and attacks part of the body

Hypersensitivity occurs when immune response is the damage the body's own tissues. It could be for example an immediate or anaphylactic reaction or when antibodies bind to antigens on the patient's own cells, marking them for destruction.

2.11.Reticuloendothelial system

The **reticuloendothelial system** (**RES**) is a part of the immune system that consists of the phagocytic cells located in reticular connective tissue.

3.Important Molecules

To answer the question why some molecules act specifically on other molecules can be found in the structure and chemical properties of the two interacting molecules. In general drugs are small molecules and the targets are macromolecules. Most of the principles in such interaction apply also to the interaction between macromolecular drugs and macromolecular targets.

3.1.Proteins

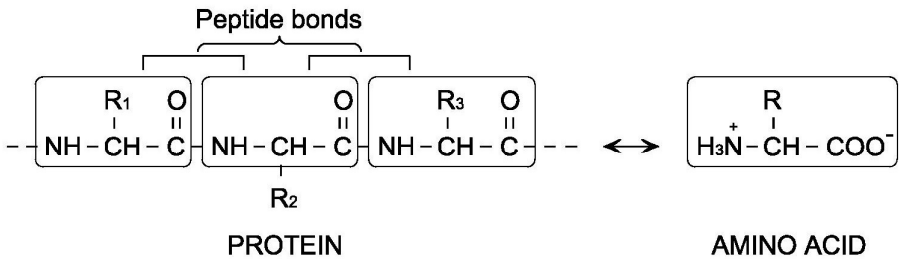
Proteins, the main components of enzymes and molecular receptors, are peptides synthesized on a ribosome. They are long chains composed of aminoacids linked by a peptide bond. The sequence of the chain are determined by the sequence of nucleotides in DNA. Within the human population, the primary structure of a protein may vary among individuals, tissue of the individual, and the stage of development. The variations arise from mutations and are passed to the next generation. The variation in phenotype contributes to our individual characteristic, or increases susceptibility to certain diseases. If the changes occur with significant frequency in the population it is referred to as polymorphism.

3.1.1.Aminoacids, polypeptide chain

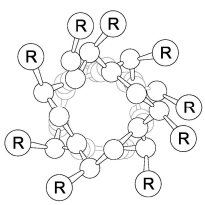
There are twenty different aminoacids commonly found in proteins, all of them are α aminoacids having the amino group and carboxylic group attached to the same carbon atom. The α carbon has two additional substituents: a hydrogen atom and an additional chemical group called side chain (R) which is different for each aminoacid. The simplest aminoacid-glycine has a hydrogen atom as side chain, so all aminoacids, except glycine, have stereogenic α carbon with four different substituents thus all aminoacids, except glycine, are chiral and can exist in D or L configuration. Mammalian proteins consist entirely of L-aminoacids. According to the polarity and structural features, aminoacids are classified into different groups: aliphatic, aromatic, sulphur containing, acidic, basic.

The short names, three-letter and one-letter descriptions are given in the figure above. A single letter description is usually used to denote the aminoacid sequence in polypeptide chain.

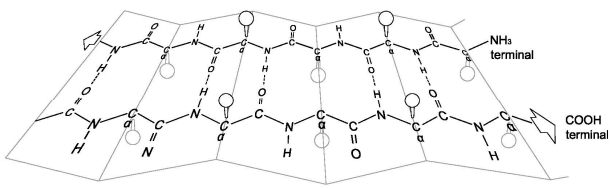
A short polypeptide chain (3 aminoacids) is presented below.



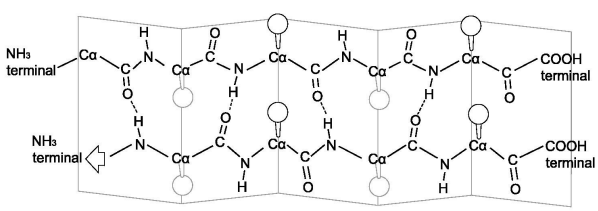
The sequence of aminoacids is referred as **primary structure**. Interaction between aminoacids in the polypeptide chain results in the formation of conformational **secondary structures** like α helix, β- pleated sheet and β- barrel (closed β sheet) or parrarel β strand.



α helix



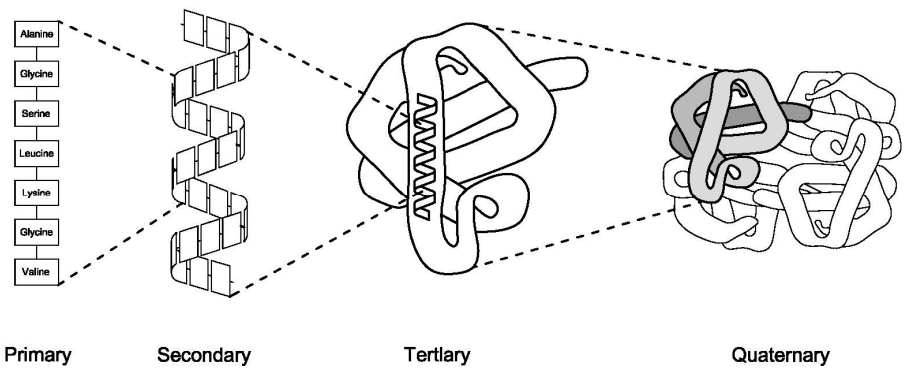
β- pleated sheet



parrarel β strand

. Interaction between aminoacid distals in the polypeptide chain results in the formation of disulphide bridges due to the interaction between two thiol groups of methionine aminoacids. This leads to the formation of **tertiary structures**.The process of formation of a three dimensional structure from a statistical distribution of shapes for all the primary structure chains is called **protein folding**. Misfolding can lead to the loss of the protein function and can be the origin of a disease.

Polypeptides may interact and form complex **quaternary structures** that result from the interaction of several polypeptides chains.



The independent three dimensional region which is formed by several aminoacids (usually from 25 to 500), that plays important function, and exists independently of the rest of the protein chain is called a domain. Many proteins consist of several structural domains

3.1.2.Interaction with other molecules

Different portions of protein have different affinity for water. There are hydrophilic segments, often located on the exterior surface and hydrophobic ones often exposed in the inside part. The specific fragment at which a substrate binds is called a **binding site**. In the case of enzymes the binding site is called **active site**.

At this site the enzymatic catalytic transformation takes place. Very often the interaction between a molecule and a target protein results in changing the conformation of the latter. Such mechanism is called an **induced fit** because it results in the improvement of the quality of the binding interaction.

The interaction between the substrate and polypeptide is a result of multiple chemical interaction. The favourability of such interaction is referred as **affinity** to the binding site. It is realized due to **van der Walls forces, hydrogen bonding, ionic interaction, electrostatic interaction, hydrophobic, hydrophilic interaction**. See the next chapter.

3.1.3.Modified aminoacids, modified proteins, regulatory modification

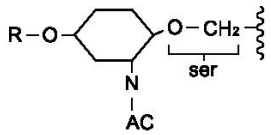
After the protein has been synthesized, some aminoacid residues in the primary sequence may be further modified in the enzyme catalysed reaction. It could be for example the addition of a chemical group or oxidation. Such changes are called posttranslational changes. The most frequent ones are: glycosylation, fatty acylation, prenylation, phosphorylation, acetylation, phosphorylation, acetylation ADP-ribosilation of arg, ser, thr, tyr.

The effect of such modification is the change of activity. For example the carboxylation of γ carbon in glutamate in certain coagulation cascade proteins is important for attaching them to the surface and the formation of blood-clot.

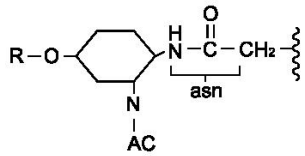
There are more than 100 such modifications in the human proteins known so far.

Carbohydrate addition

O-glycosylation: OH of ser, thr, tyr

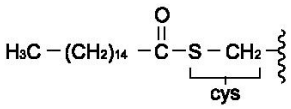


N-glycosylation: NH2 of asn

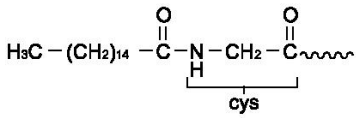


Lipid addition

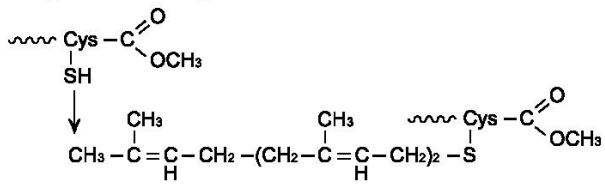
Palmitoylation: Internal SH of cys



Myristoylation: NH of N-terminal gly

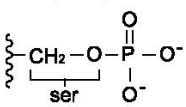


Prenylation: SH of cys

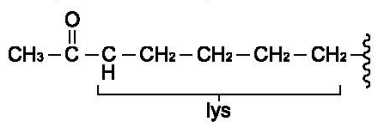


Regulation

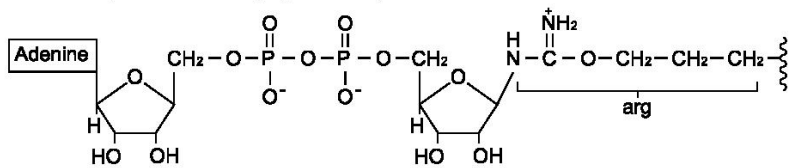
Phosphorylation: OH of ser, thr, tyr



Acetylation: NH_2 of lys, terminus

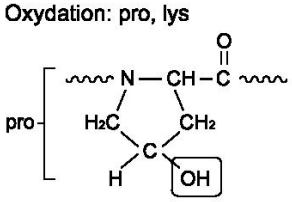


ADP-ribosylation: N of arg, gln; S of cys



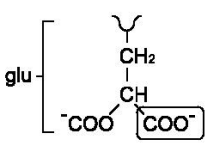
Modified amino acids

Oxydation: pro, lys



4-Hydroxyproline

Carboxylation: glu



γ-Carboxyglutamate residue

Glycosylation

Oligosaccharides are bound to proteins by N- or O- linkages. They are found in the cell surface proteins (N-linked). Their main role is to protect the cell from immune attack (protection against proteolysis). Intracellular polypeptides are linked to oligosaccharides via O-linkages. The examples are: insulin, adenyl cyclase.

Fatty acylation

Many membrane proteins are modified by covalently attached lipid groups. Palmitoyl and mirystoyl are the most frequently found ones.

3.1.4.Enzymes

Proteins which are catalysts of biochemical reactions are called enzymes. They speed up the reaction by a factor of 10^6 to 10^{14}. Without the catalytic power of the enzyme, many physiologically important reactions would be too slow for the life to exist (for example the nerve signal transmission or heart contraction).
Enzymes are divided into six classes:

Oxidoreductases catalyzing the oxidation and reduction reactions (electron transfer processes).

Transferases catalyzing the group transfer reactions from one molecule to another molecule.

Hydrolases catalyzing the hydrolysis reactions in which the bonds are cleaved by the addition of water.

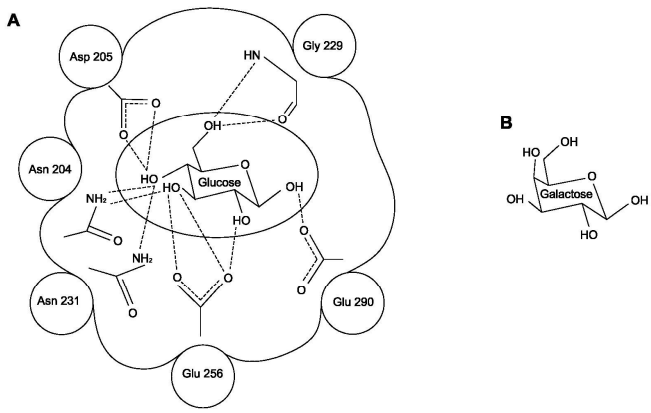
Lyases which catalyze the C-C o other bonds by means other than hydrolysis.

Isomerases which catalyze the isomerisation reactions

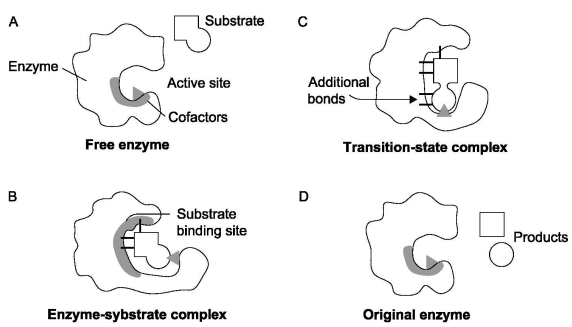
Ligases which catalyse the formation of C-C, C-S, C-O and C-N bonds.

In the process of catalysis the substrate binds to the active site of the enzyme forming the complex enzyme-substrate due to many interactions. The binding of glucose in glucose binding site of glucokinase is shown below. Glucose has a hydroxyl group on the carbon 4 in the equatorial position. Galactose shown on the right has a hydroxyl group on the carbon 4 in the axial position. Such difference in the geometry of the substrate makes a big difference in

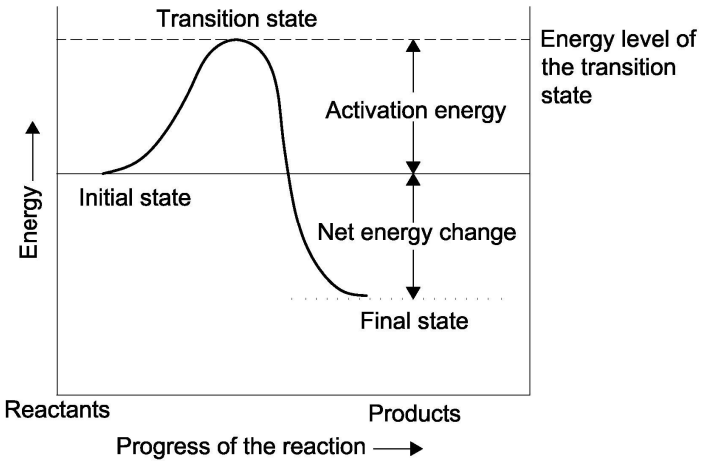
the interaction between the substrate and enzyme. In the case of galactose the interactions with Asp 205, Asn 204 and Asn 231 and galactose hydroxyl group at carbon 4 are not possible.



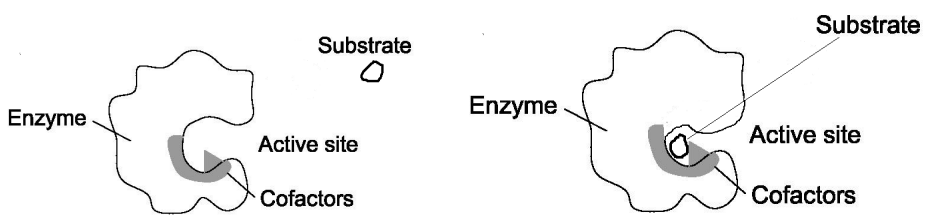
Active site contains also functional groups participating in the catalyzed reaction. The interaction between substrate and enzyme leads to transition state complex which then decomposes to enzyme and product. The enzyme binds to another substrate molecule and repeats the process.



The energy diagram in the figure below shows the energy change in the reaction path for the enzymatic catalyzed and noncatalyzed reaction.



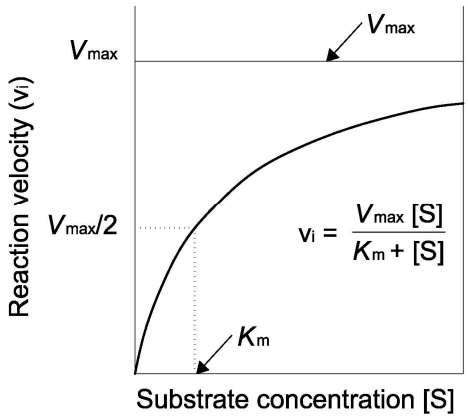
There are two models of binding of the enzyme to the substrate: "lock and key" and "induced fit". The lock and key model assumes that the three dimensional substrate binding site of the enzyme and the three dimensional structure of the substrate are complementary to each other. The induced fit model assumes that complementarity of the active site and substrate is only the first recognition step. The next stage is the conformational change of the enzyme-substrate complex resulting in the increased number of the interactions between enzyme and substrate and thus stronger binding. The figure below shows the changes of the glucokinase after interaction with glucose molecule.



free enzyme *complex enzyme-substrate*

Kinetics

The velocity of reaction catalyzed by all enzymes is dependent on substrate concentration. The simplest quantitative description of the above dependence is Michaelis-Menten equation. It relates the initial velocity (vi) to the concentration of substrate [S]. It applies to a simple reaction in which the enzyme and substrate form an enzyme-substrate complex (ES) that can dissociate back to free enzyme and substrate .



For the reaction

$$E + S \underset{k_2}{\overset{k_1}{\rightleftarrows}} ES \xrightarrow{k_3} E + P$$

the Michaelis-Mentel equation is given by

$$v_i = \frac{V_{max}[S]}{K_m + [S]}$$

The are two parameters in the equation; Vmax describes the maximal velocity of the enzymatic reaction that can be achieved at an infinite concentration of the substrate and Km is the concentration of substrate required to reach ½ Vmax, so the higher Km the higher concentration of the substrate is required to reach the ½ Vmax.
Michaelis-Menten model is not applicable to multi substrate enzymes and to enzymes present in higher concentration than their substrates.

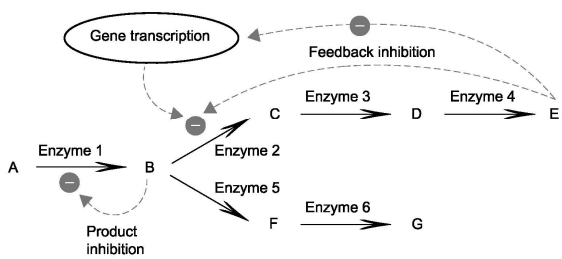
Enzyme activity regulation, inhibitors, transition state analogs.

Altering the enzyme activity is possible thanks to the compounds binding in the active site (competitive, noncompetitive, uncompetitive) or by changing the conformation of the enzyme (allosteric, by covalent modification, by protein-protein interaction). Covalent inhibitors form covalent bonds with the enzyme in the active site region preventing the enzyme substrate interaction.

Transition state analogs are compounds the structure of which resembles the substrate in transition state stage. Thus they are specific and strong inhibitors since they bind tightly with the enzyme preventing their interaction with substrate. Many drugs act as enzyme inhibitors
Heavy metals like mercury, lead, aluminium, iron bind tightly to functional groups in the enzyme or replace the normal functional metal in the enzyme active site inhibiting the action of the last one.
The enzyme catalyzing a reaction can be regulated also through changes in the amount of the enzyme. For example, most of the proteases involved in blood clotting circulate in an inactive form. They are cleaved to the active form by other proteases.
The concentration of the enzyme can be regulated also by the rate at which different proteins are synthesised (gene transcription, or stabilization of messenger RNA) or degraded.

Regulation of metabolic pathways

The enzyme activity regulation described above is used to control metabolic pathways, cellular events, and physiological processes. Metabolic pathways are series of reactions in which the final product is obtained from the substrate via several intermediates. Every step is catalyzed by different enzyme. Some intermediates could be substrates for many different subsequent steps. The product of an enzyme or a sequence of enzyme catalyzed reactions can be an inhibitor of the enzyme in the path in which it is produced. In this way the product controls its own synthesis.

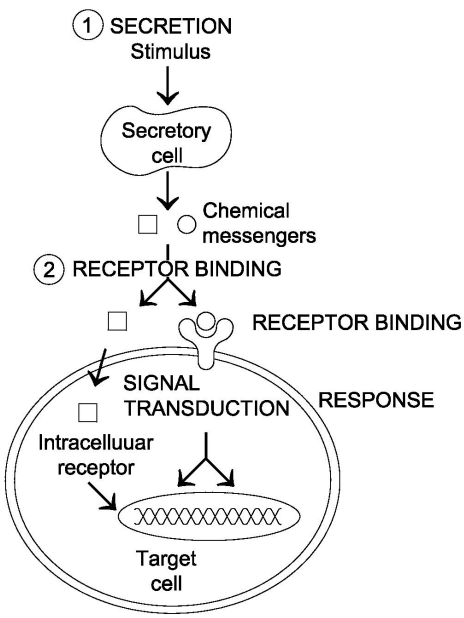


3.1.5.Coenzymes

Coenzyme is a nonprotein molecule which participates in the enzymatic reaction

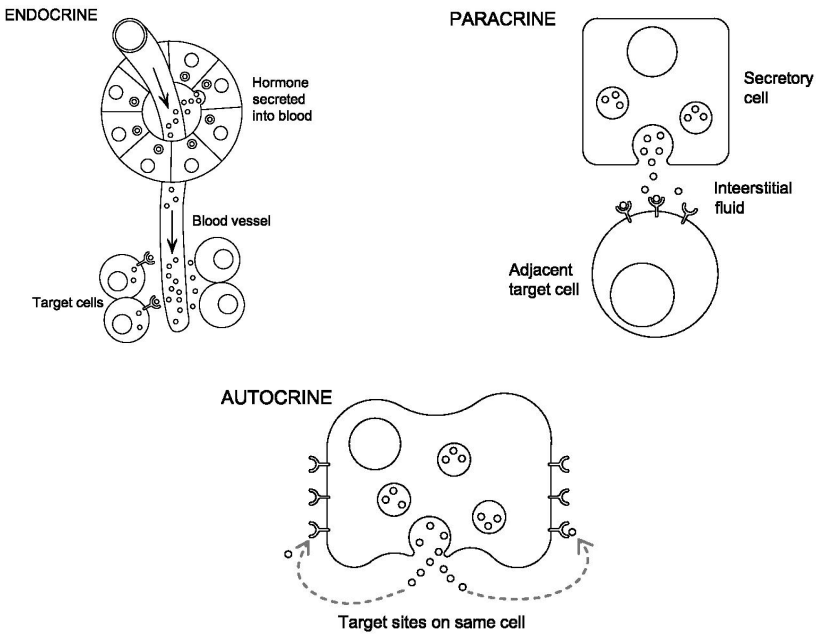
3.1.6.Receptors, receptor action

In the complex assembly of cells such as a human, there are many very specialized cells, organs, tissues, each with their specific function. There are necessary mechanisms of cooperation and communication which is carried out by chemical messengers. Such compounds are molecules of low or high molecular weight secreted by some stimulus from one cell, which then moves to the target cell, binds to the receptor and elicits a response. The schematic presentation of a receptor and its functioning is shown below.

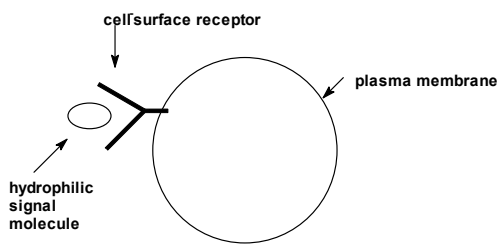


In the nervous system they are called - neurotransmitters, in the endocrine system - hormones and in the immune system - cytokines. There are other messengers like eicosanoids and growth factors, however, it is difficult to place them in one of the above categories.

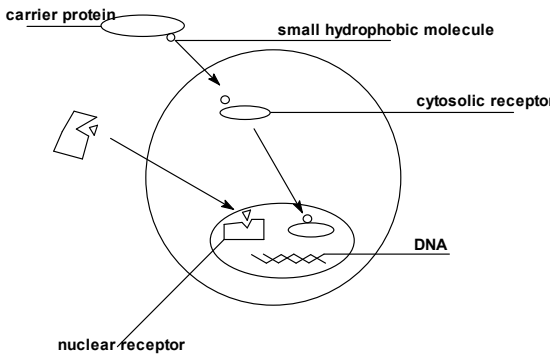
The chemical messengers are also classified as edndocrine, paracrine or autocrine. Endocrine in general is secreted by one cell, then transported by blood to a specific target cell located in some distance. Paracrine acts on nearby cell whereas autocrine acts on the cell from which it was secreted.



The receptor could be plasma membrane or intracellular receptors. The first one has extracellular binding domains the second must diffuse into the cell.



cell surface receptor

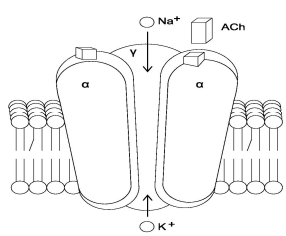


intracellular receptor

Another classification of the receptors is based on the mean of their action. So we have ion-channel, kinase related or heptahelical receptors.

Ion channel

As an example of an ion channel receptor, nicotinic acetylocholine receptor is presented in the figure below. The receptor is composed of five polypeptide subunits forming the channel in the middle. The whole receptor is a membrane spanning structure. The channel is closed in a chemical messenger, in this case acetylcholine, it binds to a specific binding region of two identical α subunits. Binding two molecules of acetylcholine induces the conformational change which results in channel opening and the free movement of the ions is possible. The result is the change of the potential of the membrane which means that information has been passed to the postsynaptic part by a chemical messenger.



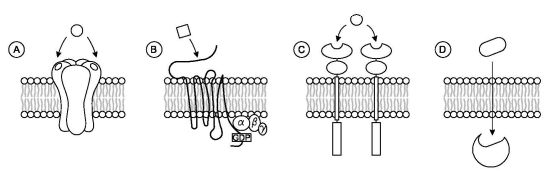
Kinase related

Kinase is an enzyme that transfers phosphate groups from donor molecules, like ATP, to target substrates in the process named *phosphorylation*. There are about 20 different types of kinase receptors. They play a substantial role in regulation processes as well as cancer development. Kinases related receptors are proteins that span the cell membrane. After the messenger is bound to their extracellular domain the activation of the kinase inside the cell takes place, leading to a protein phosphorylation cascade and altering cellular activity in a specific way. For example an insulin receptor is a member of kinase family receptors.

Heptahelical

Heptahelical receptors contain transmembrane protein spanning seven time through the membrane. They work by formation of a non-protein small second messenger, (for example cAMP) which is generated inside the cell in response to the first messenger (hormone, neurotransmitter or cytokine) binding to a receptor in the outer part of the cell.

In summary, including the intracellular receptors, we can say that there are four major types of interaction between a drug and a receptor as shown in the figure below.



A. Drugs can bind to an ion channel spanning the plasma membrane and changing the channel conductance.

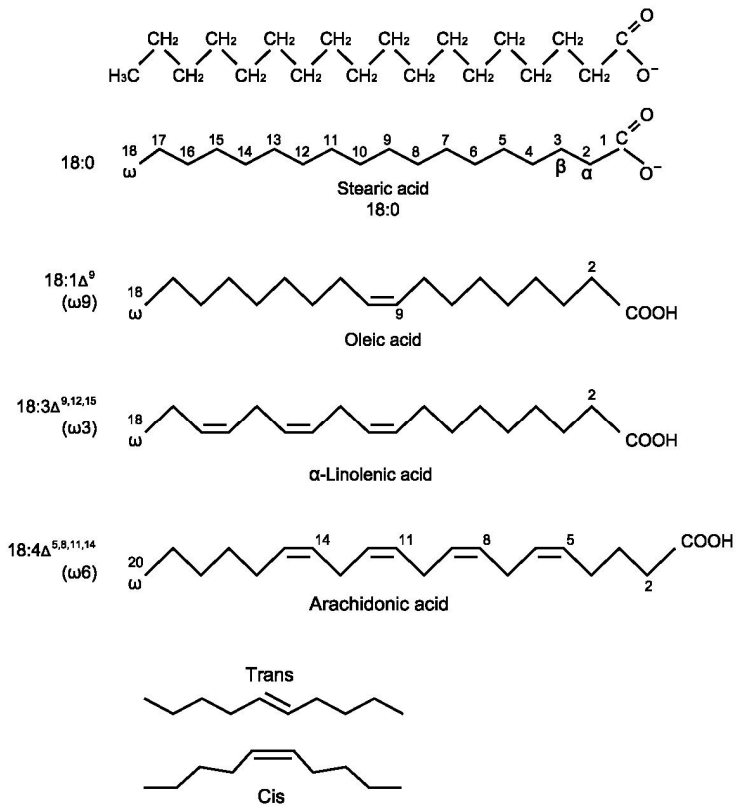
B. The heptahelical receptor, when activated in the extracellular part, activates the G protein in the intracellular part.
C. Drugs binding to extracellular domain cause a change in signalling by activating or inhibiting the intracellular enzymatic domain of the same receptor molecule.
D. Drugs can diffuse through the membrane and act on cytoplasmic or nuclear receptors.

Tissues may vary in their level of response to messenger. It can be done by changing the number or activity of the receptors. The number of the receptors can be changed by the process of degradation or endocytosis (lowering the number of receptors) or by recycling back (increasing the number).
The time after which the regulation process is stopped is also different. Some signals should be turned off rapidly (neurotransmition) some should stay longer (memory, proliferation) and some may persist for the whole cell life (differentiation).

3.2.Lipids

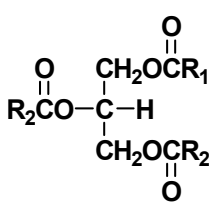
3.2.1.Fatty acids

Fatty acids, see table below, have usually straight aliphatic chain with 16-20 carbon atoms, carboxyl group at the end. Some of them have only single bonds-**saturated fatty acids**, others contain one or several double bonds- **unsaturated fatty acids**.



3.2.2.Acylglycerols

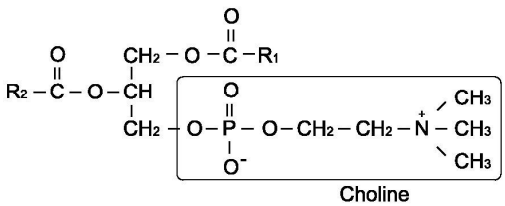
Acylglycerols are esters of glycerol and fatty acids. There are mono-, di-, and triacylglycerols.



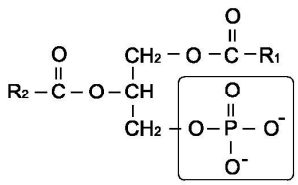
.triacylglycerols

3.2.3.Phosphoacylglycerols

Phosphoacylglycerols are triesters of glycerol. Hydroxyl groups at carbon atom 1 and 2 are esterified by a fatty acid . When the third hydroxyl group is esterified by the phosphorous acid the resulting compound is named phosphatidic acid. Phosphatidic acid is a basic structure for other phosphoacylglycerols like phosphatidylcholine.



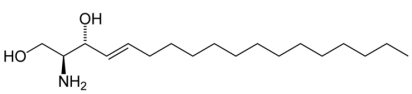
PHOSPHATIDYLCHOLINE



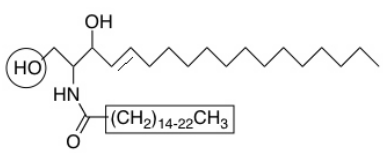
PHOSPHATIDIC ACID

3.2.4.Sphingolipids

Sphingolipids are derivatives of amino alcohol sphingosine and palmitic acid. They do not have a glycerol. Sphingosine and sphingolipids structures are shown below.



sphingosine



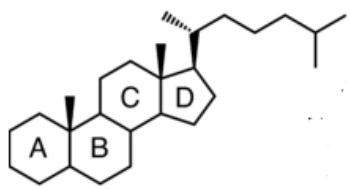
sphingolipids

These compounds play important roles in signal transmission and cell recognition. Disorders of sphingolipid metabolism, have particular impact on neural tissue. Other derivatives of sphingosine are ceramides.

Ceramides are amides formed from sphingosine and a fatty acid. Different groups can be also attached to the hydroxyl group of ceramide to form sphingomyelin, galactocelebrosides, gangliosides, NANA, N-acetylo neuarominic acid (sialic acid).

3.3.Steroids

Steroids are compounds with a characteristic arrangement of three sixmembered and one five membered ring as shown below. The examples of steroids are cholesterol, estradiol, testosterone.



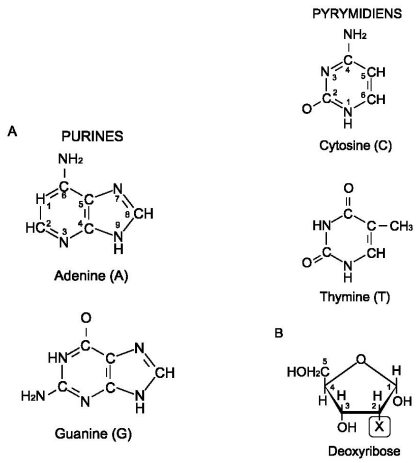
They play many regulatory functions in the body. There are also many drugs derivatives containing a characteristic steroid four ring structure.

3.4.DNA, RNA, tRNA, mRNA

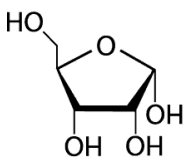
Purines, pyrimiidines, pyridines (its tautomers), nucleosides and nucleotides

There are two purine and three pyrimidine bases. They are the components of nucleosides (when attached to saccharide ribose or dezoxyrybose).

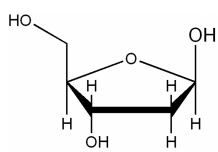
Nitrogenous bases



Carbohydrates

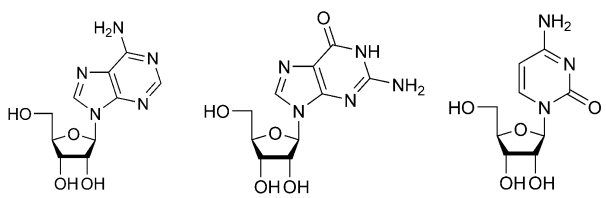


ribose



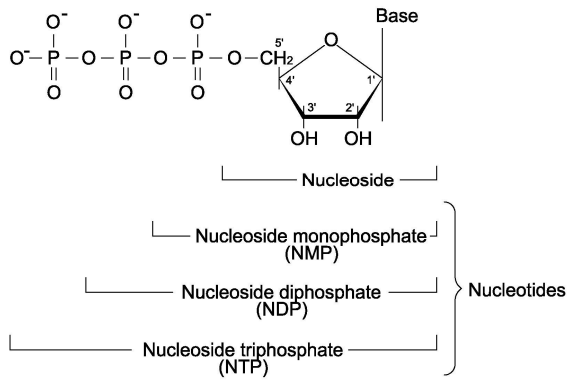
deoxyribose

Examples of nucleosides

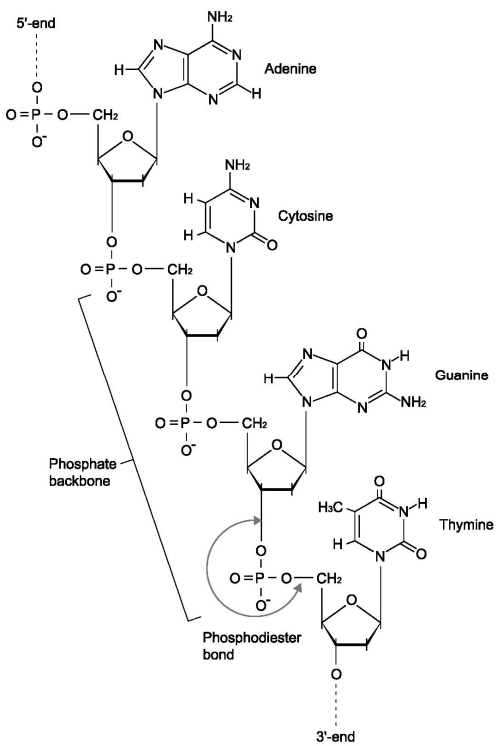


adenosine guanosine cytidine

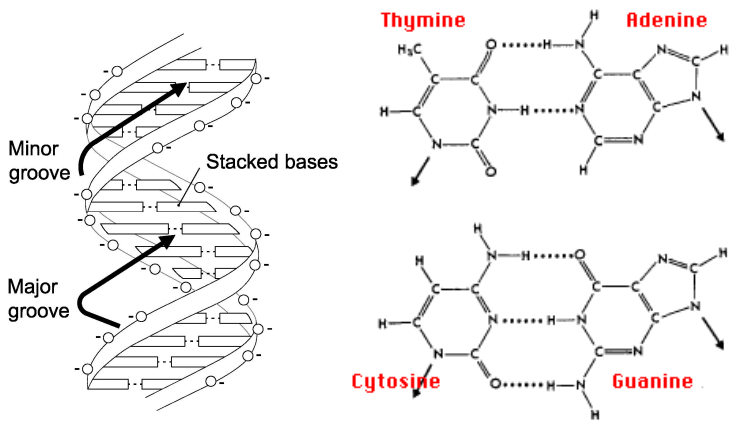
Additional attachment of phosphate units results in the formation of nucleoside mono- di and triphosphates. Nucleoside with the attached inorganic phosphate group is named nucleotide.



Polymerization of nucleotides (dezoksyryboadenine, dezoksyrybocytosine, dezoksyryboguanine or dezoksyrybothymine like in DNA or ryboadenine, rybocytosine, ryboguanine or rybothymine like in RNA) by forming additional phosphate bond between nucleotides leads to polynucleotide chains.



The DNA molecules consist of two polynucleotide chains (strands) forming the double helix in an antiparallel fashion, one chain is running from 5 prime to 3 prime and the second one from 3 prime to 5 prime.

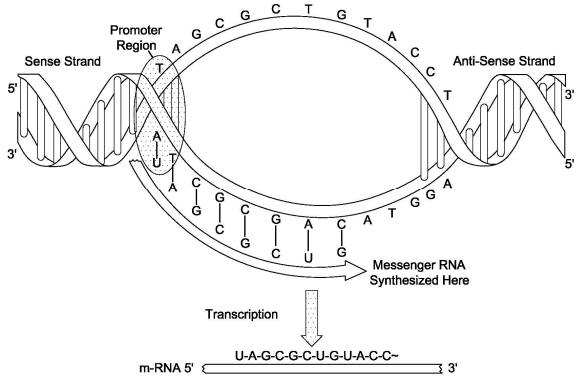


The essential concept for the formation of the double helical structure is due to the interaction between the corresponding nucleotides (TA or CG) via hydrogen bonding as shown in figure

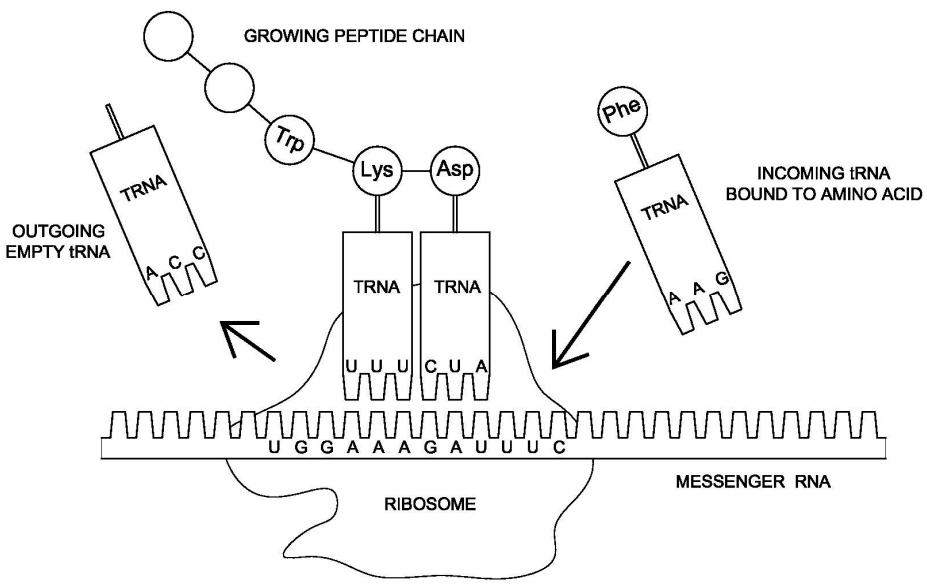
The linear double helix forms a chromosome. The whole Human genetic content contains 23 chromosomes.

RNA is similar to DNA, however, three bases are the same but thymine is replaced by uracil (differs from thymine by the absence of a methyl group at position 5) and sugar dezoxyrybose is replaced by ribose. Another difference is that RNA is usually a single strand and it lacks the continuous helical structure, however, it can form a structure with a base pairing with other regions of the same chain, then loops are formed.

There are three major types of RNA- mRNA, rRNA, tRNA. They participate in protein synthesis. mRNA is transcribed from a DNA template.



It carries coding information to the sites of protein synthesis: the ribosomes. Transfer RNA (tRNA) is a small molecule (74-95 nucleotides) and it takes part in the translation process. It transfers a specific amino acid to a growing polypeptide chain at the ribosomal site of protein synthesis.



Ribosomal r RNA is the component of the ribosome and provides a mechanism for decoding mRNA into amino acids and interacts with tRNAs during translation. It provides peptidyl transferase activity.

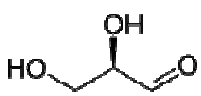
Some other RNA types in the cell play a specific role for example as primers for DNA replication.

3.5.Carbohydrates

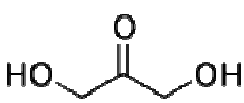
A **carbohydrate** is an organic compound with the empirical formula $C_m(H_2O)_n$, Depending on the number of carbon atoms there are: **triose** - a monosaccharide containing three carbon atoms, **tetrose** - a monosaccharide containing four carbon atoms, **pentose** - a monosaccharide containing five carbon atoms, **heksose** - a monosaccharide containing six carbon atoms.

Aldoses, ketoses

Another classification depends on the presence of aldehyde or ketone group.
For example the D-Glyceraldehyde is D-aldotriose.

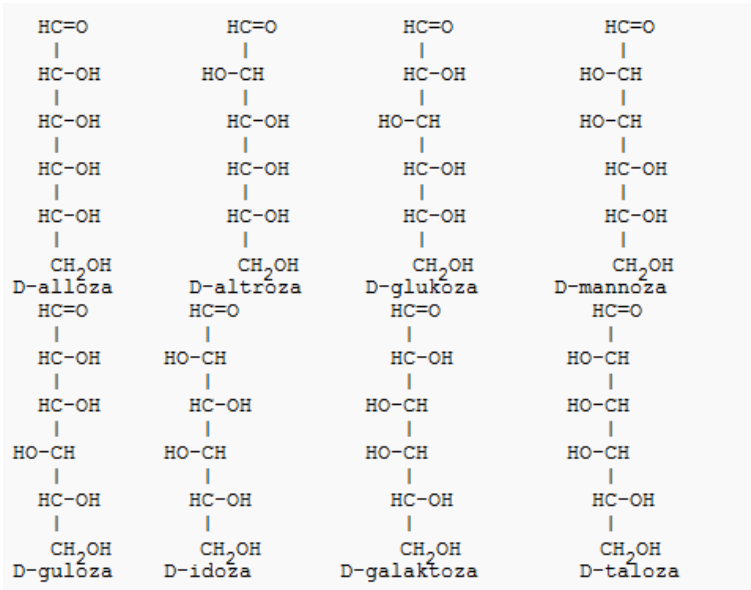


The dihydroxyacetone is ketotriose:

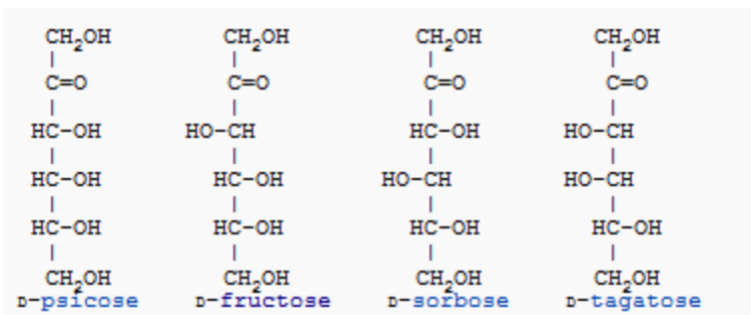


Some carbon atoms might be stereogenic (for simple sugars all carbon atoms except terminal and carbonyl). Thus many stereoisomers are possible. A diagram below shows the possible diastereoisomers of hexoses of D-series in Fisher notation. Enantiomers of them provide L-series. D and L refers to the configuration of the carbon atom in D and L glyceraldehyde.
The classification is according to the molecular configuration at the stereogenic carbon atom furthest from the aldehyde or ketone group. The configuration at this carbon is compared to the that of carbon 2 on glyceraldehyde. If it is the same as in D-glyceraldehyde's C2, the sugar is D otherwise sugar is L.

D-aldohexoses



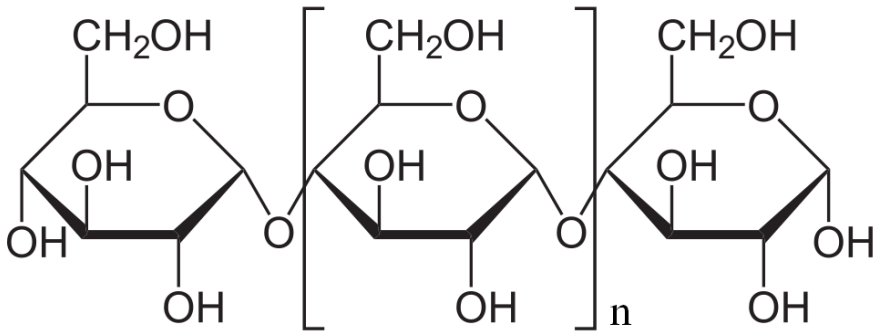
D-ketohexoses



Polysaccharides

The carbohydrates (saccharides) can also be divided into chemical groupings according to the number of sugar units: monosaccharides, disaccharides, oligosaccharides, and polysaccharides.

Linear polysaccharide



Carbohydrates perform numerous roles: storage of energy (e.g., starch and glycogen), structural components (cellulose and chitin), an important component of coenzymes (ATP, FAD, NAD, RNA, DNA). Saccharides play other important roles in the immune system, fertilization, preventing pathogenesis, blood clotting,

Some biological substances commonly called "monosaccharides" do not conform to the formula $C_m(H_2O)_n$ (e.g., uronic acids, deoxy-sugars such as deoxyrybose, fucose and inositol, $(CH_2O)_6$).

The open-chain forms of a monosaccharide are in equilibrium with a closed ring form where the aldehyde/ketone carbonyl group carbon (C=O) and hydroxyl group (-OH) form a hemiacetal or hemiketal with a new C-O-C bridge resulting in the formation of heterocyclic ring.

Rings with five and six atoms are called furanose and pyranose forms, respectively. The hemiacetal or hemiketal carbon atom in a cyclic form is called the anomeric carbon. It becomes a new stereogenic centre with two possible configurations: The oxygen atom may take a position on the same side of a plane like CH_2OH group or not. The resulting stereoisomers are called *α anomer*, if the -OH substituent on the anomeric carbon rests on the opposite site of the ring than the CH_2OH group. The alternative form is called the *β anomer*

Glycoproteins

Glycoproteins are proteins that contain oligosaccharide chains (glycans) covalently attached to polypeptide side-chains of protein in a cotranslational or posttranslational modification

called glycosylation. Glycoproteins are important for white blood cell recognition, especially in mammals and in the immune system. Some hormones are glycoproteins (Follicle-stimulatin hormone, Luteinizing hormone, Thyroid-stimulating hormone, Human chorionic gonadotropin, Alpha-fetoprotein, Erythropoietin - EPO). Cell-surface polysaccharides form a barrier between the cell wall and the environment

Lipopolysaccharide

Lipopolysaccharide, (lipoglycans), are large molecules consisting of a lipid and a polysaccharide joined by a covalent bond. They are responsible for example for membrane integrity and for mediation of host-pathogen interactions.
Polysaccharides are polymeric carbohydrate joined together by glycosidic bonds.

3.6. Vitamins

A **vitamin** is an organic compound required as a nutrient in tiny amounts by an organism when it cannot be synthesized in sufficient quantities by an organism
Some vitamins have hormone-like functions others are antioxidants (vitamin E, vitamin C). Most of vitamins (e.g. B complex vitamins) function as cofactors, in enzyme catalysis
Below there is a list of vitamins.

The discovery dates of the vitamins and their sources (year is approximate, depending on the definition of "discovery.")

Year of discovery	Vitamin	Food source
1913	Vitamin A (Retinol)	Cod liver oil, carrots
1910	Vitamin B_1 (Thiamine)	Rice bran
1920	Vitamin C (Ascorbic acid)	Citrus, most fresh foods
1920	Vitamin D (Calciferol)	Cod liver oil
1920	Vitamin B_2 (Riboflavin)	Meat, eggs
1922	Vitamin E (Tocopherol)	Wheat germ oil, unrefined vegetable oils
1926	Vitamin B_{12} (Cobalamins)	Liver, eggs, animal products
1929	Vitamin K (Phylloquinone/phytol naphthoquinone)	Leafy green vegetables
1931	Vitamin B_5 (Pantothenic acid)	Meats, whole grains, in many foods
1931	Vitamin B_7 (Biotin)	Meats, dairy products, eggs
1934	Vitamin B_6 (Pyridoxine)	Meat, dairy products.
1936	Vitamin B_3 (Niacin)	Meat, eggs, grains
1941	Vitamin B_9 (Folic acid)	Leafy green vegetables

3.7.Minerals

There are many minerals required in the diet. They are: electrolytes (inorganic ions dissolved in the fluid), minerals (required in a large quantity), trace minerals and ultratrace minerals.

Sodium, potassium and chloride are major electrolytes, maintaining water balance, establishing the gradient across membranes, neutralizing positive and negative charge on molecules.

Calcium and phosphorus are structural components of bones. Hormone action and blood clotting depends on calcium. Phosphorus is necessary in the synthesis of many phosphorylated molecules. Magnesium is necessary for activation of many enzymes. Iron is a component of hemoglobin. Zinc and molybdenium are required in small quantities.

Sulphur is found in tissues like cartilage and skin. It plays an important role in metabolism (see for example coenzyme A).

Minerals have adverse effect if they are in excessive amount.

4.Introduction to Chemistry of Drug Action

There are large groups which act because they resemble the structure of a natural substrate or messenger molecule. To understand the action of these classes of drugs it is necessary to understand the nature of interactions between the molecules

4.1.Interaction – forces involved in drug-target complex

The strength of interaction depends on the interaction energy. All discussed below interactions are applicable to all types of receptors/targets

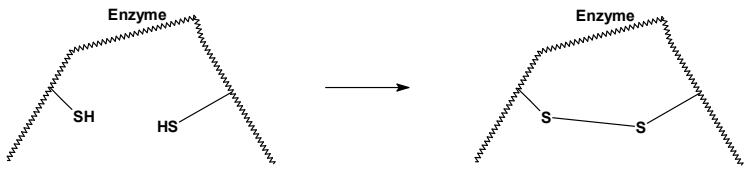
Electronic structure of the molecules

In order to understand the reaction mechanism and discuss the interaction between molecules it is essential to construct Lewis structures for any organic compound. This is especially important since in most chemical literature including textbooks the lone pairs, which play an important role, are not pictured.

Step 1
Each atom contributes to the electron supply with the number of electrons in outer shell (H=1, C=4, N=5 and so on)
Step 2
Electron demand for each atom is the number of electrons to complete the outer shell (H=2, all others 8 except group III B, Al, Ga =6)
Step 3
Number of bonds = (total electron demand-total electron supply)/2=number of bonds
Example C2H5OH

total electron supply= 2*4+5*1+1*6_1*1=20
total electron demand=2*8+5*2+1*8+1*2=36
number of bonds=(36-20)/2=8

Such bonds are called covalent bonds and they are the strongest possible bonds, ranging from 40-110 kcal.



covalent bonding

They are very rarely formed in drug receptor/enzyme/targeted interaction. Some exceptions are for example alkylation of DNA by alkylating agents or deactivation of the enzyme by a suicide inhibitor. In general the formation of such bond is not reversible**.**

Step 4

Once the two calculated electron bonds are drawn (sometimes it is necessary do draw the double or triple bonds) the lone pairs should be added for oxygen, nitrogen, halogens and sulphur. There should be 2 electrons for hydrogen, 6 for B, Al, Ga, 8 for the others around the atom. One two electron bond counts 2 for both connected atoms.

Formal charge on atom

For prediction of electrostatic interactions it is necessary to know the formal charges on particular atoms.

Step 5

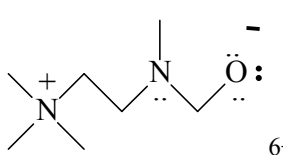
Calculation of the formal charge on atom number of unshared electrons +number of shared electrons/2=N

if N=to valence shell of the neutral atom (see periodic table) the charge on atom is 0

if N is more than valence shell of the neutral atom then charge is negative (1 for each extra electron

if N is less than valence shell of the neutral atom then charge is positive (1 for each extra electron

2+6/2=5

example 

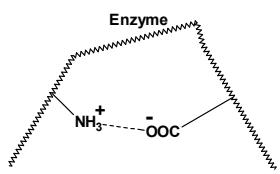
6+2/2=7

0+8/2=4

Nitrogen is in group 5, oxygen in group 6 so the valence shell for neutral atom is 5, for oxygen 6. First nitrogen atom lacks one electron so the charge is +1, the second nitrogen atom has no extra and lacks one electron so formal charge is 0. For oxygen one electron is extra so the charge is minus one.

Electrostatic interactions

The formal charge is important in ionic (electrostatic interactions). It provides from 5 to 10 kcal. It is important that such interactions are effective at distances farther than for other types of interactions and they can persist longer. The formal charge declines according to Coulomb law by the square of distance between interacting centers. In the physiological pH aminoacids there are zwitterions with protonated amine group (charge +1) and deprotonated carboxylic group (charge -1) and this fact is important in the interaction of aminoacids as well as proteins with other macro and low molecular weight molecules.



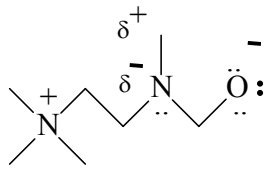
ionic bonding

Ion-dipoel, dipole-dipole interactions

Atoms differ in electronattracting properties. Such property is defined as electronegativity. The more electronattracting elements the larger the electronegativity value.
A useful scale of electronegativity was established by Linus Pauling

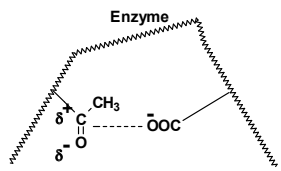
If the covalent bond is formed between two atoms of different electronegativity the electron distribution is such that greater electron density is close to more electronegative element. It forms the partial(fractional) charge on atoms delta + or delta -. The Greek symbol delta indicates that charge separation is not complete just like in ionic structures.

For example:



If two molecules have dipole fragment the possible interaction is dipole-dipole interaction. Such interaction take place for example between two water molecules or a molecule of water and alcohol.

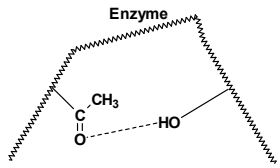
An example of ion dipole and dipole dipole interaction between pyrazolomidine derivative, benzodiazepine like sedative and hypnotic drug zaleplon and $GABA_A$ receptor is shown in figure below.



ion dipole interactio

Hydrogen bond interactions

One of the dipole-dipole type interaction is hydrogen bond. It occurs between protons of group X-H and group Y if both X and Y are electronegative atoms. Strong hydrogen bonds are formed when X and Y are N,O,F. Hydrogen bond can be formed even when X is a carbon atom, however, these interactions are very weak. The figure below shows an example of intra and intermolecular hydrogen bond.

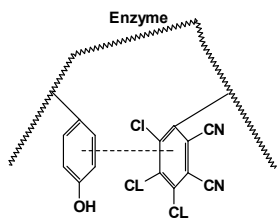


hydrogen bonding interaction

Such bonding plays an important role in the structure of peptides and DNA molecules. See chapter describing alpha helix, beta sheet, beta turn, DNA helix.

Charge transfer complexes

Such interactions take place between two molecules when one is a good electron donor and the other one is an electron acceptor.
An example is shown below:



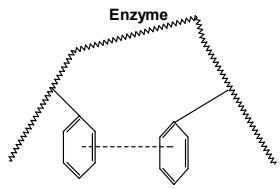
charge transfer interaction

The charge transfer interaction is important for example in the activity of antimalarial or anticancer intercalating drugs.

Dispersion and Van der Walls interactions

This is a very weak interaction between induced dipoles. They exist even in the noble gases. When two atoms are close to each other there is a dyssymetry of charge distribution and thus dipoles are induced. Two formed dipoles interact in the same manner as was described in the case of dipole-dipole interaction. These interactions are very weak (2kcal) and operate at effective distance as short as 0.4-0.6 nm so very often they are overshadowed by stronger interactions. They strongly decrease with distance (in proportion $1/R^6$). While individual van

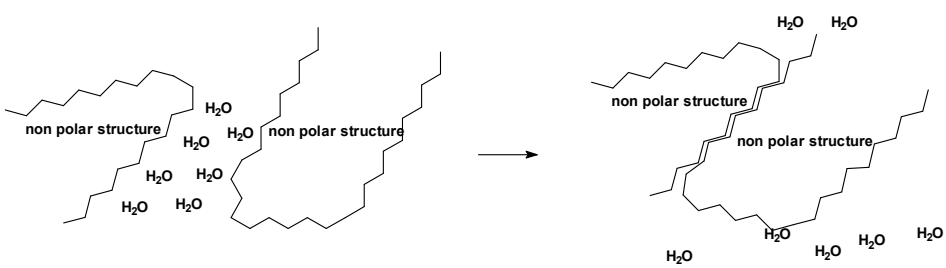
der Walls interaction is weak, a large number of such interactions can add to a sizable amount of energy.



van der Waals interaction

Hydrophobic and hydrophilic interactions

When water molecules are mixed with oil molecules the state which has lower energy takes place when water molecules associate with each other and oil molecules with each other. As a consequence a two phases are formed. The forces which are responsible for the association of nonpolar molecules and no affinity toward polar molecules are called hydrophobic interactions and forces which result in the attraction of polar molecules and repulsion of nonpolar ones are called hydrophilic interactions.



Formation of hydrophobic interactions

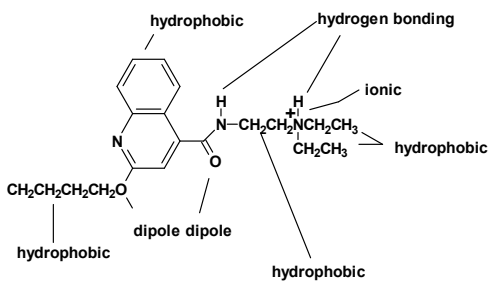
Summary

The drug receptor/target interaction is composed of several interactions. Some of them are strong, some weak. The order of binding strength is: ionic>polar nonionic>nonpolar

In the case of ionic interactions the strongest ones are formed by ammonium groups (11.5 kcal) then phosphate (10.0 kcal) then carboxylate (8.2 kcal). Such values are given for the conformationally free fragments.

In general the noncovalent interactions are weak but the cooperativity of several types makes them produce a strong binding.

The possible interaction for anesthetic dibucaine is presented in the figure below.

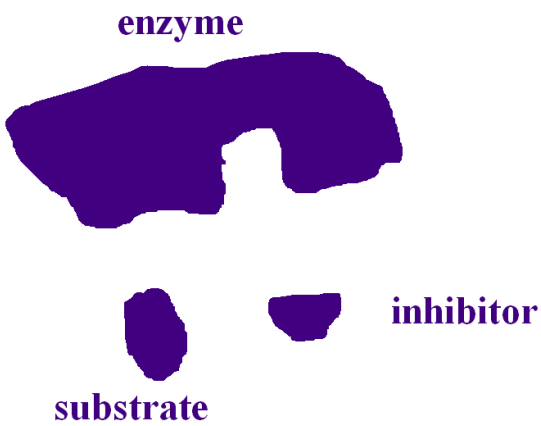


example of potential interactions

4.2.The Role of Enzyme and Receptor

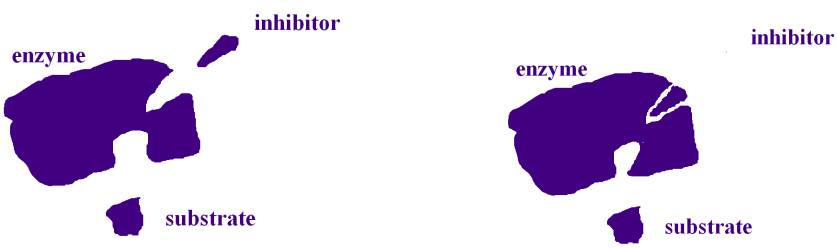
The role of an enzyme is to catalyze the reaction by lowering the transition state energy. The role of a receptor is to recognize the messenger molecule and initiate the biological response. Also the specialized transport protein recognizes the substance and allows it to access the target. The recognition in most cases is highly specific.

If a drug has to change the response of an enzyme or receptor in all cases it should mimic the natural molecule and fit to the cavity of an enzyme or receptor. In the case of an enzyme the effect will be the inhibition of the reaction (competitive or noncompetitive inhibition of an enzyme). The equilibrium depends on the ratio of dissociation constants druge-enzyme and natural substrate-enzyme.



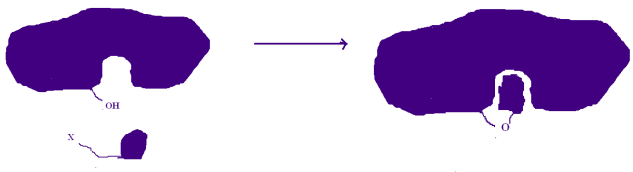
competitive inhibition

In other cases it is not necessary for a drug to interact exactly with the active site, the effect of drug interaction is such that it changes the geometry of the active site making interaction with the natural molecule impossible or weak (allosteric inhibition).



noncompetitive inhibition . Left before and right after interaction with inhibitor

The inhibition is not be reversible if the reaction occurs at the receptor site which results in covalent (permament) bonding of the drug with enzyme.



irreversible inhibition

In the case of receptor/enzyme inactivation or activation, or in the case of a transporter molecule when the break of the transport has to be achieved, the structure of the drug should resemble the geometry and charge distribution of the natural compound in order to be recognized by the target molecule. Some modification has to be made in order to prevent the next step which is crucial for biological response.

Substituents which have similar physical properties are called bioisosteres. Examples of classical bioisosteric groups are given below.

CH_3	NH_2	OH	F	Cl
CH_2	NH	O	S	Se
$COCH_2R$	CONHR	CO_2R	COSR	
	$-C\equiv$	$-N\equiv$		
	$=C=$	$=\overset{+}{N}=$		

The enzyme achieves the enhancement of the rate of the reaction since it lowers the transition state energy of the reaction. Since the intraction between the enzyme and transition state is strong, the best potent inhibitor would be the one which resembles the transition state of the reaction. A compound of this type is called a transition state analog inhibitor.

5.Major Drug Targets

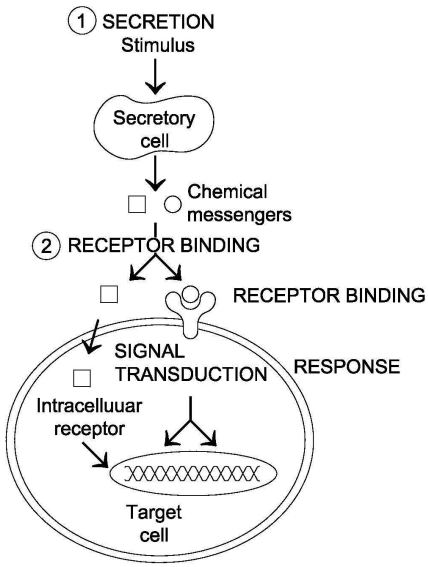
5.1.Proteins as targets

Receptors

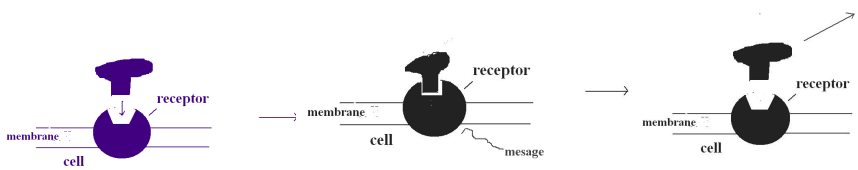
In a complex system, like a human body, the system of communication between particular cells and organs is necessary. Otherwise they would not operate in a coordinated and controlled fashion. When such coordinate operation is disturbed a pathological stage is achieved. So one of the most important drugs in medicine are drugs which interact with receptors and reduce the pathological state.

The introduction to the structure of the receptor was given in previous section. Here we will concentrate on the mechanism of its action.

As it has been mentioned above, receptors are mostly membrane bound proteins with a special part, called binding site, located on outer surface which selectively interacts with small molecules. When such a molecule is attached (chemical messenger) to this special part of the receptor, it triggers a series of responses in the chemistry of the cell. Some receptors, for example steroid receptors, are intracellular.

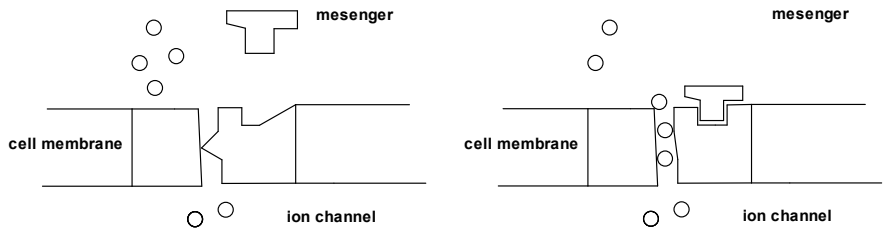


The binding site in nature resembles the active site of the enzyme, however, in contrast to the enzyme no reaction takes place in the receptor binding site. The messenger fits to a binding site, induces the receptor action by changing its shape and leaves the place unchanged. Schematically it is shown in the figure below.



The biological effect is expressed in two general ways – ion channels and membrane bound enzymes.

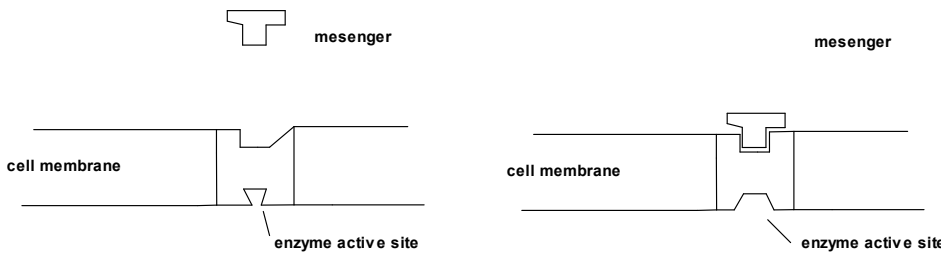
Ion channels can be controlled by a chemical messenger (ligand gated ion channel) or by an electric signal, i.e. a change in the membrane potential (voltage gated ion channel). Opening the channel allows free movement of ions which changes the potential of the membrane. It means that message was passed to the cell.



ion chamnnel closed ion channel opened

lock gate mechanism

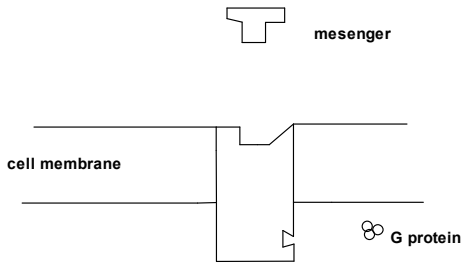
In the case of a membrane bound enzyme, changing of the shape of the receptor activates the enzyme. As long as the messenger is bound the enzymatic activity is expressed.



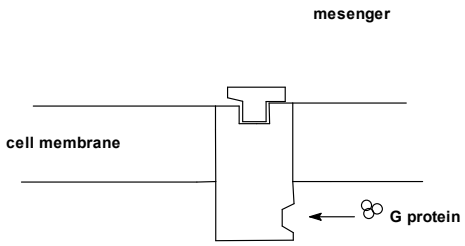
active site closed acive site opened

enzyme actication mechanizm

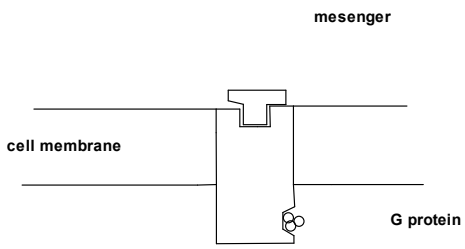
Some receptors control the activity in indirect manner through the use of a protein messenger called G-protein. In this case the receptor is also embedded within the membrane with the binding site on the outer surface. However, on the inner surface there is another binding site. When the messenger is attached to the outer surface the inner binding site opens and is recognized by the G-protein. G-protein decomposes and one of the subunits travels to the membrane bound enzyme, activates it and starts a new reaction. The existence of G-protein mechanism allows different receptors to control the same enzymatic reaction.



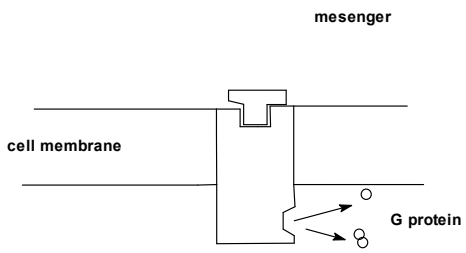
A.binding site closed



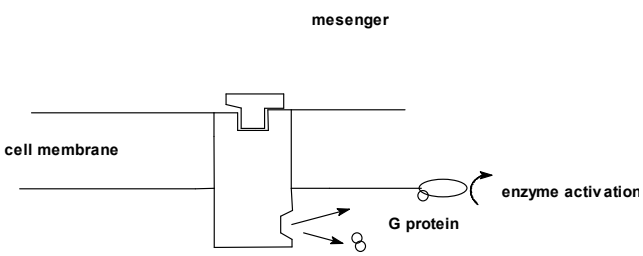
B. binding site opened



G protein addition



G protein dissociation



activation of membrane bound enzyme

Mechanizm via membrane bound enzyme activation

The receptors are identified by a special messenger compound- neurotransmitter or hormone. Thus the receptor activated by dopamine is called a dopaminergic receptor. Similarly we have cholinergic (activated by acetylcholine), adrenergic (activated by adrenaline or noradrenaline). Not all receptors activated by the same messenger are exactly the same. For example those in the lungs can be different from the ones in the heart, however, both of them

are stimulated by adrenaline and both of them are adrenergic. In fact they are different subtypes.

Interaction between a receptor and a messenger molecule as well as a drug molecule is provided by several interactions like: ionic, electrostatic, ion dipole, dipole-dipole, hydrogen bonding, charge transfer, hydrophobic or van der Walls interaction. Such interactions were described in detail in the previous section.

There are also several theories, the major ones are:

-Occupancy theory states that the intensity of the drug effect is proportional to the number of the occupied receptors.

-Rate theory states that the intensity of the drug effect is proportional to the total number of encounters with the receptor per unit time.

-Induced fit theory and its modification states that the receptor adapts to the conformation to the approaching molecule.

Now we can try to explain how drugs might influence the receptor activity.

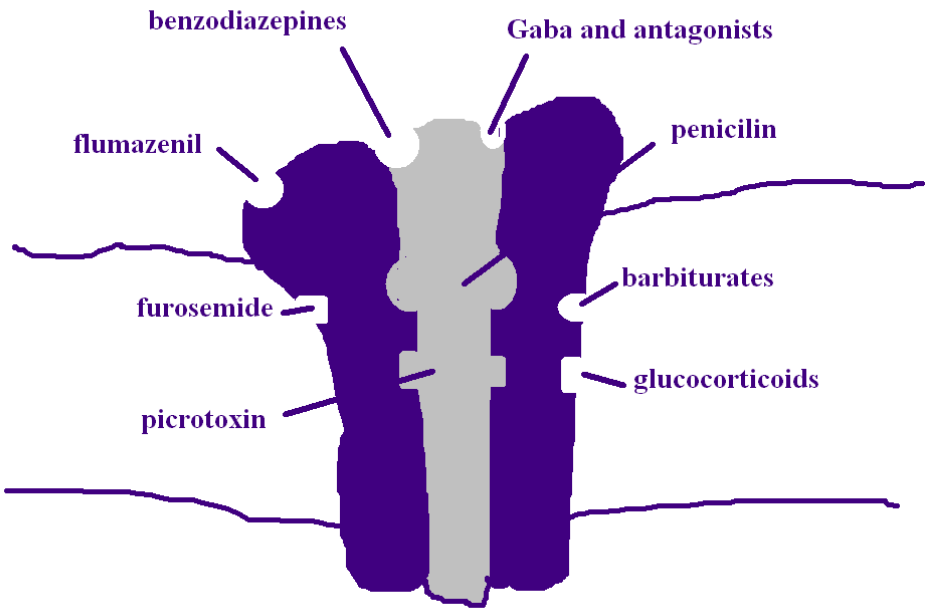
An **agonist** is a chemical that binds to a receptor, induces active conformation of the receptor protein and triggers the response of that cell.

Antagonist blocks the action of the agonist by selecting and stabilising the inactive form of a receptor molecule.

Partial agonist stimulates the effect similar to the agonist but the action is not very effective.

Inverse agonist causes an action opposite to that of the agonist.

The specific type of receptor can be stimulated by several different molecules (drugs). For example GABA-A has modulatory binding sites for several drugs.



Enzymes

Many diseases and symptoms of diseases arise from the deficiency or excess of some metabolites in the body. The normalization of the level of metabolite results in the healing of the disease. Such control can be carried out by specific enzyme inhibitors. Any compound which slows down or blocks the enzyme catalysis is called enzyme inhibitor. The mechanism of the enzyme inhibition was pointed out in the previous section. The ideal enzyme inhibitor should be selective in order to avoid side effects. Drug resistance may occur when a formerly effective drug (for example against pathogenic bacteria) is no longer effective. It could happen due to natural selection, when mutation in colony will result in the appearance of new generation resistant to that drug.

The effect of the mixture of drugs could be antagonistic, subadditive, additive or synergistic. Drug synergism appears when two drugs are more effective that the sum of the effects of drugs administered individually.

It could happen if:
-the second compound administered has no therapeutic properties but is the inhibitor of an enzyme destroying the drug;
-if the two drugs inhibit two different steps in the metabolic pathway;
-if two metabolic pathways producing a particular metabolite are blocked;
-two different drugs are used for the same target. For example one in 10^7 tumor cell may be resistant to a particular drug but as few as 10^{14} when two different inhibitors are used.

5.2.DNA, RNA as target

We can classify the drugs which interact with the DNA as

- intercalating agents

  Compounds which are capable of slipping between the layers of nucleic acid base and disrupting the shape of the double helix. The effect of such intercalation is the prevention of replication and transcription. Examples are antibacterial proflavine, antitumor dactinomycin or doxorubicin and also antiparasitic antimalarial chloroquine.

- alkylating agents

  Compounds which are highly electrophilic and react forming covalent bonds with a nucleic base. Many anticancer drugs act in this way, for example cisplatin.

- chain cutters

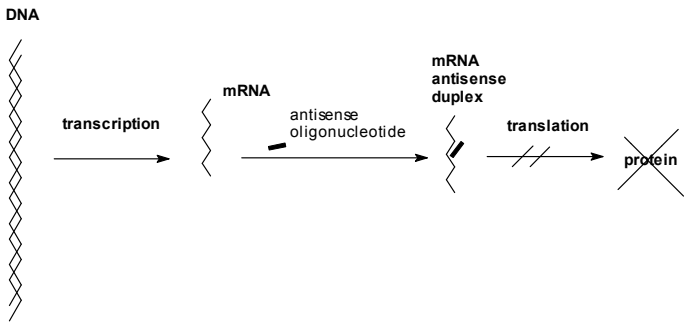
  Compounds which cut the strands of DNA and prevent repairing by DNA ligase. Most of these compounds act by creating the radicals on DNA which subsequently lead to the decomposition of the strand.

- Topoisomerase inhibitors

Topoisomerase I and II enzymes control breaking and rejoining DNA structure during the normal cell cycle. **Topoisomerase inhibitors** interfere with the action and disrupt the normal cell cycle subsequently leading to apoptosis and cell death. Recently topoisomerase inhibitors have become popular targets for cancer chemotherapy treatments or as antibacterial agents.

- antisense therapy

This is a promising method in anticancer, antiviral treatment and some genetic disorders. The idea of antisense therapy is presented in the figure below.



antisense therapy

In this treatment the oligonucleotides with a complementary base sequence to specific stretch of mRNA molecule are used. When such molecule is mixed with mRNA the oligonucleotide recognizes the complementary section in mRNA, interacts forming duplex and in consequence prevents the translation process and protein synthesis. The first antisense drug was formivirsen, antiviral drug approved in the market in 1998.

5.3.Carbohydrates as Targets

For a long time carbohydrates were considered as energy storage molecules (glycogen, glucose) or structural ones (cellulose). Now we know that carbohydrates play an important role in various cellular processes recognition, regulation as well as growth. Many diseases are connected with these processes. Bacteria and viruses recognize the host cell due to carbohydrate structures on cell surface. So blocking these places with complementary drugs will block the ability of the pathogen in invasion. Many autoimmune diseases and cancers are associated with the changes in the carbohydrate structure on the cell surface. Many of these polysaccharide structures are linked to proteins or lipids to form glycoconjugates (glycoproteins or glycolipids). Lipids and proteins in general are embedded in the membrane whereas the carbohydrate plays a role of a tag for recognition. The tag sometimes plays the role of a receptor and frequently it is different between individuals. In such situation they act as antigens. Immune system recognizes the molecular tags as foreign and produces antibodies,

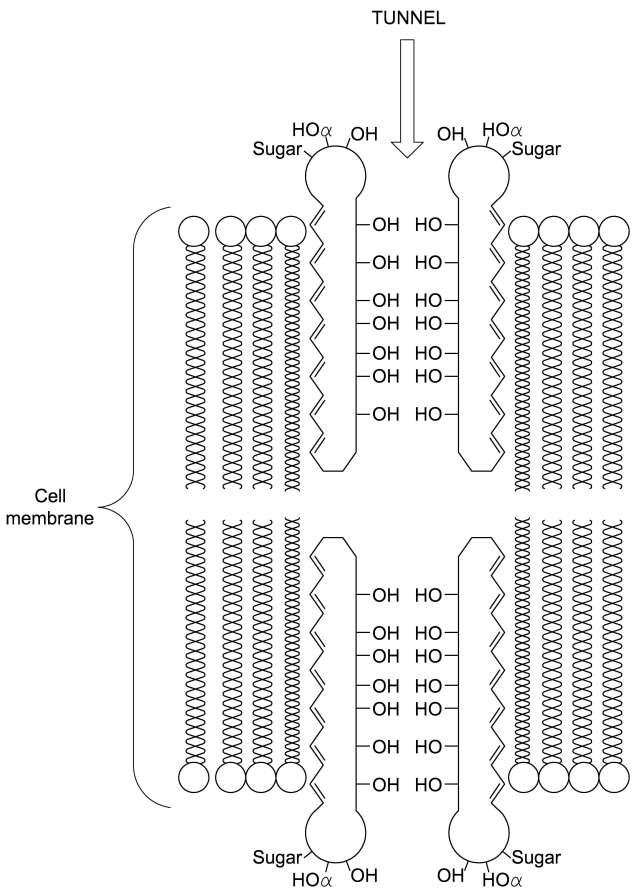
and triggers the immune response, the aim of which is to destroy the invader. The important consequences of the presence of individual molecular tags are observed in processes like blood transfusion or organ transplant.

There are some drugs which mimic the natural carbohydrate tags. They are used to block viral infection (Tamiflu, Relenza) or bacteria infection, or are used as anticancer drugs.

In addition to the drugs for which carbohydrate structure is a target, there are many drugs which contain a sugar or polysaccharide part and the activity is connected with the presence of the carbohydrate fragment.

5.4.Lipids as Targets

Many drugs interact with the cell membrane and disrupt it. Anesthetics are believed to interact with the membrane and change their conducting properties. Antifungal agent amphotericin B nomycininteract acts in a such a way that it forms a tunnel through membrane. Others like antibiotic valinomycin or anticancer cephalostatin 1 act by spanning and disrupting the cell membrane structure.



5.5.Cell Membrane

All microorganisms including pathogens have plasma membrane with some common characteristics. Many drugs act on enzymes and receptors in the cell membrane and walls by inhibiting the enzymes involved in the formation of the cell wall or in the production of compounds necessary for maintaining the integrity of the cell. Some drugs make the cell wall more porous which leads to the death of the cell. Antifungal azoles, alkylamines and phenols

work in this way. Also antibiotics make the plasma membrane more permeable or inhibit the cell wall synthesis. Local anesthetics blocks the nerves transmitting the pain located mainly on the cell membrane.

6.Selected Examples of the Action of Selected Drug Classes.

6.1.Chemotherapeutic

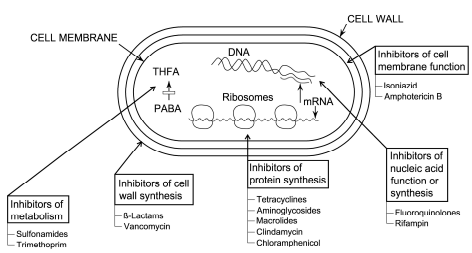
6.1.1.Antibiotics

Antibiotics are microbial metabolites or synthetic compounds which in small doses inhibit the growth of microorganisms without serious toxicity to the host cell.

The term antibiosis was used for the first time in 1889 by Vuillemina in the description of the antagonism between bacteria. In 1901 Wilders introduced the term biotic to describe the compounds which are advantageous for growing the bacteria, and in 1942 Waksman named compounds which inhibit the growth and division of bacteria as antibiotics**.**

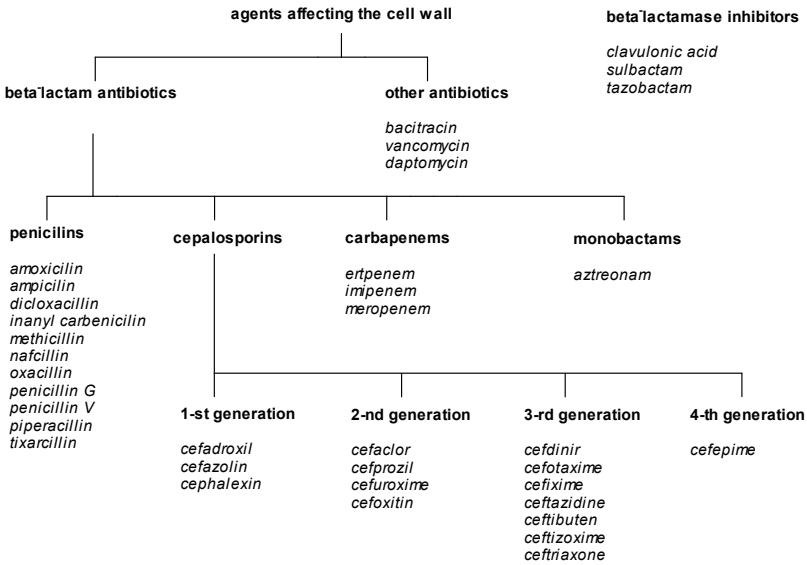
Today the term is used for the description of all compounds that inhibit the enzymatic and metabolic processes substantial for the growth of all microorganisms- antibacterial, antiviral, antifungal antiprotozoa and others including cancer.

6.1.2.Antibacterial



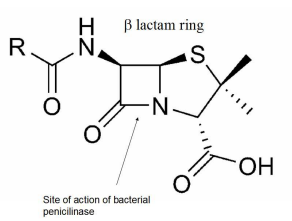
Two results can be observed: bactericidal effect (bacteria are killed) or bacteriostatic (bacteria survive but is not multiplying). Drugs can affect only a few types of bacteria (narrow-spectrum) or many types (broad-spectrum).

Cell wall synthesis inhibitors



summary of antimicrobial agents affecting cell wall synthesis

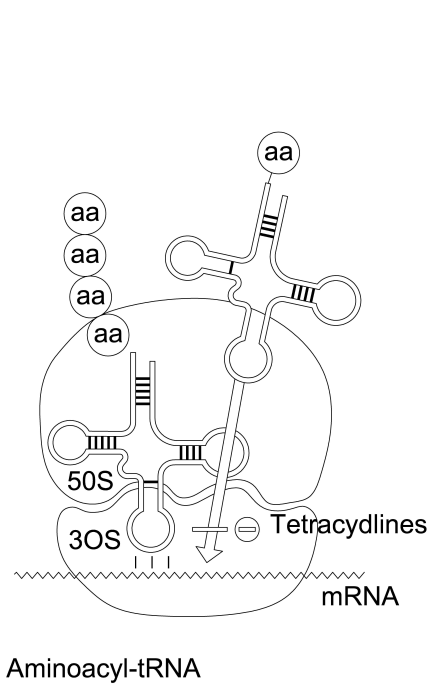
This group of compounds inhibits the synthesis of the bacterial cell wall – peptidoglycan – the structure which is not present in the mammalian cells. The most important members of this group are beta lactam antibiotics (penicilins, cephalosporins, carbapenems, monobactams), the structure of which is presented below. The beta lactam antibiotics are desactivated by the enzyme beta lactamase. To avoid such desactivation the inhibitors of beta lactamase are formulated in combination with beta lactam antibiotics.



Beta lactam antibiotics

Protein synthesis inhibitors

The antibacterial effect is achieved by targeting the bacterial ribosome which has components that are structurally different from those of the mammalian cytoplasmic ribosome. The main protein synthesis inhibitor includes: tetracyclines, glycylcyklines, aminoglycosides, macrolides and others (see figure below). They inhibit the synthesis of bacterial protein synthesis. For example tetracyclines bind to the 30S ribosomal subunit and thus prevent the binding of aminoacyl t-RNA to the ribosome (see figure below). Some toxic effect is observed since mammalian mitochondrial ribosome somewhat resembles the bacterial one.



protein synthesis inhibitors

tetracyklines

demeclocycline
doxycycline
minocycline
tetracycline

glycylcyclines

tigecycline

aminoglycosides

amicacin
gentamycin
neomycin
streptoycin
tobramycin

mactrolides/ketolides

azithromycin
clarithromycin
erythromycin
telithromycin

chloramphenicol

clindamycin

quinopristin/dalfoprystin

linezolid

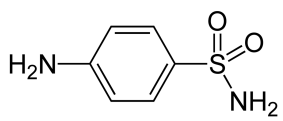
protein synthesis and its inhibitors (aa=aminoacid)

Inhibitors of nucleic acid synthesis

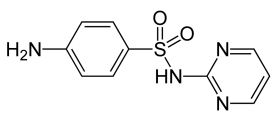
Folate synthesis inhibitors

Tetrahydrofolic acid is a coenzyme in the synthesis of purine bases and thymidine which are constituents of DNA and RNA. They are required for the cell growth and function. A lack of them leads to the inhibition of cell proliferation. Humans must obtain the precursor – folic acid – in the diet. Bacteria are impermeable for the folic acid and must rely on their synthesis de novo. The precursor of tetrahydrofolic acid, dihydrofolic acid in many organisms is synthesized from p-aminobenzoic acid, pteridine and glutamate. Sulphonamides shown in the figure below are inhibitors of the folic acid synthesis. Due to their similarity to p-aminobenzoic acid, they are inhibitors of bacterial enzyme dihydropteroate synthetase.

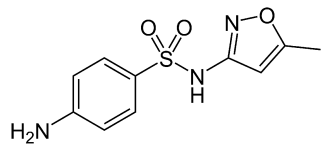
PABA ANALOGUES



sulphanilamide



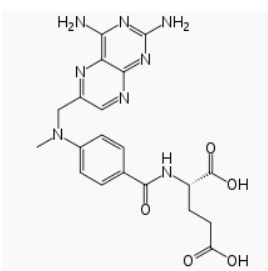
sulfadiazine



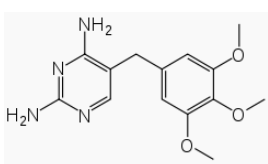
sulfamethoxazole

Dihydrofalate reductase inhibitors

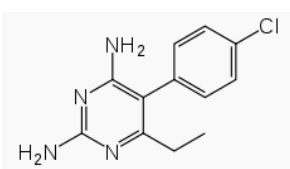
Tetrahydrofolate coenzyme required for the synthesis of purine and pyrimidine is obtained from dihydrofolic acid in the reaction catalysed by the DHFR (dihydrofolate reductase). The inhibitors of this enzyme – trimethoprin is used as an antibacterial as it has stronger affinity to bacterial DHFR. Some other DHFR inhibitors like pyrimethamine and methotrexate are used mostly in parasitic infection and cancer treatment respectively.



methotrexate



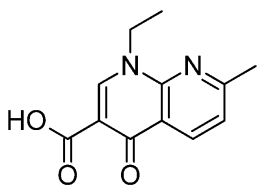
trimethoprin



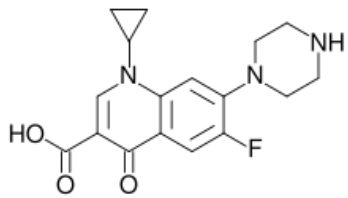
pyrimethamine

Inhibitors of DNA functioning

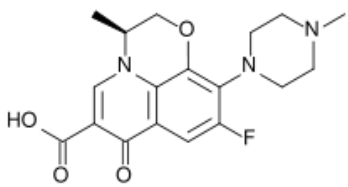
Fluoroquinolones



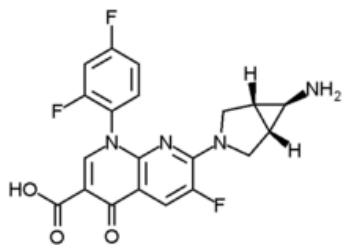
nalidixic acid



ciprofloxacin

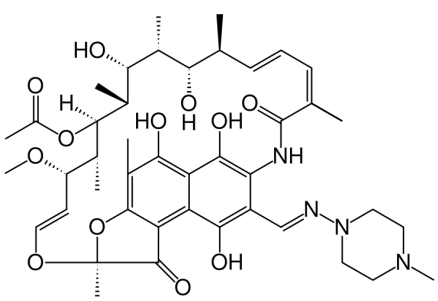


levofloxacin



trevafloxacin

Fluoroquinolones, and quinolones like ciprofloxacin, levofloxacin, trevafloxacin, nalidixic acid, enter the bacterium by passive diffusion and inhibit the replication of bacterial DNA by interfering with topoisomerase II and IV. Topoisomerase regulates the supercoiling of DNA. The inhibition of topoisomerase results in the cleavage of DNA and leads to the death of the cell.

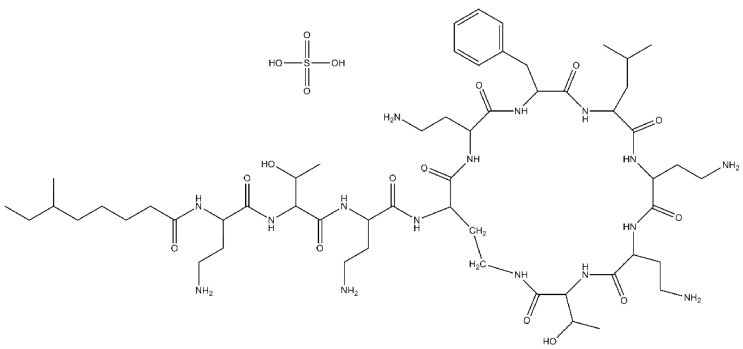


Rifampicin

Rifampicin, for example, inhibits the bacterial enzyme that catalyses the DNA template-directed RNA transcription i.e., DNA depended RNA polymerase

Inhibitor of cell membrane function

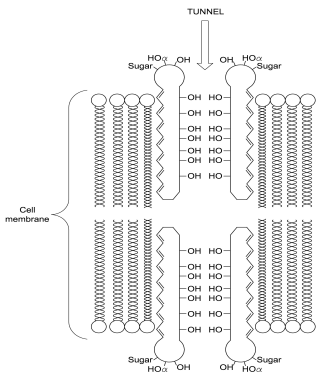
Polymyxins are antibiotics, with a general structure consisting of a cyclic peptide with a long hydrophobic tail. They interact with phospholipids and disrupt the structure of the bacterial cell membrane.



polymyxin B

Ionophoric antibiotic action are substances that penetrate the membrane and increase their permeability. They are natural compounds like gramicidin A, valinomycin or synthetic like cryptate compounds. Most of the known compounds, however, do not differentiate between bacterial and mammalian cells so they have little clinical use.

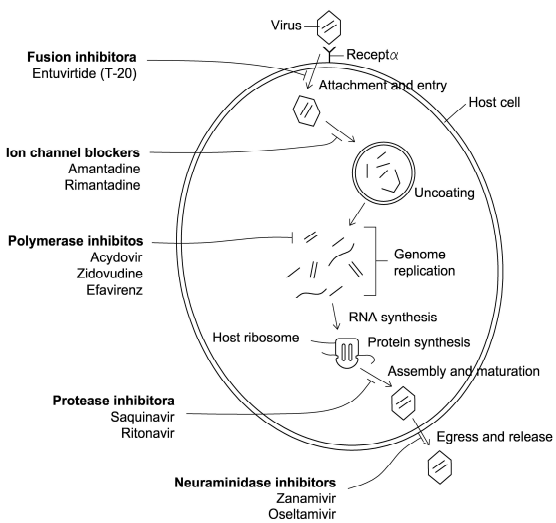
Isoniazid is a prodrug and when activated by a bacterial catalase-peroxidase enzyme, it forms isonicotinic acyl-NADH complex. This complex blocks the action of fatty acid synthase and inhibits the synthesis of mycolic acid, required for the mycobacterial cell wall.



Amphotericin forming channel through the cell membrane

Amphotericin B, like other polyenes nystatin and natamycin, is mainly antifungal but can be used as antibacterial, it inserts itself into the membranes and causes the formation of hydrophilic channels thus disturbing the function of the cell membrane.

6.1.3.Antiviral



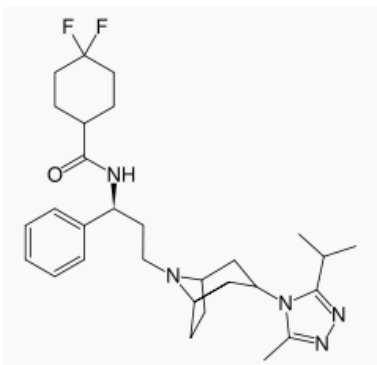
The figure shows a typical viral life cycle and places of pharmacologic interventions.

Fusion inhibitors (entrance inhibitors)

Enfuvirtide and maraviroc are representatives of entrance inhibitors. Viruses like HIV, for example, must fuse its membrane with that of a host cell. This is accomplished by conformational changes of the viral transmembrane glycoprotein gp41. Enfuvirtide, structuralle similar to gp41, binds to gp41. The native gp41 protein is trapped in a conformation that prevents its ability to fuse membrane and thus inhibits the virus entrance.
Maraviroc blocks the chemokine receptor CCR5 which is used by HIV as a coreceptor to bind and enter a human macrophage.

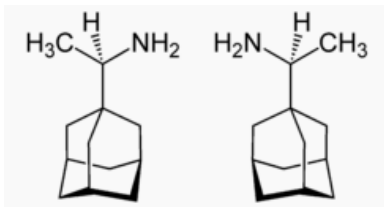
Enfuvirtide

Ac-Tyr-Thr-Ser-Leu-Ile-His-Ser-Leu- Ile-Glu-Glu-Ser-Gln-Asn-Gln-Gln-Glu- Lys-Asn-Glu-Gln-Glu-Leu-Leu-Glu- Leu-Asp-Lys-Trp-Ala-Ser-Leu-Trp-Asn- Trp-Phe-NH_2

Maraviroc 

Viral uncoating inhibitors

Amantadine and rimantadine are inhibitors of viral uncoating, active exclusively against influenza A virus (not B an C). Amantadine blocks a channel protein in the viral coat that permits influx of protons and thus uncoating is prevented.

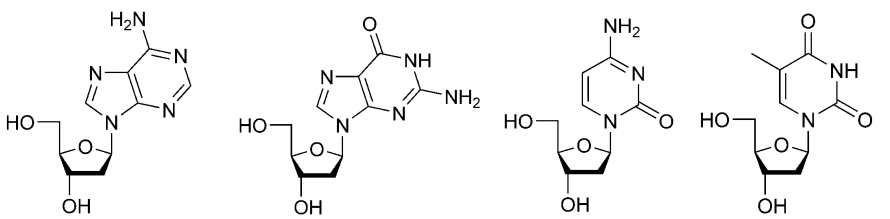


amantadine and rimantadine

Polymerase inhibitors

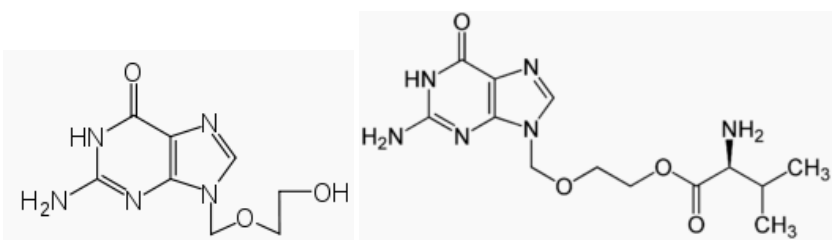
Every virus uses the polymerase to replicate its genome. Most viruses encode their own polymerases, which makes them an excellent target for antiviral drugs. A few viruses use cellular DNA polymerase. In this case drugs targeting polymerase are unacceptably toxic. Most of these drugs are nucleoside analogues, some are non-nucleoside inhibitors of DNA polymerase or reverse transcriptase.

Native nucleotides

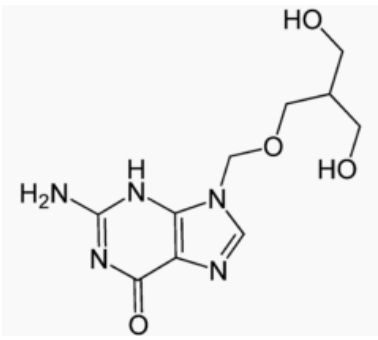


deoxyadenosine deoxyguanosine deoxycytidine eoxythymidine

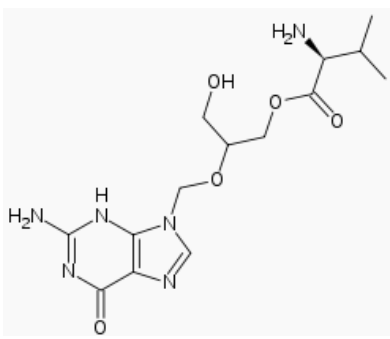
Antiherpesvirus nucleosides and nucleoside analogues



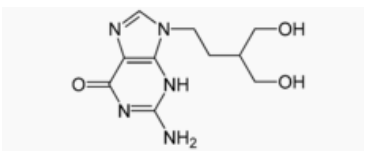
acyclovir valacyclovir



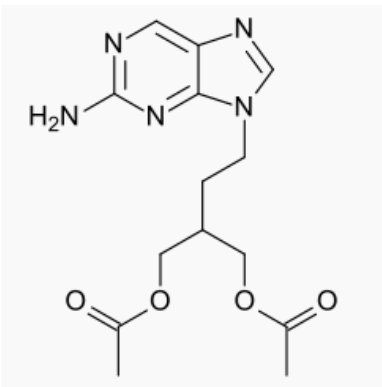
ganciclovir



valganciclovir

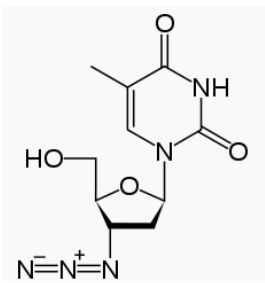


penciclovir

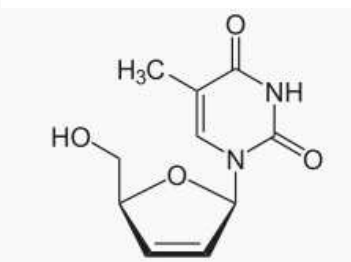


famciclovir

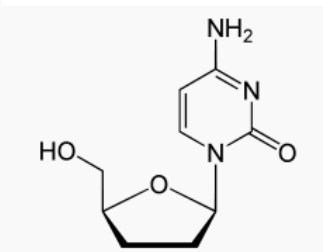
Antihiv nucleosides and nucleoside analogues



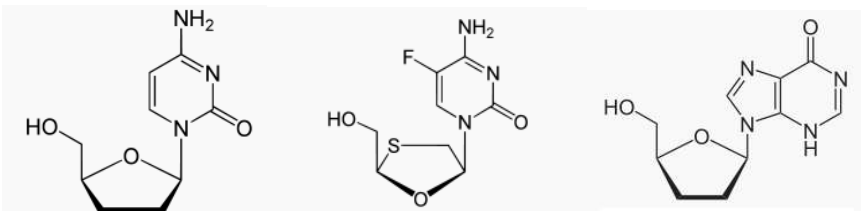
zidovudine



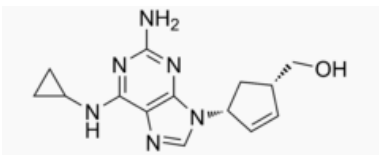
stavudine



zalcitabine

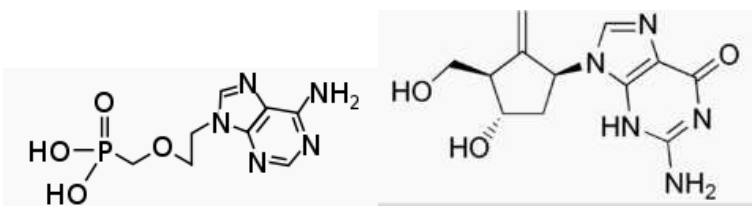


lamivudine emtricitabine didanosine



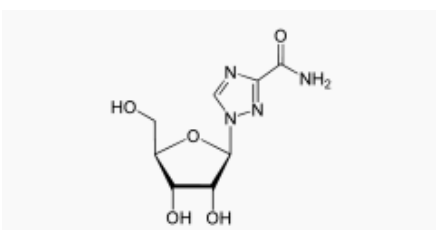
abacavir

Antihepatitis nucleosides and nucleoside analogues



adefovir entecavir

Anti RNA nucleosides and nucleoside analogue



ribavirin

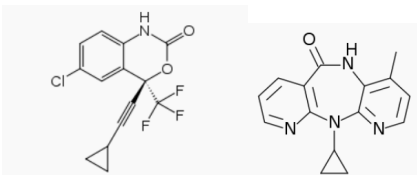
The figure shows several antiviral drugs.

Acyclovir for example is a guanine base attached to an incomplete sugar ring, zidovudine is nucleoside analogue with an altered sugar fragment.

Foscarnet is non-nucleoside inhibitor of DNA and RNA polymerases encoded by many viruses. It mimics a natural product of DNA polymerization – pyrophosphate.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Drugs presented in the figure below were discovered by screening methods. X ray studies have shown that they bind to catalytic site of reverse transcriptase. Delaviridine, efavirenz, nevirapine, delaviridine are nucleoside analogues.

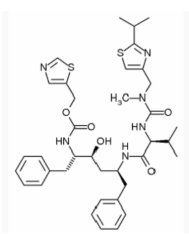


efavirenz, nevirapine

Inhibitors of assembly and maturation

The assembly of nucleic acids and proteins is not sufficient to produce infectious virions – virus particle. The step called maturation is necessary. In most cases viruses encode the proteases that are necessary for that step. So the compounds which are effective against viral proteases will be a good antiviral drugs.

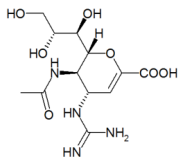
Ritonavir was discovered in the process of modelling the transition state analogue of the cleavage of a substrate by HIV protease. Some anti HIV protease inhibitors are shown in the figure below.



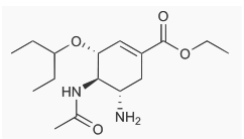
ritonavir

Inhibitors of viral release

At the end the development, the virus has to be released from the surface of the cell. For this purpose the viruses encode the enzyme called neuraminidase which cleaves sialic acid from the membrane glycoprotein and permits the release of the virus. Without neuraminidase the virus cannot spread to other cells. In 1992 an analogue of sialic acid was designed – zanamivir and soon after also oseltamivir.



zanamivir



oseltamivir

They bind to the active site of neuraminidase (neuraminidase inhibitor).

Antiviral compounds with other or unknown mechanisms

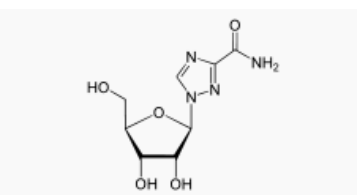
Fomivirsen (brand name **Vitravene** 1998).

It is a synthetic 21 member oligonucleotide with phosphorothioate linkages (sulphur replaces one of the oxygens in the phosphodiester backbone which makes the oligonucleotide resistant to degradation by nucleases), it has the sequence:

5'-GCG TTT GCT CTT CTT CTT GCG-3'

It blocks translation of viral mRNA by binding to a coding segment of a key CMV gene. So it is the antisense antiviral drug.

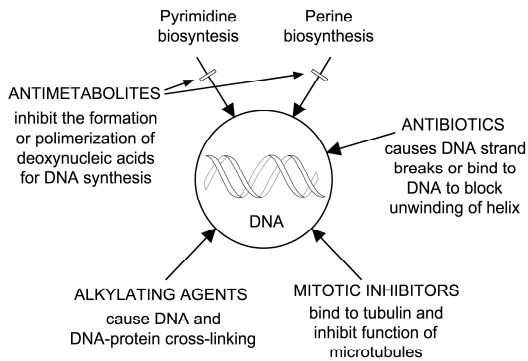
There are several antiviral drugs whose mechanism of action has not been completely discovered yet; one of them is ribavirin.



ribavirin

6.1.4.Antineoplastic (Anticancer)

Neoplasia is characterized by uncontrolled proliferation of the transformed cell at the expense of the host. In the beginning the antineoplastic drugs were classified according to the stage of the cell cycle. More useful classification can be made on the basis of their mechanism of action. Such classification is presented in this book and is schematically drawn in the figure below.



antineoplastic drug classes

The name list of drugs according to the mechanism of their action in each class is given below.

antimetabolites

capecitabine
cladribine
cytarabine
flaxuridine
5-fluorouracil
gemcitabine
6-mercaptopurine
methotrexate
6-thioguanine
fludarabine

antibiotics

bleomycin
dactinomycin
daunorubicyn
doxorubicin
epirubicin
idarubicin
actinomycin D
mitoxantrone

alkylating agents

busulfan
carmustine
chlorambucil
cyclophpsphamide
dacarbazide
ifosfamide
lamustine
mechlorethamine
melphalan
streptozocin
temozolomide
nitrogen mustard
nitrosoureas
cisplatin and carboplatin
procarbazide
mitomycin C

microtubule inhibitors

docetaxel
paclitaxel
vinblastine
vincristine
vinorelbine

steroid hormones and their antagonists

aminoglutethimide
anastrozole
bicalutamide
estrogens
exemestane
flutamide
gaserelin
letrozole
leuprolide
megestrol acetate
nilutamide
prednisone
tamoxifen
toremifene
glucocorticoids
progestational agents

monoclonal antibodies

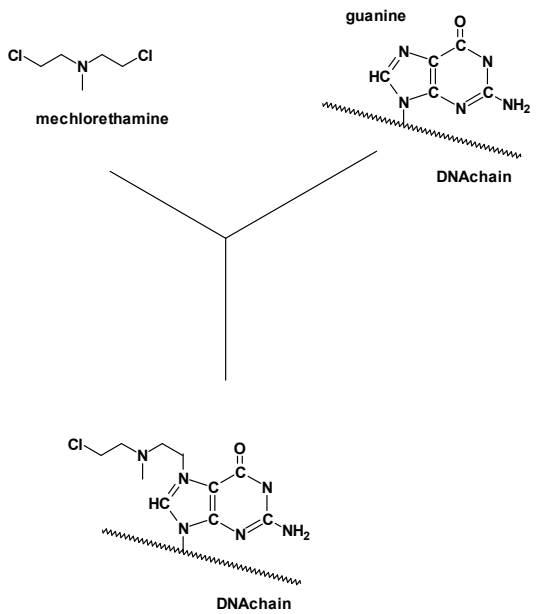
bevacizumab
cetuximab
rituximab
trastuzumab

others

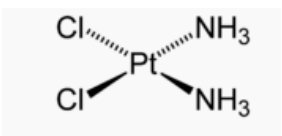
asparaginase
interferons
etoposide
gefinitib
imanitib
irinotecan
procarbazine
tobotecan

Alkylating agents

Alkylating agents exert their cytotoxicity by forming the covalent bonding to nucleophilic groups on various cell components. The most important one is the alkylation of DNA. Alkylating agents do not discriminate between the cells but they are most toxic for the rapidly dividing cells. In long term treatment they may cause serious side effects on the host genetic material. An example of action of an alkylating agent is given below.



Very old and well known alkylating agents are platinium coordination compounds.

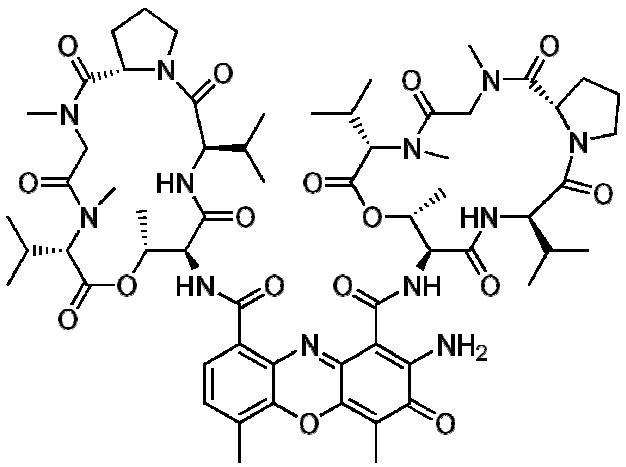


cisplatin

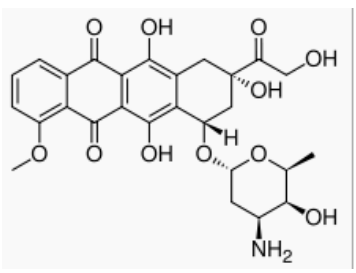
Antibiotics

In many books DNA binding agents and DNA strand breakers are classified in this class of antineoplastic agents.

The example of DNA binding agent is actinomycin and doxorubicin, see figure below.

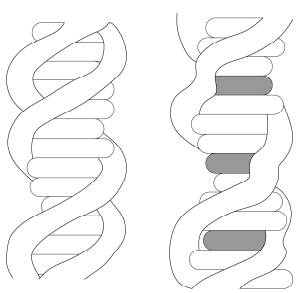


general structure of actinomycins



doxorubicin

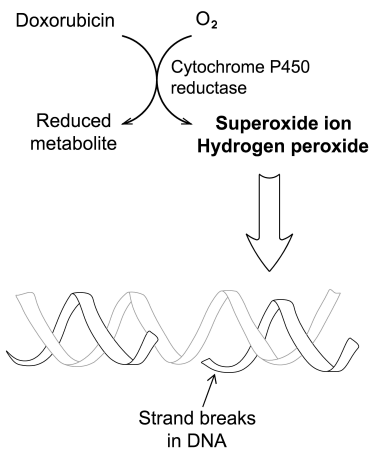
It acts by intercalation between pairs of DNA and thus inhibits synthesis of RNA.



Intercalation induces the structural changes. Left unchaged, right after intercalation.

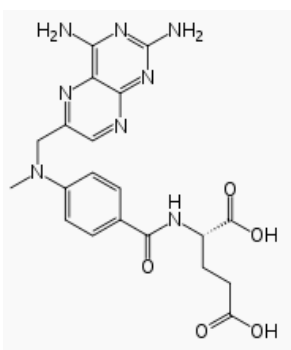
Doxorubicin does several other activities.

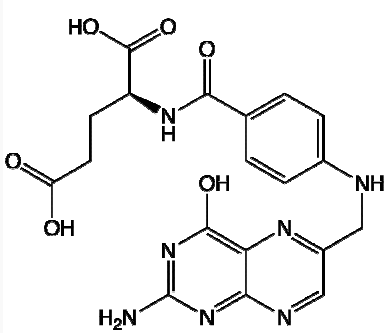
One of them is called strand braeker. Doxorubicin intercalates and interacts with molecular oxygen, producing superoxide ions and hydrogen peroxide, which cause the single strand breaks in DNA.



Antimetabolites

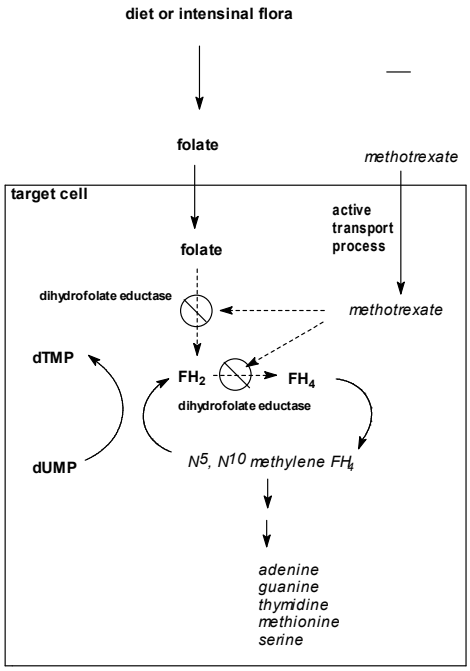
Antimetabolites are synthetic drugs that act as inhibitor of critical biochemical pathways. It is a chemical often similar in structure to the metabolite that it interferes with in the synthesis of DNA producing abnornal DNA. For example antifolate, like methotrexate, interferes with the use of folic acid. The presence of antimetabolites can have toxic effects on cells. They stop cell growth and cell division, and thus are used as chemotherapy for cancer. The comparison of the structure of folic acid and methotrexate is shown below.



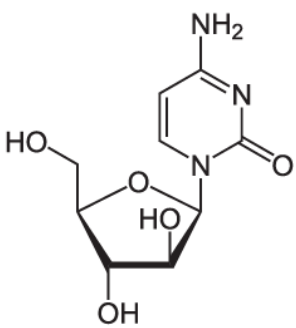


methotrexate folic acid

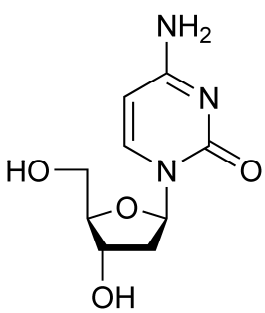
Folic acid obtained from the diet has to be reduced and then it is a precursor of nucleic bases. Being similar to folic acid, methotrexate strongly binds to DHFR (dihydrodrofolate reductase) and stops the purines biosynthesis.



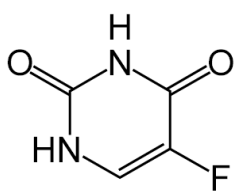
5 fluorouracil as a pyrimidine analogue, is an inhibitor of tymidylate synthase. It is also transformed inside the cell and then incorporated into DNA and RNA, finally inducing cell cycle arrest and apoptosis. Other nucleoside analogues which are also incorporated into DNA are cytosine arabinoside or deoxycytydine.



cytosine arabinoside



deoxycytydine



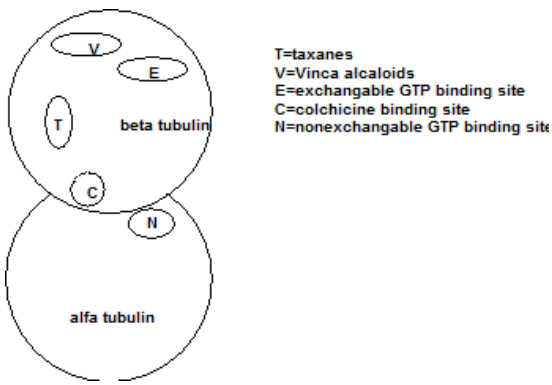
5 fluorouracil

Natural plant antineoplastic

Natural antineoplastic compounds interfere with the mitosis phases by interfering with tubulin molecules formation or degradation. Tubulin molecules should stack to form mitotic spindle in the metaphase. However, they fail to polymerize in the presence of vinca alkaloids making the mitosis freeze in the metaphase.

If the process of mitotic spindle formation is not inhibited, the mitotic spindle should then dissolve in the later mitosis phase allowing a cell to divide. Taxanes stabilize the microtubules. The result of unusually stable tubulin is making the cell remain in methaphase and finally causes its death.

Both taxanes and vinca alkaloids interfere with spindle formation or stability and thus are called spindle poisons.

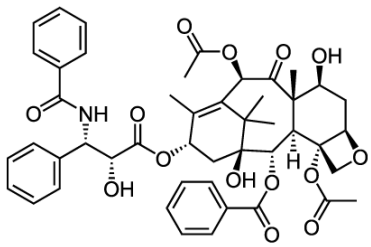


tubulin binding sites of microtubule inhibiting drugs

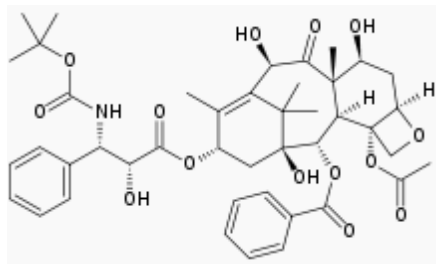
Taxanes

Taxanes are complex terpenes originally obtained from the plants of the genus *Taxus* (yews), now they are synthesized artificially. They inhibit the cell's division through the inactivation of the microtubule function of a cell which is essential to mitotic reproduction.

Paclitaxel a mitotic inhibitor used in cancer chemotherapy was isolated in 1967 from the bark of the Pacific yew tree, *Taxus brevifolia* and named **taxol**.



Paclitaxel

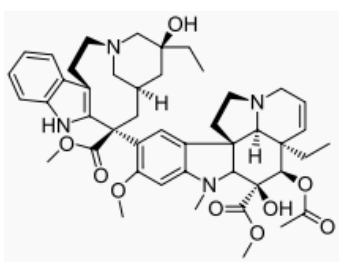


docetaxel

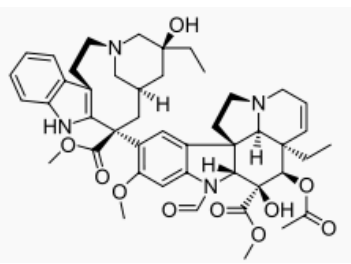
Docetaxel is the chemotherapy semi-synthetic analogue of paclitaxel, and is a semi-synthetic analogue of paclitaxel (Taxol), an extract from the rare Pacific yew.

Vinca alkaloids

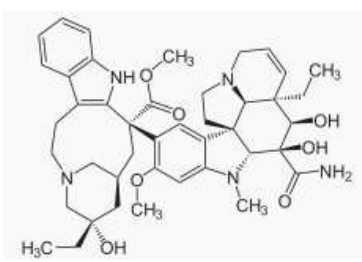
The commonly used drugs, vincristine or vinblastine, are obtained from plant *Vinca rosea.* As expressed above, they are inhibitors of spindle formation. Both drugs are given intravenously and are useful in the treatment of lymphoma, breast cancer, testicular cancer and sarcomas. They have certain toxicity.



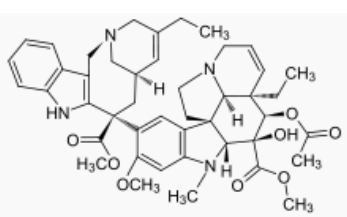
vinblastine



vicristine



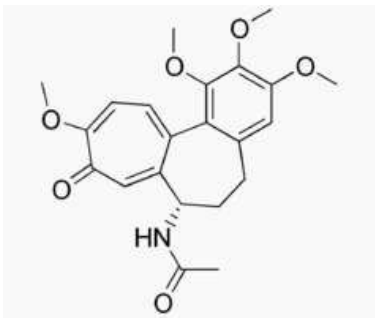
vindesine



vinorelbine

Colchicine

Colchicine is an alkaloid derived from the autumn crocus (*Colchicum autumnale*). It inhibits mitosis by inhibiting microtubule polymerization. However, the therapeutic value of colchicine against cancer is limited by its toxicity against normal cells. While colchicine is not used to treat cancer in humans, it is commonly used to treat acute attacks of gout.

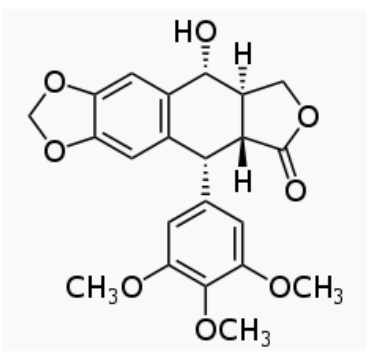


colchicine

Lignans

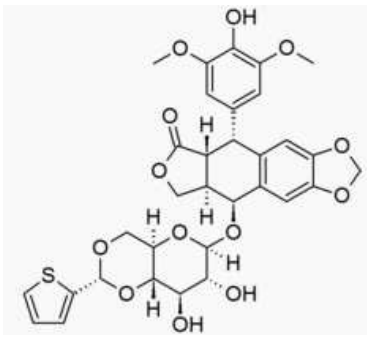
It is another class of drugs known as podophyllotoxin derivatives which slow the growth of cancer cells in the body. **Podophyllotoxin** (**PPT, podofilox)**, is a non-alkaloid toxin lignan extracted from the roots and rhizomes of Podophyllum species; *Podphyllum peltatum* and *Podophyllum emodi*. The therapeutic use is limited due to their toxicity.

Their anticancer activity has been studied and used in various chemotherapies, including lung cancer, lymphomas, and genital tumours.



podophyllotoxin

Better properties are posessed by semisynthetic teniposide (teniposidum, Vunom), antimitotic plant compound active in the S phase of mitosis. The mechanism of action appears to be related to the inhibition of type II topoisomerase activity



teniposide

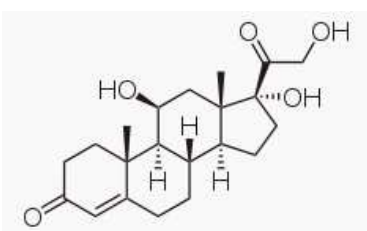
Hormones and their antagonists

Some tumours are steroid hormone sensitive. They are:

- hormone responsive when tumour regresses after treatment
  hormone dependent when removal of hormone stimulus causes tumour regression
- both

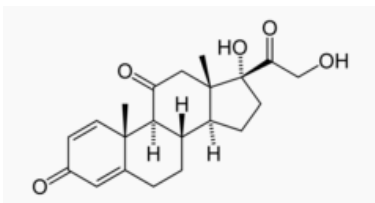
Glucocorticoids

Glucocorticoids (GC) are a class of steroid hormones that bind to the glucocorticoid receptor (GR), which is present in almost every vertebrate animal cell.



cortisol

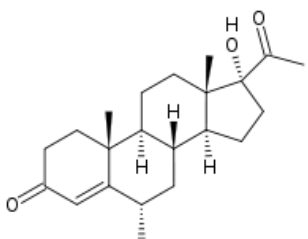
Prednisone is a synthetic drug particularly effective as an immunosuppressant and at higher doses as anticancer, but it has significant adverse effects. Prednisone is a prodrug which after reduction to prednisolone binds to the receptor responsible for the production of some specific proteins. Prednisone belongs to the class of glucocorticoids which are effective in the treatment of leukemia, myeloma, lymphomas, breast cancer.



prednisone

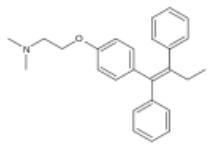
Prostate cancers are stimulated by androgens. High level of estrogens inhibits androgen synthesis, thus estrogens like diethylstilberol or antandrogens like flutamide and nilutamide are effective drugs in the prostate cancer therapy.

Medroxyprogesteron, megestrol and gonadotropinrelesing-hormone agonists are also known to be active against hormone-sensitive cancers, however, their action is not fully understood.



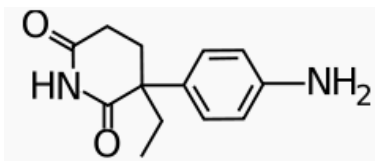
Medroxyprogesteron

Many breast cancers grow more rapidly in the presence of female hormones so hormonal treatments of this cancer include usage of antiestrogens, for example tamoxifen, the nonsteroidal antiestrogen.



tamoksyfen

Aminoglutethimide is an anti-steroid used clinically. Aminoglutethimine is an inhibitor of the enzyme responsible for the conversion of androgens to estrogens and cholesterol to pregnenolone. This antiestrogenic effect is useful in managing metastatic breast cancer.



Aminoglutethimide

6.1.5.Miscellaneous

Urea derivatives have also been reported as anticancer drugs. They inhibit the ribonucleotide reductase and bloc the cell transformation cycle from phase G1 and S1.

For some cancerogenic cell asparagin is necessary for development. In this case, the treatment with the enzyme asparaginase reduces the concentration of aparagin in the body fluids and thus inhibits the growth of tumour cells having no asparagine synthase.

Monoclonal antibodies have become an active area for anticancer therapy.

6.2.Neural Disorder

6.2.1.Types of neurotransmitters

Neurotransmitters are the most important chemical signalling species for communication between cells. In addition to them, there exist local mediators that act locally in their immediate environment (for example histamine, prostaglandins) and hormones secreted by endocrine cell which travel to broadly distributed target cells in the body.
As explained above, the only direct action of a neurotransmitter is to activate a receptor. Therefore, the effects of a neurotransmitter system depend on the connections of the neurons that use the transmitter, and the chemical properties of the receptors that the transmitter binds to.
Below there are a few examples of important neurotransmitter actions:

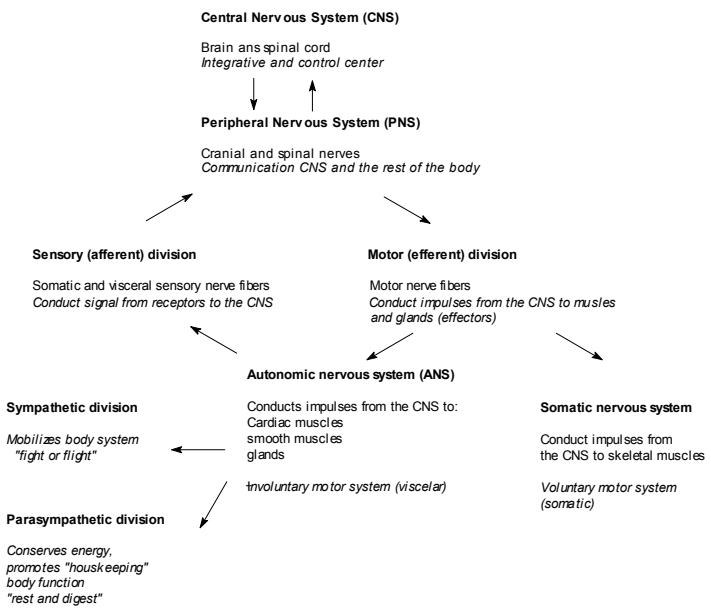
- Glutamate excitatory neurotransmitter is present in the majority of fast excitatory synapses in the brain and spinal cord.
- GABA inhibitory neurotransmitter is present in fast inhibitory synapses in almost every part of the brain. Many sedative/tranquilizing drugs act by enhancing the effects of GABA.
- Corresponding glycine is the inhibitory transmitter in the spinal cord.
- Acetylcholine is the transmitter at the neuromuscular junction connecting motor nerves to muscles and in many parts of the brain.
- Dopamine plays a critical role in the reward system, dysfunction of that system is implicated in Parkinson's disease and schizophrenia.
- Serotonin is produced by and found in the intestine (approximately 90%) and in central nervous system. It regulates appetite, sleep, memory and learning, temperature, mood, behaviour, muscle contraction and the function of the cardiovascular and endocrine system. It probably plays an important role in depression.
- Substance P is an undecapeptide responsible for transmission of pain from sensory neurons to the central nervous system.

Over fifty signal molecules in the nervous system were identified, only six of them are involved in the action of therapeutically useful drugs – norepinephrine (epinephrine), acetylcholine, dopamine, serotonin, histamine, gamma – aminobutyric acid.

Most of the receptors have several subtypes with different functions which are affected by different drugs.

6.2.2.Nervous system

The nervous system is divided to two anatomical divisions: central nervous system – CNS (brain and spinal cord) and peripheral nervous system (nerves outside the brain and spinal cord). The peripheral system is divided to efferent (signals are going away from brain) and afferent (signals are going to brain). The efferent part is composed of two different divisions; somatic (voluntary controlled – for example muscle contraction in locomotion) and autonomic (functioning without the conscious participation, for example cardiac muscle, blood flow, glandular secretion).



The autonomic system is divided to:

-sympathetic

Its role is adjusting to stressful situations such as trauma, fear, cold resulting in blood pressure, heart rate and so on). It is the "**fight and flight"** response.

-parasympathetic

It is essential for bodily functions like digestion for example. In contrast to the previous one, parasympathetic system is "**rest and digest"** type.

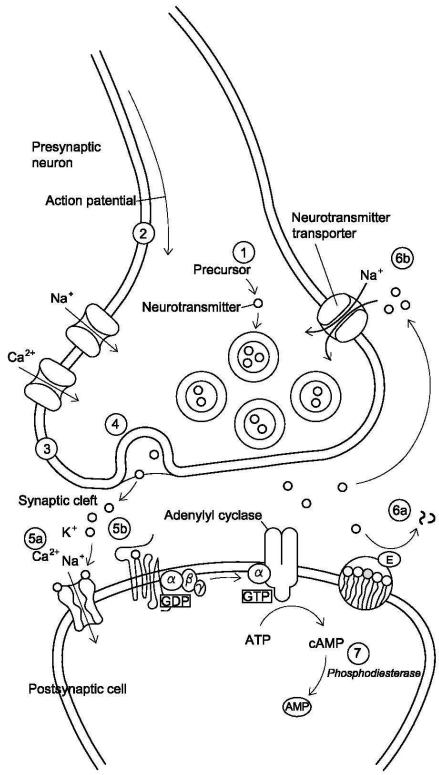
-*enteric.*

This system functions independently of the CNS and controls the motility, endocrine and exocrine secretion and microcirculation of the gastrointestinal tract. It constitutes the "**brain of the gut**" and is modulated by sympathetic and parasympathetic nervous systems.

Since the nervous system influences the number of physiological processes, including homeostasis, neurons are one of the most important targets in drug design.

Neurons communicate with one another and with other cell types through the regulated release of small molecules or peptides known as neurotransmitters. The specialized connection is called synapse. An electric signal in plasma membrane of presynaptic cell induces the release of chemical signal-neurotransmitter. The typical steps in the synaptic transmission are presented in the figure below.

6.2.3.Examples of drugs acting on neurotransmission in peripheral nervous system



Synaptic transmission

1.neurotransmitter synthesis from precursor

2. action potential travel down the neuron and depolarizes the presynaptic nerve terminal

3. membrane depolarization activates voltage-depended channel Ca+2 which allows entering calcium ions

4. the release of neurotransmitter into synaptic cleft

5. neurotransmitter travels to postsynaptic receptors; 5a ionotropic, 5b metabotropic

6 neuro transmittionr is accomplished by removal of the transmitter from the synaptic cleft:

6a it can degradated by enzyme

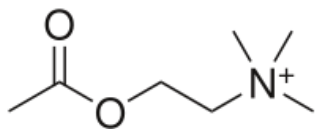
or 6b it can be recycled to presynaptic part by reuptake transporters

7. signal can be accomplished by degradation of intracellular signalling molecules (like cAMP)

The main neurotransmitters of the peripheral nervous system are acetylcholine and noradrenaline.

Cholinergic

The **acetylcholine** (**ACh**) is a neurotransmitter in both the peripheral nervous system (PNS) and central nervous system (CNS). From the perspective of drug design it is the most important neurotransmitter in the human brain. Neurons associated with acetylcholine are named cholinergic. Parasympathetic system is mainly modulated by cholinergic neurotransmission whereas the sympathetic one by adrenergic



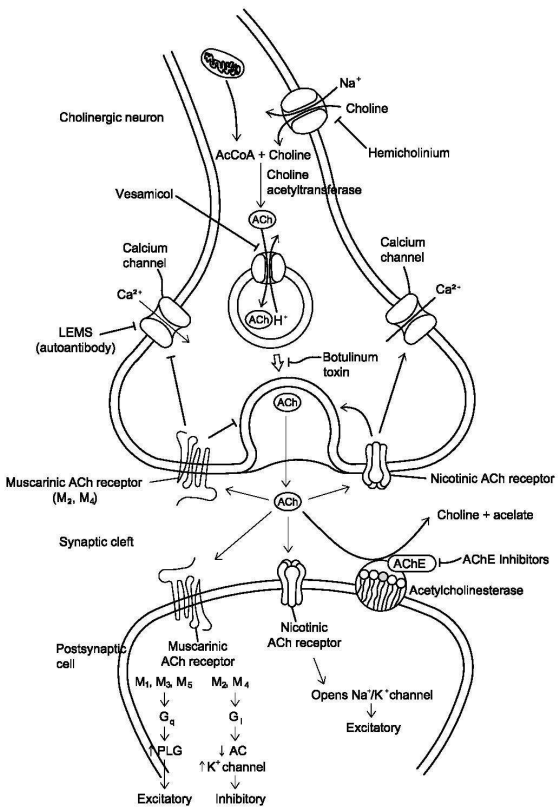
acetylcholine

There are two main classes of acetylcholine receptor (AChR), nicotinic acetylcholine receptors (nAChR) and muscarinic acetylcholine receptors (mAChR). The name comes from the ligands which activate the receptors.

However, more detailed studies have identified 17 nAChR subunits, these are divided into muscle-type and neuronal-type subunits. Of these 17 subunits, α2-α7 and β2-β4 have been cloned in humans.

Neuronal type					Muscle type
I	II	III			IV
		1	2	3	
α1, α10	α7, α8	α2, α3, α4,α6	β2,β4	β3, α5,	α1, β1,δ, γ,ε

The cholinergic synaptic transmission is presented below.



Acetylcholine is synthesized by the enzyme choline acetyltransferase. It is decomposed to choline and acetic acid by the enzyme acetylcholinesterase in the synaptic cleft. This process is necessary for clearing the synapse from acetylcholine and proper muscle function.

Acetylcholinesterase inhibitors

Some neurotoxins are inhibitors of acetylcholinesterase which lead to excess acetylcholine at the neuromuscular junction and consequenlty to the paralysis of the muscles (they stop

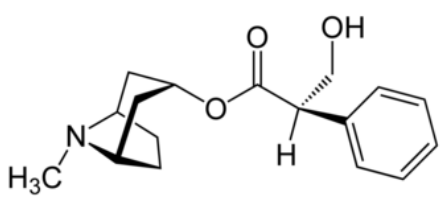
breathing and the beating of the heart). Nerve agents (sarin,VX) or pesticides work in that way. In clinical use, they are used to treat myasthenia gravis and to treat the symptoms of Alzheimer's disease (Donepezil, galantamine, Rivastigmine, Tacrine which increases cholinergic activity in the brain).

ACh receptor agonists

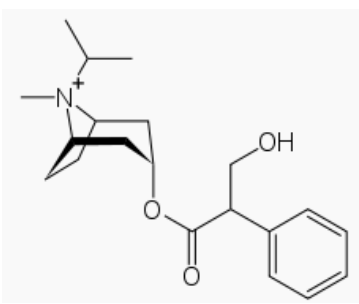
ACh Receptor Agonists, like Alvameline, are also used to treat myasthenia gravis and Alzheimer's disease. Pilocarpine another Ach agonist is used in the treatment of chronic open-angle glaucoma. These are drugs that mimic acetylcholine on the receptor to stimulate the receptors. The principal agonists used clinically are methacholine, carbachol, betnechol. The last one is used especially in the stimulation of gastrointestinal tract and urinary bladder to relieve postoperative atony. Other used agonists are muscarine, natural alcaloid from Amanita muscaria and its semisynthetic analogue muscarone. Oxotremorine is helpful in the study of antiparkinsonian drugs.

ACh receptor antagonists

Atropine, the oldest anticholinergic, is alcaloid from Atropa belladonna, it can be useful in treating hyperhidrosis, and can prevent the death rattle of dying patients. Injections of atropine are used in the treatment of bradycardia (an extremely low heart rate), asystole and pulseless electrical activity (PEA) in cardiac arrest.



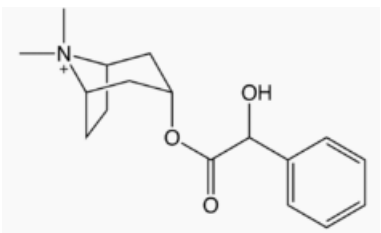
atropine



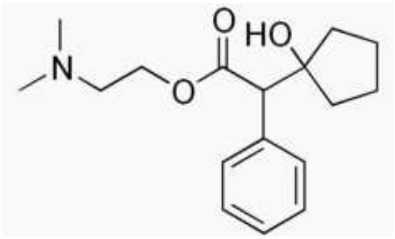
ipratropium

Ipratropium is used for the management of chronic obstructive pulmonary disease and asthma. Some other drugs are presented in the figure below: scopolamine used for motion sickness, tolderodine for suppression of adult urinary incontinence, homatropine, cyclopentolate,

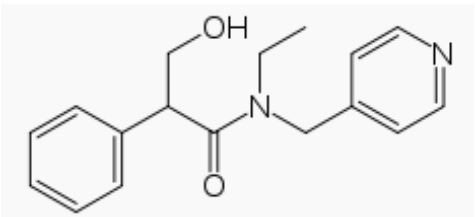
tropicamide in ophtalmologic disorders. Anticholinergics are used in the treatment of Parkinson disease in addition to more widespread dopamineergic therapy.



homatropine



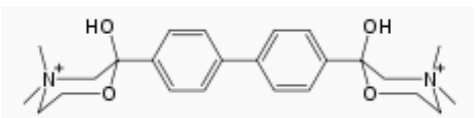
cyclopentolate



tropicamide

ACh reuptake inhibitors

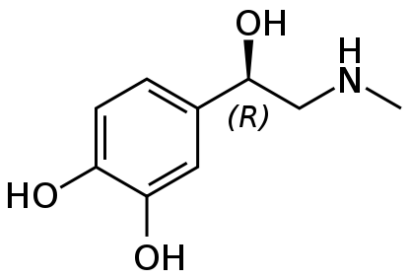
The level of the acetylcholine in the synaptic cleft can be regulated by the inhibition of the reuptake of choline. **Hemicholinium-3**, also known as **hemicholine**, is a drug which blocks the reuptake of choline.



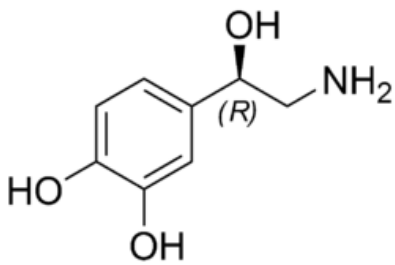
Hemicholinium-3

The reuptake of choline is the rate limiting step in the synthesis of acetylcholine which decreases the synthesis of acetylcholine. It is therefore classified as an indirect acetylcholine antagonist.

Adrenergic



adrenaline



noradrenalina

Norepinephrine is another important neurotransmitter. The receptors that respond to it are named adrenergic receptors. The neurotransmitter secreted by the nerve endings is norepinephrine and to a lesser extent, epinephrine. The **adrenergic receptors** (or **adrenoceptors**) are a class of G protein-coupled receptors that are targets of the catecholamines, especially noradrenaline (norepinephrine) and adrenaline (epinephrine). Although dopamine is a catecholamine, its receptors are in a different category. Many cells possess these receptors, and the binding of an agonist will generally cause a sympathetic response (e.g. the fight-or-flight response). For instance, the heart rate will change the rhythm. There are two major groups of adrenergic receptors alpha and beta and they are subdivided to alpha1, alpha2, and beta1, beta2, beta3.

Norepinephrine and epinephrine receptors

β_1 receptors

-epinephrine and norepinephrine are equally potent agonists
-located in the heart and cerebral cortex
-linked to adenyl cyclase
-market regional variations in brain
-practocol is a selective antagonists

β_2 receptors
-epinephrine is more potent agonists than norepinephrine

-found in high density in the lung and cerebellum
-linked to adenyl cyclase
-terbutaline and salbutamol are selective agonists

α_1 receptors
- located postsynaptically on blood vessel and in peripheral tissues
- prazosin is a selective antagonist of receptors localized in the heart

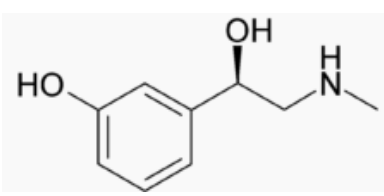
α_1 receptors
-clonidine, epinephrine and norepinephrine are selective ligands
-clonidine is selective agonist
-effects mediated through stimulation of phspholipase activity and mobilization of intracellular Ca^{+2}
+located on presynaptic nerve terminals in the periphery
+localized in the pancreas

α receptors

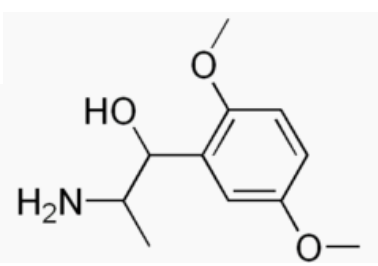
α2 receptors have several functions. Mainly they affect vasoconstriction of coronary artery, veins and they decrease the motility of the smooth muscle in the gastrointestinal tract.

Agonists

Adrenergic agonists, phenylephrine and methoxamine, are vasoconstrictors and are used in treating hypotension and nasal congestion. They also inhibit insulin release.



phenylephrine

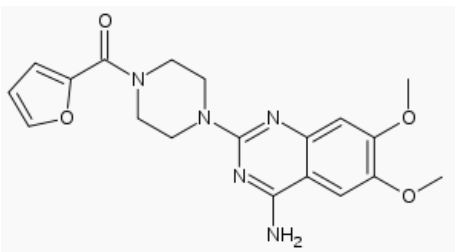


methoxamine

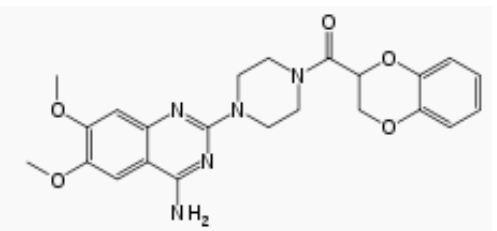
Clonidine α2 agonist is an antyhypertensive agent. It also stimulates the histame H2 receptors and has antianxiety properties.

Antagonists

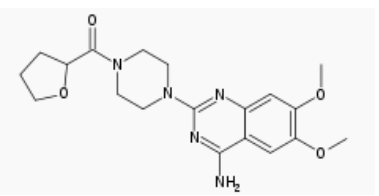
α1 receptor antagonists, prazosin, doxazosin, terazosin, are used for the treatment of benign prostatic hyperplasia (this disorder of older men involves progressive urinary symptoms as the enlarging prostate slowly pinches the urethra closed).



prazosin



doxazosin



terazosin

β receptors

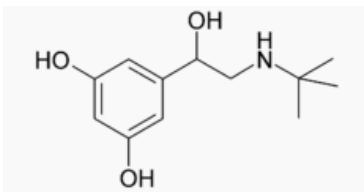
β_1 receptor is involved in the increase of cardiac output by raising heart rate and increasing impulse conduction.

β_2 receptor is involved in smooth muscle relaxation, it increases renin secretion from kidney.

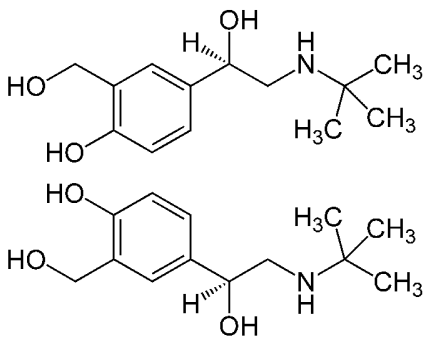
β_3 receptor is involved in the enhancement of lipolysis in adipose tissue.

Beta agonists

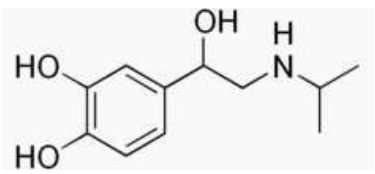
Beta agonists have many therapeutic effects in the regulation of heart function, in the treatment of asthma (terbutaline, salbumatol). Isoproterenol and methoxyphenamine are used as bronchodilators.



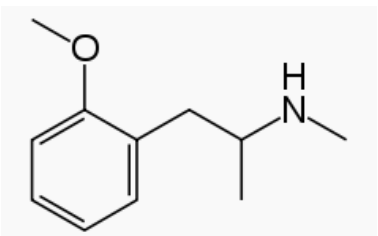
terbutaline



salbutamol

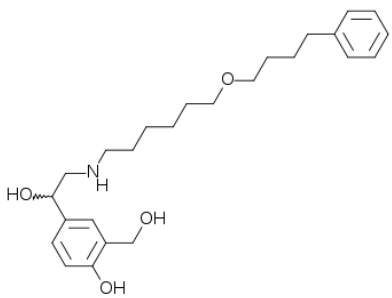


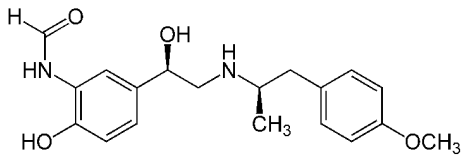
Isoproterenol



methoxyphenamine

Salmeterol and formoterol are currently prescribed for the treatment of asthma and chronic obstructive pulmonary disease.



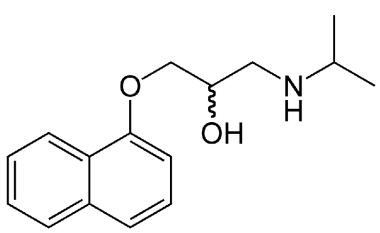


Salmeterol formoterol

Beta-3 activating drugs could be used as weight-loss agents.

Beta antagonists (beta blockers)

Beta antagonists are probably the most important adrenergic drugs and are used for various indications, but particularly for the management of cardiac arrhythmias, cardioprotection after myocardial infarction (heart attack), and hypertension. They are beta adrenergic receptor antagonists, so they diminish the effects of epinephrine (adrenaline) and other stress hormones. The first useful beta antagonist was dichloroisoproterenol synthesised in 1958 by Eli Lilly Laboratories, however, the first major beta blocker commercialized drug in the treatment of hypertension was propranolol. Propanolol was introduced into therapy in 1965. It was a milestone in the therapy of angina pectoris and one of the most important discoveries for clinical medicine of 20th century. Now we have more than 20 different analogues. Some of them are selective beta1 blockers.



propranolol

Adrenergic drugs can be also classified to:

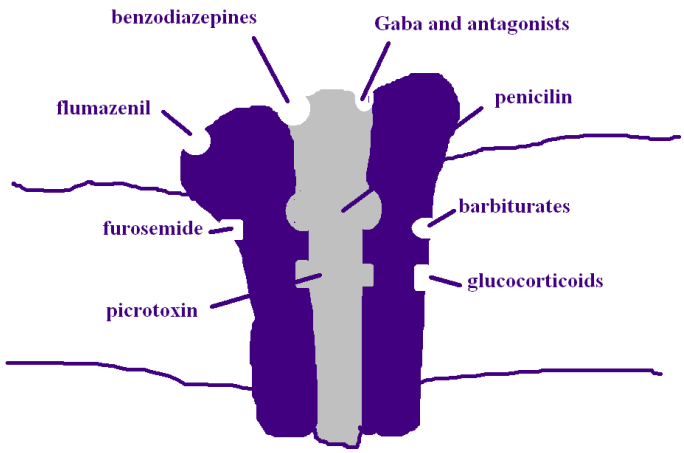
- interfering with catecholamine synthesis like alpha metyldopa. It is the inhibitor of DOPA decarboxylase which decreases the level of norepinephrine. It is used as a drug in decreasing blood pressure
- interfering with catecholamine metabolism. Most of these drugs act by blocking the monoamine oxidase (MAO)
- interfering with catecholamine storage and reuptake. Rauwolia alkaloid reserpine interferes with the membranes of synaptic vesicles and decreases the availability of norepinephrine. The effect is hypotension and sedation. Amphetamine, alpha receptor agonist, is mood elevator and psychomotor stimulant. It inhibits the neurotransmitter reuptake and increases transmitter release.
- drugs affecting catecholamine uptake like tyramine and octopamine.

Gabaergic

GABA is the main inhibitory neurotransmitter, which means that it decreases the electrochemical activity of neurons. There are many gabaergic neuronal pathways in the CNS. The great interest in this area over many past years was due to the fact that popular benzodiazepine tranquilizers (Valium, diazepam) act through GABA receptor.

Drugs that increase the amount of GABA have relaxing, anti-anxiety and anti-convulsive effects. In general, GABA does not cross the blood-brain barrier, although certain areas of the brain can be reached.

Activation of GABA(A) receptors favours sleep. There are tree generations of hypnotics acting on GABA(A) receptor. The first (barbiturates) and the second (benzodiazepines) generation of hypnotics decrease waking, increase slow-wave sleep and enhance the intermediate stage between slow-wave sleep and paradoxical sleep. The third generation (imidazopyridines and cyclopyrrolones) act similarly on waking and slow-wave sleep but with a slight decrease of paradoxical sleep during the first hours.



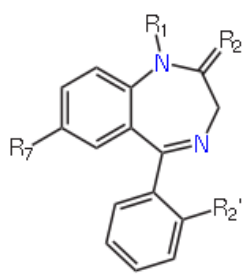
Schematic representation of GABA(A) receptor and major drug binding sites

GABA(B) receptor antagonists increase brain-activated behavioural states (waking and paradoxical sleep: dreaming stage).

Specific GABA(C) receptor antagonist was found to increase waking at the expense of slow-wave sleep and paradoxical sleep. The sensitivity of GABA(C) receptors is higher in comparison to GABA(A) and GABA(B), in future they could be remedies for troubles such as insomnia, epilepsy and narcolepsy. They could probably be administered at lower doses, so fewer side effects will be observed.

Probably the most clinically important class of GABA active compounds are benzodiazepines.

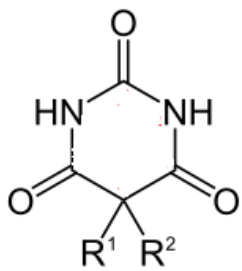
There are about 3500 compounds which have been investigated since the discovery by Leo Sternbach in Hoffman-La Roche laboratories in the year 1950.



general structure of benzodiazepines

Benzodiazepines enhance the effect of GABA which results in sedative, hypnotic (sleep-inducing), anxiolytic (anti-anxiety), anticonvulsant, muscle relaxant and amnesic action. It makes them appropriate in treating anxiety, insomnia, agitation, seizures, muscle spasms, alcohol withdrawal and in some dental procedures. The GABA ergic properties of benzodiazepines are most important for clinical applications.

A large and still used group of GABA ergic drugs are barbiturates, central nervous system depressants, sedative-hypnotic compounds. They are also called “sleeping pills”.

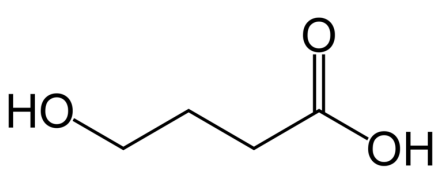


general structure of barbiturates

Both benzodiazepines and barbiturates are used as anticonvulsants in epilepsy. They act by binding to $GABA_A$ receptor but at a different site.

One of the neurodegenerative genetic diseases – Huntington disease is caused by the defective GABA metabolism.

Analogue of GABA, γ-Hydroxybutyric acid (GHB), is a naturally occurring compound found in wine, beef, small citrus fruits, in small amounts in CNS. It is an illegal drug in many countries, however, in some countries it is used to treat cataplexy, narcolepsy, fibromyalgia under the trade name Xyrem. GHB has also been used in general anaesthetic to treat insomnia, clinical depression, narcolepsy and alcoholism, and to improve athletic performance. It is also used as a date rape drug. Its action is connected with its similarity to GHB and structurally related beta-hydroxybutyrate, naturally produced in the human body cells.

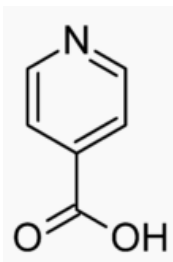


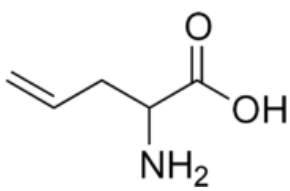
γ-Hydroxybutyric acid (GHB

The recent studies provide evidence for the role of GABA ergic mechanism in the understanding of human consciousness, the most enigmatic physiological process, at molecular level. Among many drugs affecting autonomic nervous system there are: anticonvulsants, muscle relaxant, narcotic, CNS stimulant +AZ65, antiparkinsonism, antipsychotic, antialzheimer, anxiolytic, hypnotic, anaesthetics, antidepressants, neuroleptics, antiseizure, hallucinogens and others for example antyarrhythmic drugs.

GABA synthesis inhibitors

Gaba synthesis inhibitors like hydrazinopropionic acid, allyglycine or isonicotinic acid, hydrazide act on the enzymes involved in decarboxylation of glutamic acid.



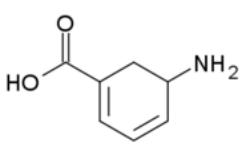


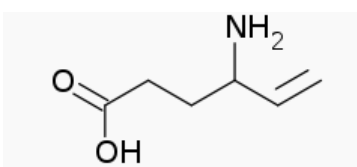
hydrazinopropionic acid isonicotinic acid allyglycine

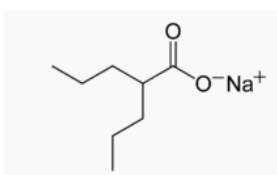
It leads to lower GABA level and thus causes seizure and convulsions.

GABA metabolism inhibitors, GABA-transaminase inhibitors

In contrast to GABA synthesis inhibitors, these drugs increase the concentration of GABA: gabaculine, phenelzine, valproate, vigabatrin, lemon balm (Melissa officinalis).







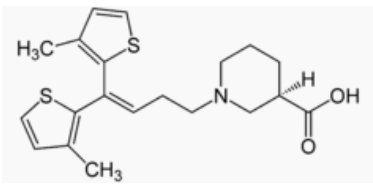
gabaculine vigabatrin sodium valproate

The most potent ones are gabaculine and vigabatrin, both ptotect against drug induced seizures.

GABA reuptake inhibitors.

They block the uptake of GABA and thus block GABA breakdown.

The mot effective ones are nipecotic acid, deramciclane, hyperforin, tiagabine.



tigabine

$GABA_A$ receptor ligands

Agonists working as positive allosteric modulators, in general bear some resemblance to GABA, some examples encompass: alcohol, barbiturates, benzodiazepines, carisoprodol, etomidate, glutethimide, L-theanine, kava, methaqualone, muscimol, neuroactive steroids, nonbenzodiazepines, propofol, scullcap, valerian, volatile/inhaled anaesthetics, halucinogenic isoxazol isolated from Amanita muscaria.

Antagonists working as negative allosteric modulators: bicuculline, cicutoxin, flumazenil, furosemide, gabazine, oenanthotoxin, picrotoxin, Ro15-4513, thujone.

$GABA_B$ receptor ligands

$GABA_B$ receptors metabotropic transmembrane receptors linked via G-proteins to potassium channels. They are found in the central and peripheral autonomic nervous system and they are considered inhibitory receptors. $GABA_B$ receptors are involved in behavioural actions of ethanol, gamma-Hydroxybutyric acid (GHB), and possibly in pain. There are suggestions that they play an important developmental role.

Agonists: baclofen, GBL, GHB, phenibut.

Antagonists: phaclofen, saclofen.

$GABA_C$ receptor ligands

GABA(C) receptors belong to the nicotinicoid group of ionotropic receptors that include nicotinic acetylcholine receptors, bicuculline-sensitive GABA(A) receptors, strychnine-sensitive glycine receptors and 5HT3 serotonin receptors. They were found in the retina, spinal cord, superior colliculus, pituitary and the gut. They influence vision, some aspects of memory and sleep-waking behaviour. The ligands that show some GABA(C) receptor selectivity are TPMPA, P4PMA, imidazole-4-acetic acid, 2-methyl-TACA and (+/-)-TAMP.

6.3. Drug resistance

Drug resistance occurs when a formerly effective drug is no longer effective. This could happen due to several reasons:

- antibiotics can kill most of the bacteria but let's say 1 in 10 millions in the colony are mutants which are resistant to that drug. These few resistant ones can replicate and become dominating;
- some organisms can have the ability to exclude the drug from the site of action by preventing the uptake of the drug,
- resistance to the inhibitors of an enzyme can be the result of overproduction of the enzyme,
- mutation which results in aminoacid change in the active site of the enzyme may result in poor binding of the drug;
- the production of the enzyme destroying the drug;
- deletion of the enzyme converting the prodrug to a drug;
- overproduction of the natural substrate of the enzyme, so more substrate molecules compete with the inhibitor;
- development of the new path for production of the product which was stopped by inhibitory action of the drug;
- Presence of transporters moving the drug from inside to outside of the cell.

6.4.Drug synergism

If two drugs are given, several actions are possible:
-antagonism
-synergism
-additive.

Synergism could be the effect of:

- inhibition of drug-destroying enzyme,
- blocking of more than one enzyme in a sequence of reactions,
- inhibition of alternative path of synthesis.

6.5.Prodrugs

Prodrug is a pharmacologically inactive compound which becomes an active compound after metabolic transformations.

There are several reasons why to use prodrugs instead of drugs:

- low solubility in water is obtained by attachment the appropriate group which is released after metabolic transformation and formation an active form of drug;
- the drug is distributed to a target place and metabolically transformed to an active form at the place of action. This could happen if the active form for of drug is not sufficiently well transported to a target;
-some fragment might be attached to a drug which directs the drug to its place of action;
-drug may be not stable in its active form;
-prodrug could be slowly converted to a drug preventing a longer time of action at the desired level;
-drug in its active form might be too toxic for other organs;
-drug might be unpleasant for patients (taste, odour, gastric irritation, it may cause pain when administered by injection);
-the form of drug could be in an undesirable form (for example too volatile).

6.6.Drug Administration

Drug therapy is to prevent, cure or control various diseases. Pharmacokinetics is devoted to the examination of the movement of the drug in the body. There are many ways of drug delivery.

Enteral administration is the simplest. When the drug is taken into the mouth it may be swallowed or placed under the tongue. Oral administration provides many advantages but drugs absorbed in gastrointestinal tract enter the portal circulation (circulation of the blood from the small intestine to the liver) and are metabolized by the liver before entering the general circulation. They are metabolized in the liver. It means that such drugs must be given in sufficient dose to overcome the liver metabolism.

Placement the drug under the tongue avoids such liver metabolism since the drug is absorbed through mucous membranes directly to the systemic circulation.

Parental administration is directly across the biological barriers into the systemic circulation.

The advantages are rapid absorption, convenience of administration, avoidance of liver metabolism. It could be intravenous (the most common and sometimes the only way if for example the drug is not absorbed from the mouth), intramuscular (drug must be aqueous solution or suspension in nonaqueous vehicle) or subcutaneous.

Other ways of drug administration involve inhalation (rapid delivery across the mucous membranes) intranasal, intrathecal (into the cerebrospinal fluid, drug needs to be given this way to avoid the blood brain barrier), topical (when the local effect is desired), transdermal (application to the skin), rectal (such administration avoids the transformation of the drug by the liver in almost 50%, also applied when for example the drug induces vomiting) .

When the drug is administered then it has to be passed to the bloodstream. It could happen by passive diffusion (concentration gradient is the driving force), active transport (when drug for example resembles the natural agent) or endocytosis (for large drug molecule).

7.Major Drug Classes

7.1.Drugs affecting the nervous system

The division of the nervous system is given chapter before.
The autonomic system along with the endocrine system coordinates the bodily functions. In contrast to the endocrine system which sends signals to targets by hormones transported through blood, the nervous system exerts its influence by the rapid transmission of electrical impulses to the targets. The last response is the release of substances called neurotransmitters. Drugs that mimic the natural neurotransmitter action of the autonomic nervous system are called autonomic drugs. They stimulate or block the action of autonomic nerves. The role of this system is described in another chapter.
Drugs used are cholinergic agonists, cholinergic antagonists, adrenergic agonists and adrenergic antagonists.

Drugs affecting the central nervous system

Cholinergic drugs which act on acetylocholine receptors

Cholinergic agonists
alvameline, muscarine (muscarinic receptors), nicotine (nicotinic receptors), pilocarpine (M_3 receptors), suxamethonium (muscle type receptors)

Cholinergic antagonists
scopolamine, dicycloverine, tolterodine, oxybutynin, ipratropium, Mamba Toxin (MT_7), pirenzepine, telenzepine

Acetylcholinesterase inhibitors (abbreviated AChEIs)
donepezil,galantamine, huperzine A, neostigmine, physostigmine, rivastigmine

Adrenergic drugs which act on receptors stimulated by norepinephrine or epinephrine.

The five categories of adrenergic receptors are: α_1, α_2, β_1, β_2, and β_3. They vary in specificity.

Adrenergic agonists

α_1 agonists examples are: methoxamine methylnorepinephrine, ometazoline, phenylephrine

α_2 agonists examples are: clonidine (mixed alpha2-adrenergic and imidazoline-I1 receptor agonist), guanfacine, (preference for alpha2A-subtype of adrenoceptor), guanabenz (most selective agonist for alpha2-adrenergic as opposed to imidazoline-I1), guanoxabenz (metabolite of guanabenz), guanethidine (peripheral alpha2-receptor agonist), xylazine,tizanidine, methyldopa, Fadolmidine

Adrenergic antagonists

More specifically, they can be divided into: alpha blockers, beta blockers

7.2. Drugs affecting the central nervous system

Antiparkinson drugs

Progressive neuorological disorder, parkinsonism, results from insufficient dopamine in some parts of the brain, so the used drugs must replenish dopamine deficiency. The following drugs are used:

1. DOPA analogs (levodopa),
2. DOPA decarboxylase inhibitors which slow down the metabolism of levodopa and thus increase its availability when used together (carbidopa),
3. inhibitor of MAO type B (monoamine oxidase inhibitor) which metabolises the DOPA. It results in decreasing the metabolism of dopa and increases the level of dopamine in the brain. (Selegiline, rasagiline),
4. inhibitors of catechol-O-methyltransferase, enzyme which metabolises the DOPA (Entacapone, tolcapone),
5. dopamine receptor agonist (Bromocriptine),
6. stimulators of dopamine release (amantadine), antimuscarinic agents (benztropine).

Drugs used in Alzheimer disease

Alzheimer's disease is the most common form of dementia, an incurable, degenerative and terminal disease. Alzheimer's disease has been identified as a protein misfolding disease. Reduction in the activity of the cholinergic neurons is a well-known symptom of Alzheimer's disease. In order to overcome it, some acetylcholinesterase inhibitors are currently used (donepezil, galantamine). Other drugs like memantine or other NMDA receptor antagonist reduce the overstimulation of glutamate receptors appearing in Alzheimer's disease. Antipsychotic drugs like marijuana was found to delay Alzheimer's Disease.

Anxiolytic and hypnotic

The main use of hypnosis is to promote the normal sleep (hypnos in Greek means sleep). Anxiolytic drugs have anti-anxiety effects, they are tranquilizers. Most of them are modulators of GABA receptor action: agonists (benzodiazepines, barbiturates) or antagonists (flumazenil). Other drugs include antidepressants – serotonin reuptake inhibitors (SSRI) like fluoxetine, fluvoxamine, paroxetine or sertraline, or 5-HT_{1A} receptor agonists azospirones like buspirone, tandospirone, gepirone.

Some herbal drugs made of:

- *Rhodiola rosea* (Arctic Weed/Golden Root)
- *Bacopa monnieri* (Brahmi)
- *Hypericum perforatum* (St. John's Wort)
- *Matricaria recutita* (German Chamomile)
- *Mitragyna speciosa* (Kratom)
- *Cannabis sativa* (Marijuana)
- *Nepeta persica* (Catnip)
- *Piper methysticum* (Kava)
- *Sceletium tortuosum* (Kanna)
- *Scutellaria spp.* (Skullcap)
- *Valeriana officinalis* (Valerian)

are also used.

CNS stimulants

CNS stimulants have several proposed mechanisms, the used drugs are: psychomotor stimulants (methylxantines, amphetamine, caffeine, cocaine), hallucinogens (lysergic acid, cannabis), CNS depressant (ethanol, barbiturates, benzodiazepines), narcotics.

Anaesthetics

Anaesthesia is defined as a reversible loss of sensation with or without consciousness. It could be general when a reversible loss of consciousness occurs, and local, which results in a reversible loss of sensation for a limited region of the body while maintaining consciousness. Anaesthetics act by blocking the nerve transmission of both sensory and motor neurons. Local anaesthetics act by reducing sodium passage through the pores by binding to selective sites of the sodium channel and thus interfering with action potential. The effect is decreasing the excitability without affecting the resting potential. General anaesthetics, by contrast, reduce membrane excitability by changes of membrane fluidility, permeability and receptor/channel function.

Procaine, amethocaine, cocaine, lidocaine, prilocaine, bupivacaine, levobupivacaine, ropivacaine, mepivacaine, dibucaine are examles of local anaesthetics. They prevent transmission of nerve impulses without causing unconsciousness by binding to fast sodium channels.

Desflurane, enflurane, halothane, isoflurane, methoxyflurane, nitrous oxide, sevoflurane, are general volatile anaesthetic drugs. Barbiturates, benzodiazepines and opioids (alfentanil, fentanyl, remifentanil, sufentanil, buprenorphine, butorphanol, diamorphine, heroin, hydromorphone , levorphanol, meperidine, methadone , morphine, nalbuphine, oxycodone, oxymorphone, pentazocine) are administered intravenously as general anaesthetic drugs.

Antidepressants

Antidepressant therapy in general is directed against major depressive disorders of the unipolar type. Most of the antidepressants belong to three group of chemicals: MAOIs (monoamineoxidase inhibitors), monoamine reuptake inhibitors and autoreceptor desentitizers and agonists. Phenelezin sulphate (nardil), tranylcypromine sulphate (parnate) are the most frequently used monoamine oxidase inhibitors. Tricyclic antidepressants like imipramine hydrochloride, desipramine hydrochloride, clomipramine hydrochloride, amitryptyline hydrochloride are examples of monoamine reuptake inhibitors. Other antidepressants act on

serotonin and/or norepinephrine receptors in the brain. Fluxetine, paroxetine, sertraline are selective serotonin reuptake inhibitors, nisoxetine, reboxetine, duloxetine are selective norepinephrine reuptake inhibitors. Other drugs are nonselective 5HT and NE reuptake inhibitors (venlafaxine), selective serotoninergic reuptake inhibitotrs and 5-HT_{2A} antagonists (trazodone, nefazodone). 5-HT_{1A} agonists and partial agonists (buspirone and other spirones), alpha2 antagonists (mirtazapine).

Neuroleptic (antipsychotic drugs)

The psychoses are mental disorders involving a loss of contact with reality. They include schizophrenia, manic phase of bipolar illness (manic-depressive), acute idiopathic psychotic illness. The most common is schizophrenia characterized by altered perception, thinking, communication, social functioning. Typical antipsychotics (known as first generation) developed in 1950s include phenothiazines, thioxantenes, butyrophenones, diphenylbutylpiperidines, dihydroindolones. Atypical (second generation) antypsychotics act mostly on 5-HT_{2A} receptors.

Most antipsychotics act selectively on blocking dopamine receptors, mostly D_2, in the brain and in the body. Some cases, however, indicate further level of complexity since some individuals have decreased the level of D_1 receptor density. The affinity of antipsychotic drugs to D_3, D_4, HT_{1A} has also been recorded. The used drugs encompass: promazine, chlorpromazine, thioridazine, perphenazine, prochlorperazine, fluphenazine, trifluophenazine, chrorprothixene, thiothixene, clozapine, haloperidol, olanzapine, quetiapine, risperidone, trifluoperazine, ziprasidone, aripiprazole.

Other receptors like NMDA and serotonin have also been implicated especially in the reductions of side effects symptoms induced by D_2 receptor antagonists.

Drugs currently used in schizophrenia act also on cholinergic-muscarinic (thioridazine, chlorpromazine), alpha-adrenergic (chlorpromazine), dopamine (haloperidol), serotonin (clozapine), H_1 histamine (chlorpromazine) receptor.

Analgesics, opioids

Pain differs in causes, symptoms and neurobiological mechanisms and is classified into three types: physiological, inflammatory and neuropathic. Pain is further categorized into: cutaneous (skin and surface tissues), somatic (ligaments, tendons, bones, blood vessels), and visceral (body organs, and internal cavities).

An **opioid** is a chemical compound that works by binding to opioid receptors, which are found in the central nervous system and the gastrointestinal tract. The analgesic (painkiller) effects of opioids are due to the decreased perception of pain, decreased reaction to pain as well as increased pain tolerance.

Opioids interact with protein receptors on the membrane of some cells in the CNS, on nerve terminals in the periphery and on cells in gastrointestinal tract and other anatomic regions. They act on the same receptor as the endogenous peptide ligands – enkephalin endorphins, dynorphins, and endomorphins.

There are a several classes of opioids:

Natural like morphine, codeine and thebaine;

Semi-synthetic like hydromorphone, hydrocodone, oxycodone, oxymorphone, desomorphine, diacetylmorphine (heroin), nicomorphine, dipropanoylmorphine, benzylmorphine and ethylmorphine and buprenorphine;

Fully synthetic like fentanyl, pethidine, methadone, tramadol and dextropropoxyphene.

For moderate pain there are nonopioid analgesics like acetaminophen and nonsteroidal antiinflammatory agents (NSAIDs) sometimes with a combination of a weak opioid such as codeine.

Antiepileptics, anticonvulsants

Antiepileptics, anticonvulsants are drugs used to provide seizure control in patients with epilepsies. The etiology of epilepsy in generally unknown. Some recent evidence suggests that it has genetic origin with further development. Seizures are symptoms of disturbed electrical activity in the brain, characterized by abnormal excessive synchronic discharge of a group of neurons and imbalance between excitatory and inhibitory processes in the brain. The effect is involuntary movement, sensation or thought.

Current anticonvulsants sold in the market act by:

-modulation of voltage gated ion channels (sodium, potassium, calcium) – (phenytoin)

-enhancement of gamma-aminobutyric acid ($GABA_A$) mediated inhibitory neurotransmission by:

-enhancement of GABA biosynthesis (gabapentin, pregabalin, valproic acid-VPA),

-inhibition of GABA degradation (vigabatrin),

-inhibition of GABA reuptake (tiagabine),

-binding to allosteric site of postsynaptic GABA receptor which results in modulating chloride influx (barbiturates mainly phenobarbital, benzodiazepines, neurosteroids, FBM, TPM),

-attenuation of excitatory (mainly glutamate) neurotransmission in the brain.

7.3.Drugs affecting the cardiovascular system

Heart failure

Heart failure means disorder when the heart is unable to pump a sufficient amount of blood. The cause is arteriosclerotic heart disease, myocardial infarction, hypertensive heart disease, vascular heart disease, dilated cardiomyopathy, congenital heart disease.

Drugs to treat heart failure are: rennin- angiotensin blockers (captopril, enalapril), beta-blockers (atenolol), diuretics (furosemid), direct vasodilators (hydralazine), ionotropic agents (amrinone), aldosterone antagonists (spironolacton).

Antiarhythmics

The heart also contains specialized cells that generate rhythmic action potential. Dysfunction of impulse generation leads to abnormality in cardiac rhythm. Oxygen, potassium, and sodium bicarbonate relieve the cardiac arrhythmias. Digitalis, propranolol, phenylephrine, edrophonium, and neostygmine affect the heart muscle.

Other drugs alter the electrophysiological mechanism causing arrhythmia. They include: sodium channel blockers (lidocaine), beta-adrenoreceptor blockers (propanolol), potassium channel blockers (amiodarone), calcium channel blockers (diltiazem) and others (digoxin).

Antianginal

Angina pectoris is characterized by a sudden chest pain, caused by insufficient coronary blood flow and a low level of oxygen delivery. The episode lasts from 15 seconds to 15 minutes and is not the cause of death like myocardial infarction. The principal goal in the prevention and relief of angina is to limit the oxygen requirement of the heart, so that the amount of the blood supplied is adequate. For example a well known nitroglycerine act by reducing myocardial oxygen demand.

Drugs used: organic nitrates (nitroglycerin, erythrityl tetranitrate, pentaerythritol),

beta-blockers (propanolol), calcium channel blockers (ditiazem, nifedipine), sodium channel blocker (ranolazine), antithrombotic (aspirin, dipyridamole, clopidogrel, ticlopidine).

Antihypertensives

Hypertension appears when blood pressure regulating mechanism is affected and is defined as a sustained systolic blood pressure greater than 140 mmHg or diastolic blood pressure greater than 90 mmHg. Several categories may be defined: normal (120/80), prehypertension (139/89), stage 1 (159/99), stage 2 (160/100). It could be a consequence of many diseases, like failure of components of the central nervous system, abnormalities of hormonal system, kidney and peripheral vascular system diseases. All of them can create a hypertensive state in humans. Environmental factors, stress, diet (sodium intake especially), age, obesity, smoking, all of these factors also predispose to the occurrence of hypertension.

Drugs which are used: diuretics reducing blood volume (furosemide), beta-blockers (propanolol), ACE inhibitors (captopril), angiotensin II receptor antagonists (Losartan), rennin inhibitors (aliskiren), calcium channel blockers (nifedipine), alpha-blockers (prazosin, terazosin, doxazosin), agents that reduce peripheral vascular resistance like calcium channel blockers, vasodilators (hydralazine hydrochloride, USP, sodium nitropruside), sympathetic nervous system depressant, endothelin receptor antagonists (ambrisentan, bosentan, sitaxsentan sodium), agents depleting neurotransmitter stores (active components of *Rauwolfia serpentine* mainly reserpine), potassium channel agonists (diazxide, minoxidil), positive ionotropic agents (digitalis glycosides first used as 1500 BC in ancient Egypt and other cardiac glycosides like cardenolides, and bufadienolides, digoxin, digitalis), and others (clonidine).

Blood drugs

There are three very important dysfunctions of blood:

- thrombosis (formation of unwanted clot) treated with anticoagulants, antiplatelets and fibrynolytics,
- bleeding (failure of hemostasis, hemophilia) treated with transfusion of factorVIII,
- anaemia (nutritional deficiencies like iron for example) treated with dietary ofr pharmaceutical supplements.
- Sickle cell anaemia (genetic disorder).

The used drugs are platelet inhibitors (aspirin), anticoagulants (heparin), thrombolytic agents (streptokinase), bleeding treatment (aminocaproic acid, vitamin K), anaemia treatment (folic acid), sick cell anaemia (hydroxyurea).

Hyperlipidemias

Coronary heart disease is the cause of a number of deaths. It is related to elevated levels of low density lipoproteins, cholesterol and triacylglycerols and low level of high density lipoprotein cholesterol. Hyperlipidemia is the most prevalent indicator for susceptibility to artherosclerosis heart disease. There are several types of hyperlipidemia. Artherosclerosis means degenerative changes in the intima of medium and large arteries which include the accumulation of lipids, complex carbohydrates, blood, and blood products. The deposits or plaques decrease the lumen of the artery, reduce its elasticity and finally may create foci or thrombi and the occlusion of blood vessels. Risk factors are: genetic disorder, smoking, hypertension, obesity, diabetes, lack of exercises, consumption of saturated fatty acids.
The used drugs are: HMG CoA reductase inhibitors (lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin), fibrates (clofibrate, gemfibrozil, fenofibrate), niacin, bile acid sequestrants (colesevalam), cholesterol absorption inhibitors (ezetimibe, beta-sitosterol), resins which control the level of bile acid and cholesterol (cholestyramine resin, colestipol, colesevalam) and other (niacin, probucol).

Diuretics

Diuretics increase the urine flow. Inhibitors of renal ion transporters that decrease readsorption of sodium ions in the nephron cause greater concentration of sodium and chloride ions in the urine. To maintain the osmotic pressure the increased amount of water is present. Diuretics decrease the blood volume and thus are used in the treatment of hypertension. Other usage is in abnormal fluid retention (edema).
The used drugs are: thiazide diuretics (metolazone), loop diuretics (bumetanide), potassium sparring diuretics (spironolacton), carbonic anhydrase inhibitors (acetazolamide), osmotic diuretics (mannitol, urea).

7.4.Drugs affecting the central endocrine system

Pituitary and thyroid

Pituitary gland, or **hypophysis**, is an endocrine gland. The size is about the size of a pea and the weight is 0.5 g, it is composed of two lobes: anterior pituitary and the posterior pituitary. The pituitary gland is functionally linked to the hypothalamus and together with hypothalamus, it controls the neuroendocrine system. In contrast to the nervous system which communicates locally by electrical impulses and neurotransmitters, the neuroendocrine system releases hormones into the blood. The nerve impulses act within milliseconds whereas the hormone action induces the responses acting from seconds to months. These two systems cooperate, for example in many cases the hormone release is stimulated by the nervous system and vice versa, the secretion of hormones can stimulate the nervous system.

The pituitary gland secretes hormones regulating homeostasis, including tropic hormones that stimulate other endocrine glands.

Hormones secreted from the pituitary gland help control the following body processes:

-growth – excess of HGH can lead to gigantism,

-blood pressure,

-some aspects of pregnancy and childbirth including stimulation of uterine contractions during childbirth,

-breast milk production,

-sex organ functions in both men and women.

Thyroid gland functions:

-the conversion of food into energy (metabolism),

-water and osmolarity regulation in the body,

-secretes ADH (antidiuretic hormone) to control the absorption of water into the kidneys,

-temperature regulation,

-the hormones secreted by hypothalamus and pituitary are peptides or low molecular weight proteins which act by binding to the corresponding targets.

The **thyroid** is one of the largest endocrine glands in the body, it is found in the neck. It controls the body usage of energy, makes proteins, and controls sensitivity to other hormones. Thyroid produces thyroid hormones triiodothyronine (T_3) and thyroxine (T_4) which regulate

the rate of metabolism. The thyroid gland also produces a hormone called 'calcitonin', which plays a role in calcium homeostasis.
The thyroid gland is controlled by the hypothalamus and pituitary.

A number of pituitary hormones are currently used therapeutically for hormonal deficiencies. They are administered intramusculatory, subcutaneously or intranasally, not orally because they are peptides and susceptible for destruction in the digestive system.

The used drugs are:
Hypothalamic and anterior pituitary hormones: corticotropin, cosyntropin, goserelin.
Hormones of the posterior pituitary: desmopresin, oxytocin, vasopressin.
Drugs affecting the thyroid: iodide, levothyroxine, methimazole, thyroxine.

Insulin and hypoglycemic drugs

Pancreas is an endocrine gland that produces the peptide hormones: insulin, glucagons and somatostatin, it is also exocrine gland producing digestive enzymes. The produced hormones play an important role particularly in the homeostasis of blood glucose. The relative or absolute lack of insulin like in diabetes mellitus can lead to severe complications.
The used drugs are: insulin, amylin analog – pramlintide. Another drug is acarbose, which inhibits glycoside hydrolases needed to digest carbohydrates, the inhibition of these enzyme systems reduces the rate of digestion of complex carbohydrates, oligosaccharides, trisaccharides, and disaccharides to glucose. Sulphonylureas like glipizide, glimepiride, tolazamide, tolbutamide and glinides stimulate the secretion of insulin. Thiazolidinediones (rosiglitazone, pioglitazone,) are also another class of hypoglycemic drugs. Biguanides are a class of insulin sensitizing agents. Alpha glucosidases inhibitors slow down the breakdown of disaccharides and starch derived polysaccharides.

Estrogens and androgens

Sexual hormones produced by gonads are necessary for conception, embryonic maturation, development of primary and secondary sexual characteristics. All of them are produced from cholesterol. The gonadal hormones are used in the therapy for contraception, management of menopausal symptoms. Some of them are effective in cancer chemotherapy.

The used drugs are: estrogens (diethyl stilbestrol, estradiol, estriol, estrone) selective estrogen modulators (clomiphene, raloxifene, tamoxifen), progestins (desogestrel, drospirenone) antiprogestin (mifepristone), androgens (danazol, fluoxymesterone), antiandrogens (biculatamide), antiprogestin (mifepristone), androgens (danazol, fluoxymesterone), antiandrogens (bicalutamide, dutasteride, finasteride).

Adrenal hormones

The adrenal gland consists of acortex and medulla. The cortex synthesizes and secretes two major steroid hormones – adrenocorticosteroids (mineralocorticoids and glucocorticoids) and adrenal androgens. The primary glucocorticoid released by the adrenal gland in the human is cortisol and corticosterone. A**drenal cortex** mediates the stress response through the production of aldosterone and cortisol, respectively. Hormones of adrenal cortex are used in the treatment of asthma and other inflammatory diseases (rheumatoidal artritis), in the treatment of allergic reactions and in some treatments of cancer.
The most important androgens include: testosterone, dihydrotestosterone, androstenedione, dehydroepiandrosterone.
The used adrenal corticosteroid drugs are: corticosteroids (beclomethasone, betamethasone, cortisone), inhibitors of adrenorticoid biosynthesis or function (aminoglutethimide, eplerenone, ketocenazole).

7.5.Drugs affecting the respiratory system

Two of the most commonly encountered respiratory diseases are: chronic obstructive pulmonary disease (asthma) and allergic rhinitis. Asthma is characterized by hyperresponsive airways and affects about 5% of the population. Allergic rhinitis characterized by itchy watery eyes, runny nose and nonproductive cough is even more common and affects about 20% of the population. Coughing is an important natural defensive respiratory response to irritants, however, the troublesome symptom may appear as a result of the common cold, sinusitis or chronic respiratory diseases.
Drugs used to treat the respiratory system can be delivered by a nasal spray, inhalation to the lungs or can be administered orally.
Commonly used drugs.

Drugs to treat asthma (beta2 adrenergic agonists, corticosteroids, cromolyn,) allergic rhinitis (alpha adrenergic agonist, antihistamines, corticostereoids, cromalyn), chronic obstructive pulmonary diseases (beta adrenergic agonists, corticosteroids, ipratropium, tiotropium), cough (dextromethorpan, opiates).

7.6.Drugs affecting the gastrointestinal system

The most commonly encountered disease of the gastrointestinal tract is peptic ulcer, gastroestrophaegal reflux, chemotherapy-induced emesis, diarrhoea and constipation.

Pathogenesis of peptic ulcer is not completely understood, however, some major causative factors are recognized. They are: nonsteroidal anti-inflammatory drugs, infection with gram negative Helicobacter pylori, increased hydrochloric acid secretion, inadequate mucosal defence against gastric acid. The treatment encompasses the treatment with H. pylori infection, reducing secretion of gastric acid (H2 receptor antagonists), protection of gastric mucosa, neutralizing the gastric acid.

Drugs: antimicrobial (amoxicillin, bismuth compounds, metronidazole), H2 histamine receptor blockers (cimetidine, ranitidine), inhibitors of proton pump (esomeprazole, lansoprazole), prostaglandins (misoprostol), antimuscarinic agents (dicycloamine), antiacids (aluminium hydroxide, calcium carbonate), mucosal protective agents (bismuth subsalicylate, sucralfate).

Drugs used to control chemotherapy induced emesis.

Nausea and vomiting may occur due to many factors (pregnancy, locomotion), the ones which are the effect of chemotherapy demand special management.

Drugs used in this case are: phenothiazines (prochlorperazine), 5-HT3 serotonin receptor blockers (dolasetron, granisetron), substituted benzamides (metoclopramide), butyrophenones (droperidol, haloperidol), benzodiazepines (alprazolam, lorazepam), corticosteroids (dexamethasone, methylprednisolone), cannabinoids (dronabinol, nabilone), P/neurokinin-1 receptor blocker (aprepitant).

Decreased absorption of fluid may result in diarrhoea. The treatment include drugs which are antimotility agents, adsorbents and drugs modifying the transport of fluid and electrolytes.

Drugs: antidiarrheals (aluminium hydroxide, bismuth subsalicylate).

To improve the movement of food, the irritants or gut stimulants or stool softeners are used.

Drugs: laxatives (bisacodyl, bran, castor oil).

7.7.Antiinflammatory drugs

Inflammation is a normal response to tissue injury by physical trauma, chemicals, microbiological agents. The goal is to heal the tissue or destroy the invader. Our immune system should differentiate between self and nonself but in some cases the proper recognition fails, for example in rheumatoidal arthritis. Pharmacotherapy includes anti-inflammatory and immunosuppressive agents.

The used drugs are: NSAIDs – nonsteroidal anti-inflammatory drugs (aspirin, diflunisal, diclofenac), cox-2 inhibitors (celecoxib), analgesics (acetaminophen), drugs for arthritis (abadacept, adalimuab), drugs for gout (allopurinol).

7.8.Autacoids and autacoid antagonists

Prostaglandins, histamine and serotonin are called autacoids. They have various structures and activity. They are produced in the tissues on which they act (the word autocoids come from gree autos and akos – self remedy.

Drugs: prostaglandins are used as agents causing abortion or in peptic ulcer treatment (misoprostol), antihistamins are used in allergy inflammation, and anaphylaxis (acrivastine, cetirizine), drugs used to treat migraine headache (almotriptan, dihydroergotamine, eletriptan).

7.9.Antimicrobial

Antimicrobial takes the advantage of the difference between the human and microorganism.

Cell wall inhibitors

Fig 31.1

Protein synthesis inhibitors: tetracycline (demeclocycline, doxycycline), glycylglycines (tigecycline), aminoglycosides (amikacin,gentamycin), makrolides, ketolides (azithromycin), chloramphenicol, clindamycin, linezolid, quinolones (nalidixic acid, ciprofloxacin), inhibitors of folate synthesis (mafenide, sulfacetamide), inhibitors of folate reduction (pyrimethamine)

Antimycobacterial to treat tuberculosis (ethambutol, isoniazid), to treat leprosy (clofazimine)

Antifungal for subcutaneous and systemic mucoses (amphotericin, anidulafungin), for cutaneous mycoses (butaconazole).

Antiprotozoal amebias (chloroquine), malaria (artemisin), trypanosomias (benznidazole), leishmaniasis (sodium stibogluconate), toxoplasmosis (pyrimethamine), giardiasis (metronidazole).

Antihelmiths (worms) for nematodes (pyrantel), trematodes (praziquantel), cestodes (albendazole).

Antiviral; respiratory virus (amantadine), hepatitic (adefovir), herpes and cytomagalovirus infections (acyclovir), hiv (abacavir, zidovudine).

Anticancer (antimetabolites (capecitabine), antibiotics (bleomycin), alkylting agents (busulfan), microtubule inhibitors (docetaxel), steroid hormones and their antagonists (anastrozole), monoclonal antibodies (cetuximab).

7.10.Immunosupressant

Immune system protects from foreign molecules. In some cases it causes some problems, in transplantation when a foreign organ is introduced. To prevent the rejection of transplanted organ immunosupressive drugs are used.

Drugs: selective inhibitors of cytokine production and function (cyclosporine), immunosuppressive antimetabolites (azathioprine), antibodies (alemtuzunab), adrenocorticoids (methylprednisolone).