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PHARMACOLOGY

Textbook
for medical students

Translation of
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«Pharmacology» (2017)

Министерство образования и науки РФ

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II. GENERAL PHARMACOLOGY

In this Section:

1. Drug administration routes. Absorption
2. Drug distribution in the body. Biological barriers. Storage
3. Biotransformation of drugs in the body
4. Routes of drug elimination from the body
5. Local and systemic effects of the drugs. Direct and reflex effects. Localization and mechanism of action. Drug «targets». Reversible and irreversible actions. Selective action
6. Dependence of pharmacotherapeutic action on drug properties and pattern of use
7. Importance of individual characteristics of the human body and its state for the manifestation of the drug effect
8. Main types of drug treatment
9. Principal and adverse effect. Allergic reactions. Idiosyncrasy. Toxic effects
10. General principles of the treatment of acute drug poisoning

General pharmacology is the study of the common patterns of drugs pharmacokinetics and pharmacodynamics. **Pharmacokinetics**[1] is the part of pharmacology that deals with compound absorption, distribution in the body, storage, metabolism and excretion (Fig. II.1). The main subject of **pharmacodynamics**[2] is the biologic effects of compounds as well as localization and mechanism of action.

The effects of drugs are the result of their interaction with the organism. Therefore, the basic properties defining physiologic activity of the drugs are not the only thing for consideration. The effect of drugs is also dependent on method of use of these compounds as well as the general condition of the organism to which their action is directed.

The other topics for discussion are the most important types of pharmacotherapy, as well as general patterns of drugs' side effects and toxicity.

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[1] From Greek *pharmacon* — drug, *kineo* — move.
[2] From Greek *pharmacon* — drug, *dynamis* — power.

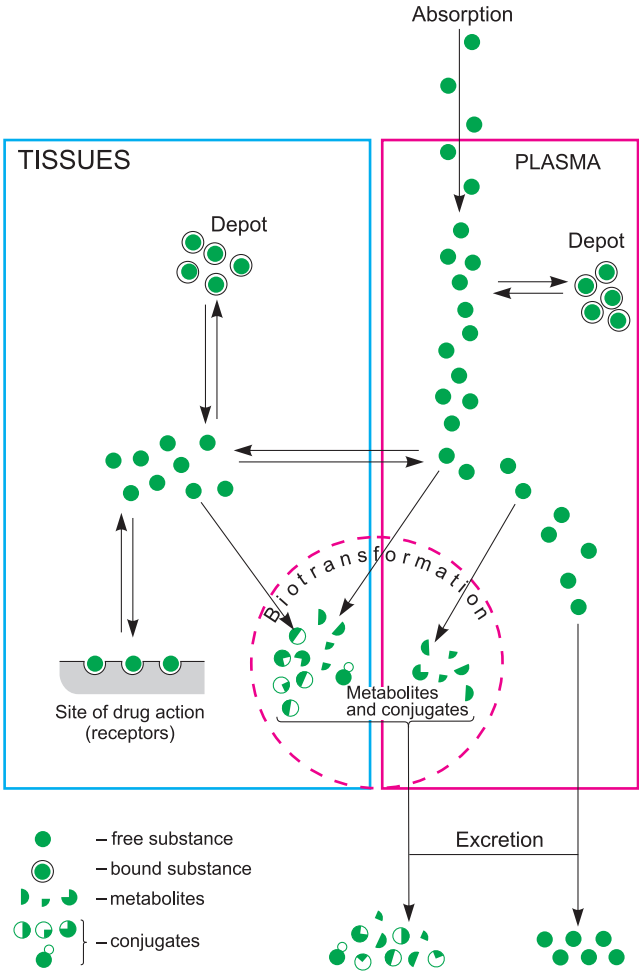

Fig. II.1. Pharmacokinetics of drugs.

1. DRUG ADMINISTRATION ROUTES. ABSORPTION

The usage of drugs for the treatment and prevention of deseases starts with their administration into the organism or application onto the body surface. The route of administration defines the speed of onset of effect, its intensity and duration. In certain cases the route of administration determines how the medications work.

Existing administration routes are usually subdivided into enteral (via digestive tract) and parenteral (not entering into the digestive tract).

Enteral administration comprises oral, sublingual, transbuccal[1], duodenal and rectal routes.

[1] From Latin *bucca* — cheek. A number of drugs are taken transbuccally as polymer pastilles. Their active components are absorbed via the oral mucous membrane.

The most common administration route is oral (by mouth; internally; *per os*). This is the most convenient and simple route of administration. Drugs do not have to be sterile to be administered this way. Absorption[1] of a number of substances (for example, acetylsalicylic acid, barbiturates and other weak electrolytes possessing an acidic nature) occurs partially in the stomach[2] (Fig. II.2). However, the majority of drugs are mainly absorbed in the small intestine. This is a favorable place for absorption due to the large absorbing surface of the intestinal mucous membrane (approximately 200 m^2) and its intensive blood supply.

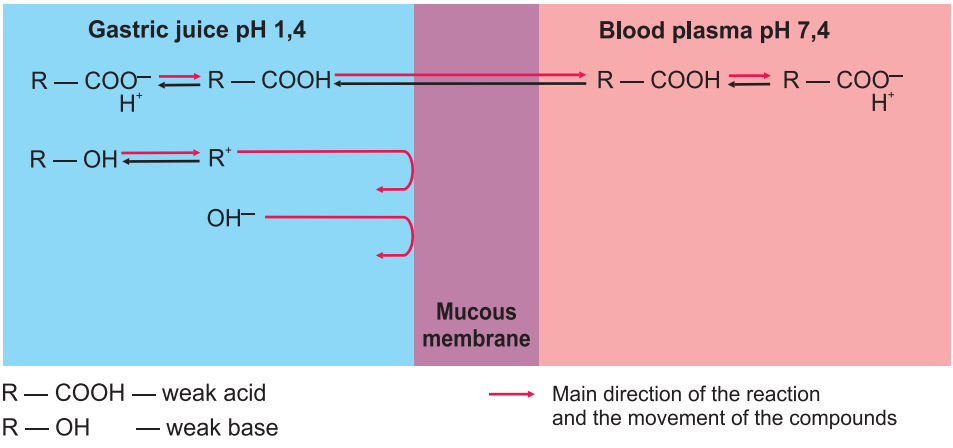

Fig. II.2. Importance of the pH of the medium for the absorption of substances from the stomach.

There are several known absorption mechanisms (Fig. II.3).

Passive diffusion occurs via the cellular membrane. It is defined by the concentration gradient of the compound. Lipophilic substances (mainly nonpolar) are easily absorbed via this route. The higher the lipophility of substances, the easier they penetrate through the cell membrane.

Facilitated diffusion. This involves transport systems functioning without energy consumption.

Filtration through the membrane pores. The diameter of the membrane pores in the intestinal epithelium is small (approximately 0.4 nm[3]). This is why water, certain ions and fine hydrophilic molecules (for example, urea) diffuse through them.

Active transport is the process that involves the transport systems of cell membranes. It has the following characteristics: selectivity to certain compounds, the possibility that two compounds compete for one transport mechanism, saturability (in high concentrations), ability of transport against concentration gradient and energy consumption (metabolic poisons inhibit active transport). Active transport provides absorption of hydrophilic polar molecules, a number of inorganic ions, sugars, amino acids and pyrimidines.

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[1] From Latin *ab* – away from, *sorbere* — to suck.

[2] In gastric acid medium these components are mainly present in unionized (lipophilic) form and are absorbed by diffusion.

[3] 1 nm (nanometer) = 1×10^{-9} m.

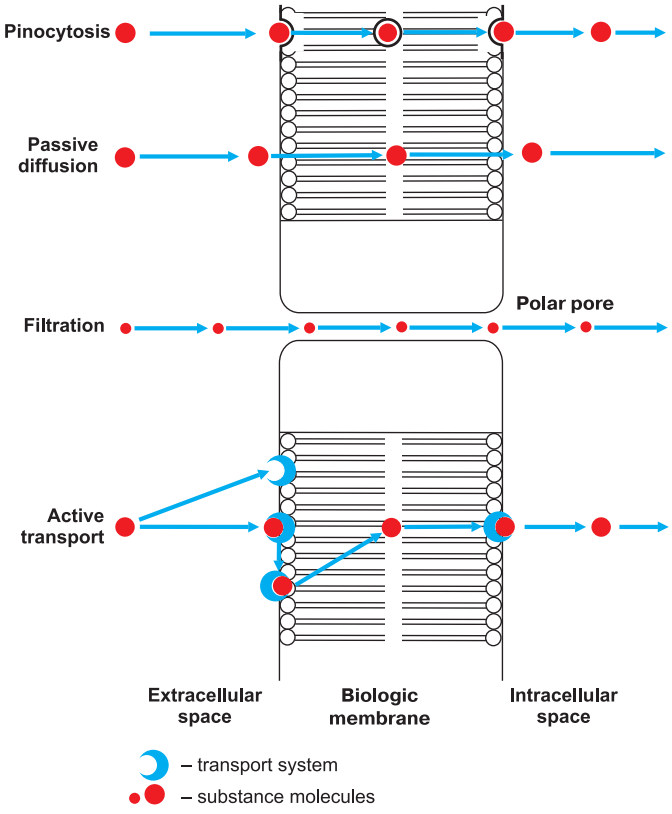


Fig. II.3. Main routes of substance absorption.

In pinocytosis[1] compounds are transported via endocytosis followed by vesicle formation (vacuole). The latter is filled with fluid and large molecules of transported substances. This vesicle migrates via the cytoplasm to the opposite side of the cell, where by means of exocytosis the vesicle content is expelled from the cell.

The above mentioned mechanisms of transport of substances through membranes are universal and play a role not only in the absorption but also in the distribution and excretion of various compounds.

The main mechanism of drug absorption in the small intestine is passive diffusion. A certain role is also played by the active transport. Absorption of a number of proteins and cyanocobalamin (vitamin B_{12}) in complex with Castle intrinsic factor appears to occur by active transport. Filtration through the cell membrane pores does not actually have any significance.

Absorption from the small intestine is relatively slow. It depends on the functional conditions of the intestinal mucous membrane, its motility and pH medium and quantity and quality of the intestinal contents. One should remember that from the small intestine, substances get into the liver (where a part of them is inactivated or excreted with bile) and only after that — into the general circulation. It has to be taken into account that some substances are not effective after oral administration because they are broken down under the influence of gastro-intestinal tract enzymes (for example, insulin) as

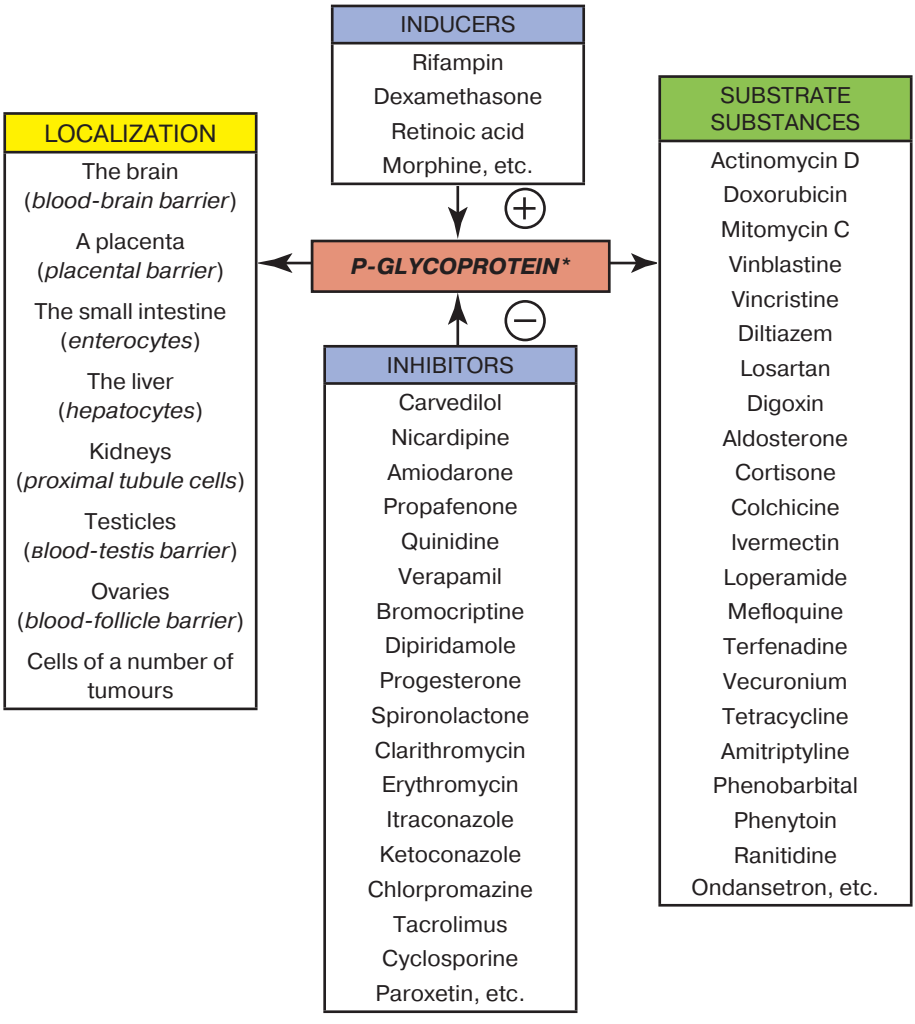
[1] From Greek *pine* — to drink.

well as under certain conditions of the medium, especially acid medium of the stomach (for example, benzylpenicillin).

If a drug can be broken down by gastric juice or has irritant action on the gastric mucosa, it is administered as a special formulation (capsules, dragee) that dissolve only in the small intestine.

An important role in providing active transport of substances through cell membranes, including their absorption, is played by membrane transporter P-glycoprotein[1], production of which is regulated by a special gene.

P-glycoprotein is located in the small intestine, liver, kidneys, histo-hematic barriers, pancreas, adrenal cortex, some hematopoietic and immunocompetent cells, and also in the number of tumour cells (Scheme II.1).



* Synonym: Multi-Drug Resistance Transporter 1 (MDR-1).

Scheme II.1. Some characteristics of P-glycoprotein.

[1] P — from *permeability* (Eng.).

The main function of P-glycoprotein transporter is to excrete drugs and other xenobiotics from cells (efflux[1] transporter).

P-glycoprotein participates in regulation of absorption, distribution, and excretion of many substances and ultimately has an impact on their effectiveness and toxicity. Essentially P-glycoprotein is a functional barrier of protecting organism cells against accumulation of toxic substances and helps to eliminate of xenobiotics and their metabolites from the body via the urine, the bile, the intestine. For example, P-glycoprotein located in an enterocytes of the small intestine is limiting absorption of a number of substances (digoxin, paclitaxel et al.) decreasing in such a way their bioavailability.

P-glycoprotein of blood-brain barrier prevents accumulation of many drugs (vinblastine, cyclosporin A, antraciclynes, etc.) in the brain by their active excretion into blood.

Of particular interest is the increased production of P-glycoprotein by a number of tumour cells, which is obviously one of the causes of development of resistance to effect of many antiblastomic drugs which are actively removed by this transporter from tumour cells.

In addition to P-glycoprotein substrates substances, drugs being inhibitors or inducers of it are known (see Scheme II.1). These substances can be used for improvement of basic treatment effectiveness, changing activity of P-glycoprotein: for example, in case of inhibition of tumour cell P-glycoprotein development, their resistance to anti-tumour drugs is suppressed.

Inhibition of P-glycoprotein of blood-brain barrier can be used for increasing concentration of many drugs substances in the brain.

Inhibitors and inducers of P-glycoprotein play an important role in drug interactions. So, P-glycoprotein inhibition of intestine, liver, and kidneys (for example by verapamil) significantly increases concentration of digoxin in blood plasma, accordingly, rifampicine, the inducer of P-glycoprotein is decreasing concentration of digoxin.

Due to the fact that the systemic effect of a substance develops only after its entrance into the bloodstream from which it moves to the tissues, the term «*bioavailability*» is suggested. It shows what proportion of the initial drug dose reached blood plasma intact. After oral administration bioavailability depends on the substance losses during its absorption from the gastro-intestinal tract and its first passage through the hepatic barrier. In bioavailability assessment, the area under the curve (AUC) is usually measured. It demonstrates the association between substance concentration in blood plasma and time (Fig. II.4) because this value is directly proportional to the amount of substance that entered systemic circulation. The other pa-

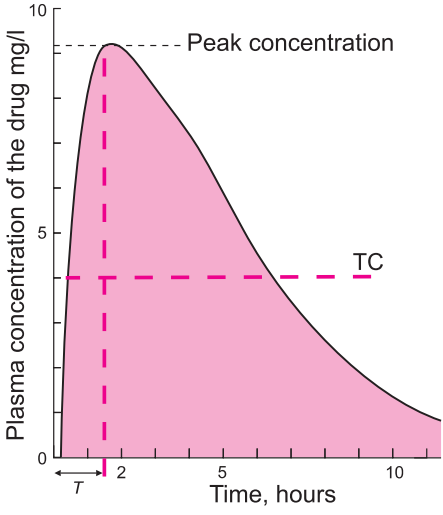


Fig. II.4. Determination of bioavailability after enteral administration
T — time to peak concentration of the drug.
TC – therapeutic concentration.
N o t e. Area under the concentration curve (AUC) for a certain period of time is measured.

[1] Efflux (Eng.) — expiration.

rameters are: maximal concentration of free (active) substance in blood plasma and the time necessary to achieve it. Bioavailability of a substance, administered intravenously, is considered to be 100%. Bioavailability can also be evaluated by measuring drug excretion with urine if it has not undergone biotransformation. In certain cases bioavailability can be measured by the extent of the pharmacological effect, if it is possible to measure it accurately.

If the drug is administered under the tongue — sublingual administration (in pills, granules, drops) — absorption starts quite quickly. In this case drugs have systemic action, bypassing the hepatic barrier in the first-pass and not interacting with enzymes and gastrointestinal tract medium. Certain highly active drugs used in small doses are administered sublingually (certain hormonal drugs, nitroglycerin).

Sometimes drugs are administered through the duodenal tube (for example, magnesium sulphate as cholagogue), which allows the creation of high compound concentration in the intestine.

After rectal administration (*per rectum*) a substantial part of the drug (about 50%) gets into the bloodstream, bypassing the liver. Besides, in this route of administration digestive enzymes do not affect the drug. Absorption from the rectum occurs by means of simple diffusion. Drugs are administered rectally as suppositories or medicinal enema (volume of 50 ml). If drugs have irritant action, they are combined with mucilage.

Drugs that have a protein, fat and polysaccharide structure are not absorbed in the large intestine.

Rectal administration is used also for local effect.

Parenteral administration routes comprise subcutaneous, intramuscular, intravenous, intra-arterial, intrasternal, intraperitoneal, inhalation, subarachnoid, suboccipital and some others.

Among parenteral routes the most common are subcutaneous, intramuscular and intravenous. The effect is especially quick after intravenous administration and a bit slower after intramuscular and subcutaneous administrations. To prolong the pharmacological effect, drugs are administered into the muscle as poorly soluble preparations (suspension) in oil and other bases, delaying absorption from the site of administration.

Intramuscular and subcutaneous routes of administration are not to be used for drugs that have marked irritant action, because it may be the cause of inflammatory reaction, infiltration and even necrosis.

Intravenous drugs are usually injected slowly. They may be given as a single dose, intermittent dosing, drip and infusion. The intravenous route is not acceptable for insoluble compounds, oil solutions (risk of embolism), drugs with marked irritant action (which may cause thrombosis and thrombophlebitis) and drugs inducing blood coagulation or hemolysis.

The disadvantages of the three abovementioned routes of administration are their relative complexity, as well as painfulness. The drugs have to be sterile, and medical staff have to be involved.

Intra-arterial administration allows to obtain high drug concentration in the area supplied by the selected artery. This route is sometimes used to inject antitumor drugs. To reduce general toxic effect of the drug, blood outflow may be artificially hindered

(by cross-clamping of the veins). Intra-arterial route is also used to give X-ray-opaque drugs, which help accurately define tumor, clot and vasoconstriction, or localize aneurism.

The intrasternal administration route (into the breastbone) is usually used in case of technical impossibility of intravenous injection (in children and elderly).

The intraperitoneal route of drug administration is rarely used (for example, antibiotics during abdominal operations).

Sometimes drugs are administered by the intrapleural route (into the pleural cavity).

For gaseous and volatile compounds the inhalation route of administration is the main one. The same route is used for some aerosols. The lungs present an extensive absorption area (90–100 m^2) with rich blood supply, and that is why absorption of the inhaled drugs occurs readily. The magnitude of effect is easily controlled by changing drug concentration in the inhaled gas. Absorption rate also depends on breathing volume, active surface of alveoli and their permeability, solubility of drugs in the blood and blood flow rate.

Drugs penetrate poorly through the blood-brain barrier can be administered under the arachnoid membrane (subarachnoidally, subdurally or suboccipitally). For example, some antibiotics can be given this way to treat infectious lesions of tissues and arachnoid membranes. The subarachnoid route of administration is used to introduce local anesthetics to perform spinal anesthesia.

Some drugs, usually highly lipophilic ones, are absorbed after skin application and have resorptive effects (for example, nitroglycerin). Transdermal drug preparations are becoming more widely used, since they help to maintain stable drug concentration in plasma over a long period of time.

Ionophoresis (diaelectrophoresis) route is sometimes used to administer ionized drugs (from skin or mucous membranes). Their absorption is caused by a weak electric field.

Certain drugs are administered intranasally (for example, adiurecrine). In this case absorption occurs from the nasal mucous membrane.

2. DRUG DISTRIBUTION IN THE BODY. BIOLOGICAL BARRIERS. STORAGE

After absorption, drugs enter the blood, then different organs and tissues. The majority of drugs are distributed unevenly, and only a small number of drugs distributes rather evenly (for example, some general anesthetics). Biologic barriers, that are encountered during drug distribution in the body, substantially influence the distribution: capillary wall, cell (plasma) membranes, blood-brain and placental barriers.

Most of the drugs go through the capillary wall easily, since it is a porous membrane (human pores average 2 nm in diameter). The exception is plasma proteins and their drug complexes. Hydrophilic (water-soluble) compounds pass through capillary wall intercellular clefts and enter interstitial space. There is barely any diffusion through the protein-phospholipid cellular membranes (they can get inside the cells only with transport systems' involvement). Lipophilic compounds penetrate well through capillary endothelium and cell membranes (Fig. II.5).

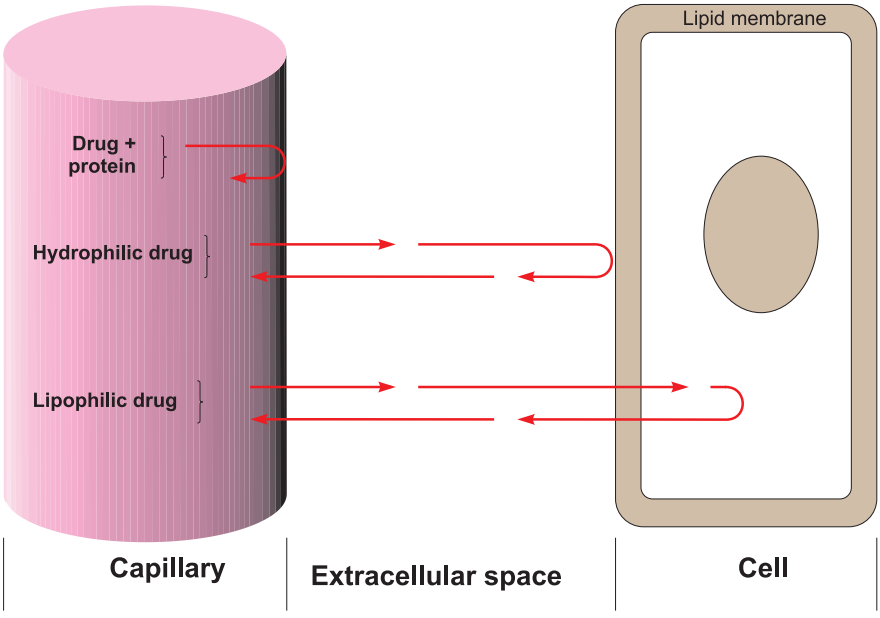


Fig. II.5. Factors influencing drug distribution.

The passage of a lot of drugs through the *blood-brain barrier*[1] is hindered. This is due to the characteristics of cerebral capillaries' structure (Fig. II.6). First of all, unlike the endothelium of periferal capillaries, their endothelium does not have intercellular clefts through which substances can penetrate well. In cerebral capillaries pinocytosis is actually absent. Glial elements (astroglia) line the external surface of the endothelium and, clearly, play the role of an additional lipid membrane. Polar compounds penetrate through the blood-brain barrier poorly. Lipophilic molecules easily pass through to the cerebral tissues. In general, drugs pass through the blood-brain barrier by means of diffusion, and some compounds — due to active transport. In certain small areas of the brain (epiphysis, neurohypophysis, medulla oblongata, and so on) there is almost no blood-brain barrier. It also has to be taken into account, that in some pathologic conditions (for example, in meningitis) the blood-brain barrier permeability is increased.

The passage of drugs through the blood-brain barrier is also controlled by P-glycoprotein transporter. It assists drugs' elimination from cerebral tissue into the blood, as well as hinders penetration of a number of compounds from blood into the CNS.

The placental barrier is a complex biological barrier. Lipophilic compounds pass through it by means of diffusion. Ionized polar drugs (for example, quaternary ammonium salts) penetrate poorly through the placenta. The placenta also has P-glycoprotein transporter.

To a certain extent drug distribution depends on the affinity of the drugs to certain tissues. Intensity of organ or tissue blood supply is also rather significant. It has to be taken into account that considerable amount of drugs may accumulate along their elimination paths. Drugs, that circulate in the body, partially bind to other molecules and form extra-

[1] There are three barriers in CNS, which limits the transport of compounds to the brain tissues:
1. Blood-brain barrier (BBB) – in the capillares in the brain.
2. Blood-cerebrospinal-fluid barrier (BCSFB) — choroid plexus in the ventricles.
3. Ependyma – epithelial layer covering the brain tissue.

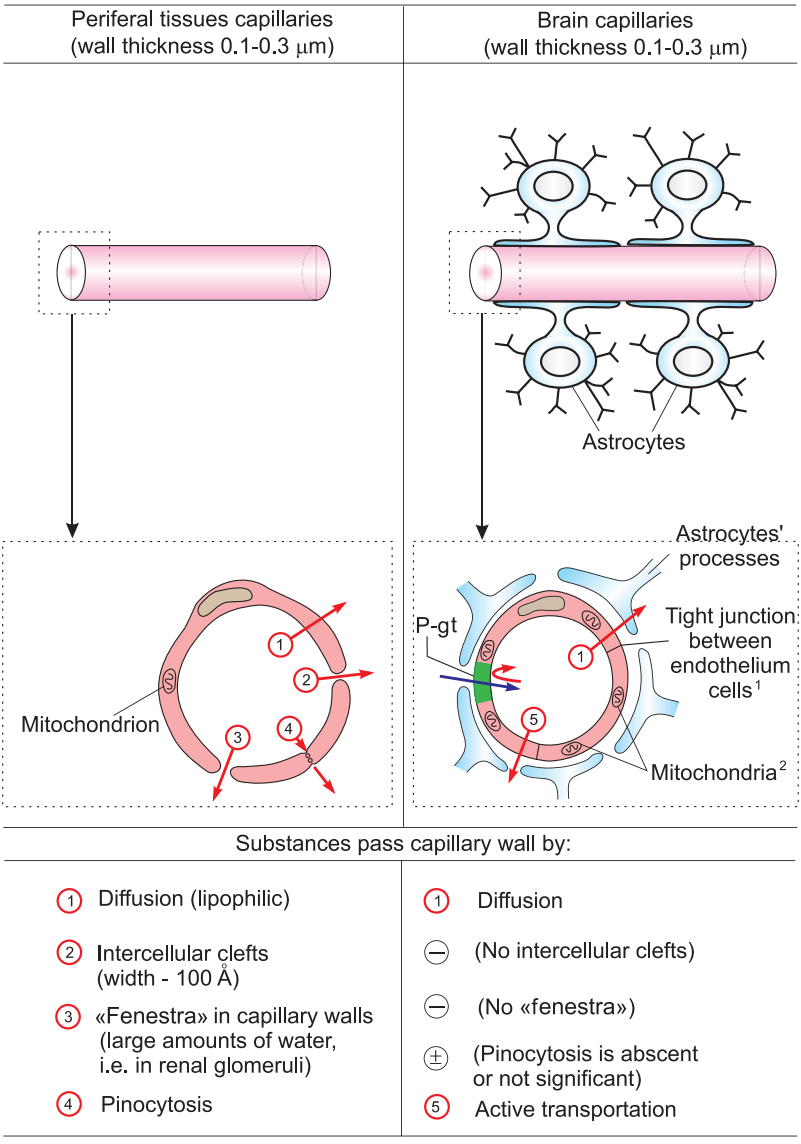


Fig. II.6. Principles of drug passage through capillaries of two types.
[1] Function as a solid membrane.
[2] Five times more than in usual capillaries.
P-gt — P-glycoprotein transporter.
Bleu arrow — direction of compounds flow under the influence of P-gt.

cellular and cellular depots. Plasma proteins can be referred to as extracellular depots (especially albumins). Many drugs bind with them rather significantly (more than by 90%).

Drugs may be accumulated in the connective tissue (some polar compounds, including quaternary ammonium salts) and bone tissue (tetracyclines).

Some drugs (particularly mepacrine) are found in cellular depots in especially large amounts. In the cells they bind to proteins, nucleoproteins and phospholipids.

Fat depots are of a particular interest, since lipophilic compounds may be retained in them (for example, some general anesthetics).

Drugs are deposited, as a rule, by means of reversible bonds. The duration of their presence in tissue depots varies widely. Thus, some sulfanilamides (sulfadimethoxine, other) form stable complexes with plasma proteins, and this partly explains the significant duration of their action. Heavy metal ions are retained in the body for a very long period.

It has to be taken into account that distribution of drugs, as a rule, does not indicate direction of their action. The latter depends on the sensitivity of tissues, i.e. on the affinity of the drug to biologic substrates, which define specificity of their action.

Clinical pharmacology often refers to the *apparent volume* of *distribution*[1] — V_d. It shows presumed volume of liquid in which a drug can be distributed (assuming that drug concentrations in plasma and other liquid media of the body is equal).

$$V_d = \frac{\text{Total amount of drug in the body}}{\text{Drug concentration in plasma}}.$$

The distribution volume demonstrates the drug fraction present in blood plasma. Lipophilic compounds that penetrate easily through tissue barriers and have wide distribution (plasma, interstitial fluid, intra-cellular fluid[2]) have high value of V_d. If the drug is only circulating in the blood, V_d values are low. This parameter is important for rational drug dosing, as well as for definition of elimination rate constant (K_{elim}) and drug half-life ($t_{1/2}$).

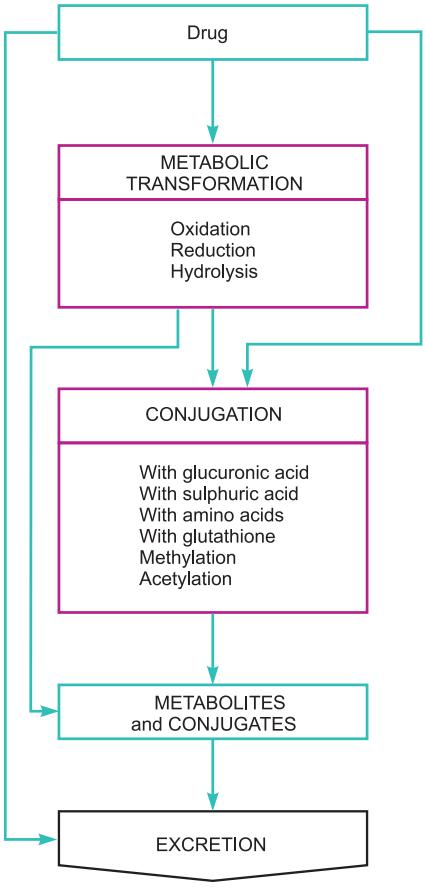


Fig. II.7. Ways of drug biotransformation.

3. BIOTRANSFORMATION OF DRUGS IN THE BODY

Most drugs undergo biotransformation in the body (Fig II.7). High-hydrophilic ionized compounds are usually eliminated unchanged. The exception among lipophilic substances are inhalation anesthetic drugs, most of which are not involved in chemical reactions occurring in the body. They are eliminated via the lungs in the same form as they had been administered. Most enzymes participate in drug biotransformation, and the most important among them are microsomal enzymes of the liver (located in the endoplasmic reticulum). They metabolize foreign lipophilic compounds (of different structure), transforming them into more hyd-

[1] Word *«apparent»* is used because the body can be viewed, for simplicity, as a single whole space (*one-compartment model*).

[2] In a human weighing 70 kg plasma consists of 3 l of water. Total amount of extracellular liquid is 12–15 l and total amount of water is 41 l.

rophilic. They do not have substrate specificity. Non-microsomal enzymes of various localizations (liver, intestine and other tissues, as well as plasma) are of very high significance, especially for the biotransformation of hydrophilic substances.

There are two main types of drugs bio-transformation: 1) metabolic transformation (I phase) and 2) conjugation (II phase). *Metabolic transformation* is a transformation occurring through oxidation, reduction and hydrolysis. For example, imipramine, ephedrine, chlorpromazine, histamine and codeine undergo oxidation. Oxidation occurs mostly due to microsomal oxidases of mixed action with participation of nicotinamide adenine dinucleotide phosphate (NADP), oxygen and P-450 cytochrome. Certain drugs undergo reduction, such as chloral hydrate, chloramphenicol, nitrazepam, etc. It occurs under the effect of nitro- and azoreductases and other enzymes. Esters (procaine, atropine, acetylcholine, suxamethonium, acetylsalicylic acid) and amides (procainamide) are hydrolyzed under the impact of esterases, carboxylesterases, amidases, phosphatases, etc. There are following examples to illustrate it (Fig. II.8).

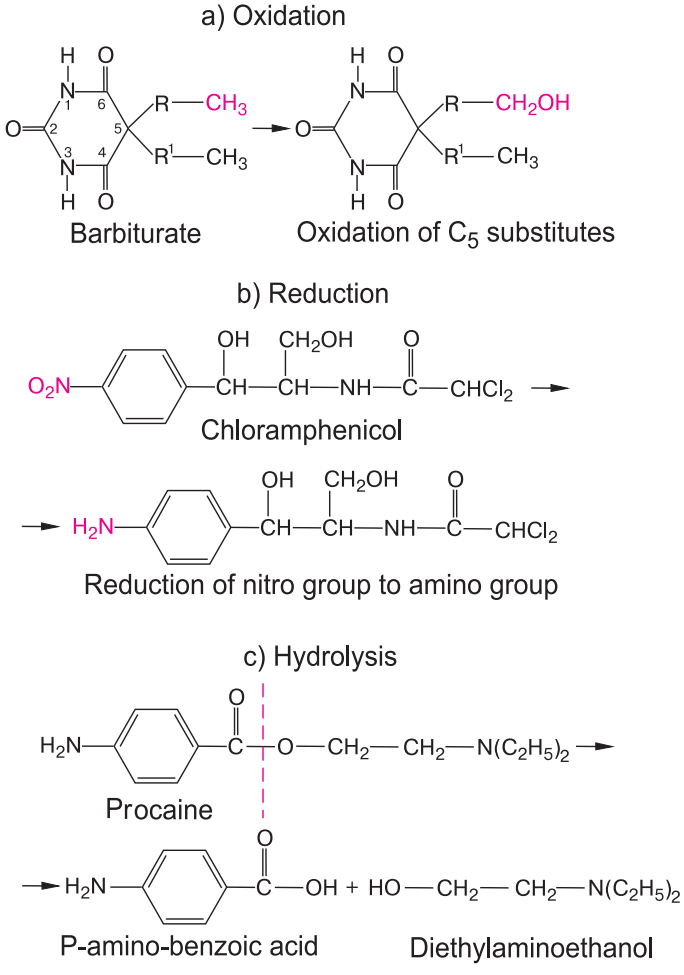


Fig. II.8. Metabolic transformation of drugs.

Conjugation is a biosynthetic process of binding of a number of chemical groups or molecules of endogenous compounds to the drug or its metabolites. The examples are: methylation (histamine, catecholamines), acetylation (sulfonamides), glucuronization (morphine, oxazepam) are binding with sulphates (chloramphenicol, phenol) or glutathione (paracetamol).

Many enzymes participate in the conjugation processes: glucoronil transferase, sulfotransferase, transacylase, methyltransferase, glutathione-S-transferase, etc.

Conjugation may be the only route of a drugs biotransformation or it may follow other routes of preceding metabolic transformation (see Fig. II.8). Examples of conjugates' formation (Fig. II.9).

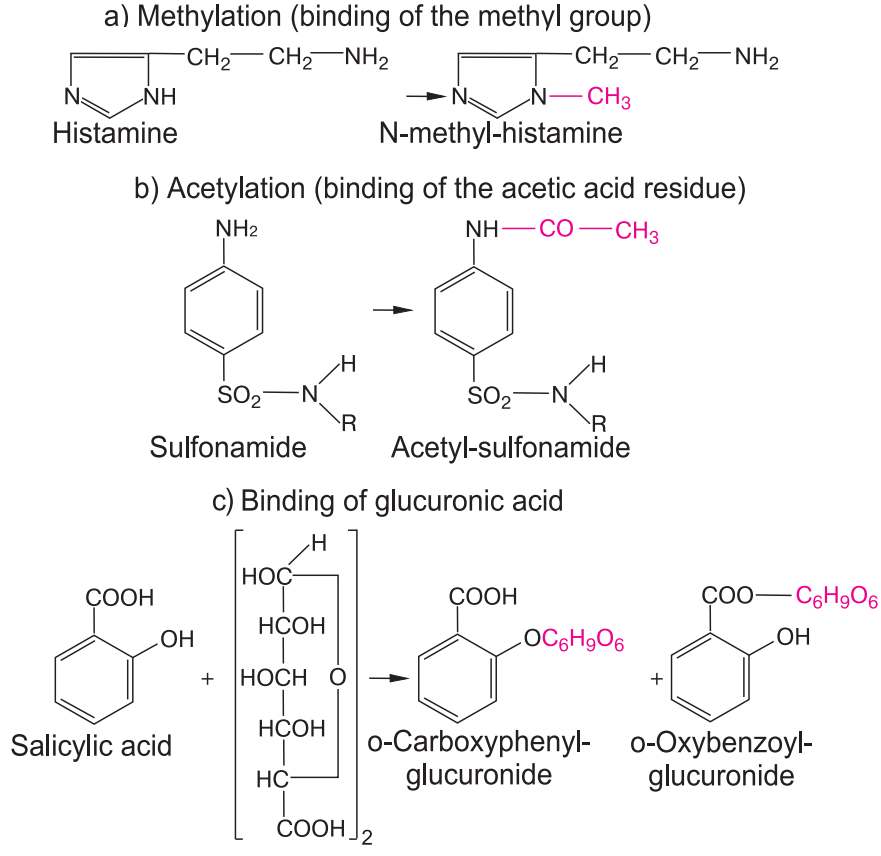


Fig. II.9. Conjugation of drugs.

In metabolic transformation and conjugation substances convert to more polar and more water-soluble metabolites and conjugates. It favours their further chemical transformations, if needed, as well as their excretion from the body. Kidneys are known to excrete hydrophilic compounds, while lipophilic ones undergo reabsorption in the renal tubules (Fig. II.10).

After metabolic transformation and conjugation drugs usually loose their biologic activity. Thus, these processes limit drug activity over time. In liver pathology associated with the reduction of activity of microsomal enzymes, duration of effect of some drugs increases. There are inhibitors of different enzymes, such as microsomal (chloramphenicol, phenylbutazone)

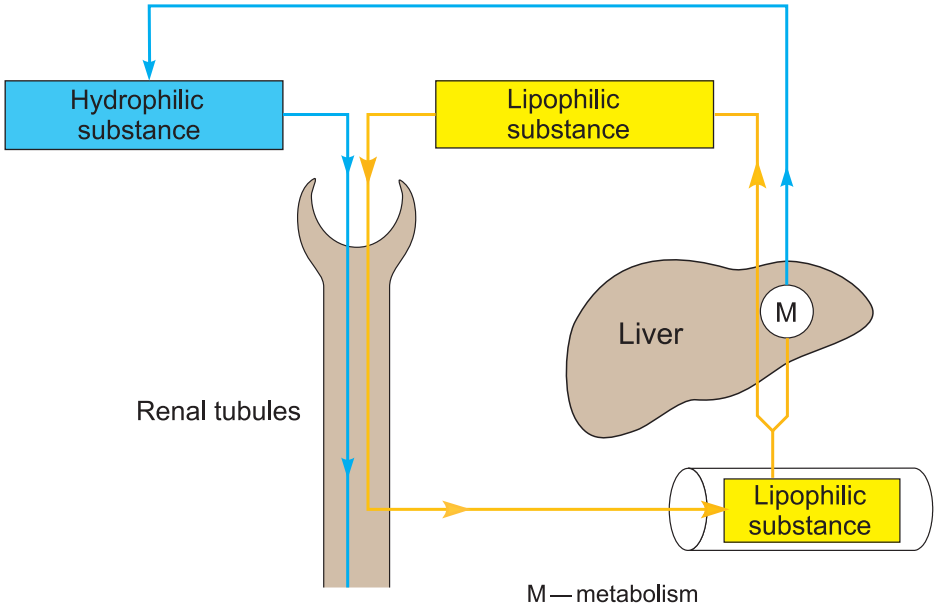


Fig. II.10. Excretion of hydrophilic and lipophilic substances.

and non-microsomal (anticholinesterase drugs, MAO inhibitors, etc.). They prolong the effect of drugs that are inactivated by these enzymes. In addition, there are compounds (for example, phenobarbital), which increase (induce) microsomal enzymes synthesis rate.

In some cases chemical transformations of the drugs in the body may lead to an increase in the resultant compound's activity (imipramine <desipramine) or toxicity (phenacetin <phenetidin). It may also change the mechanism of action (isoniazid which has antituberculous activity is one of the metabolites of the antidepressant iprazide), as well as transform one active compound into another (codeine partially converts into morphine).

4. ROUTES OF DRUG ELIMINATION FROM THE BODY

Drugs, their metabolites and conjugates are mainly eliminated with urine and bile.

In the kidneys low-molecular compounds, dissolved in plasma (not bound to proteins), are filtered through membranes of glomerular capillaries and glomerular capsules (Fig. II.11 and II.12). Besides, active secretion of substances in proximal tubules with the participation of the transport systems is essential. This is the elimination route of organic acids and bases, penicillins, salicylates, sulfonamides, quinine, histamine, thiazides, etc. Some lipophilic compounds can penetrate from blood into tubular lumen (proximal and distal) by simple diffusion through their walls.

The elimination of substances greatly depends on their reabsorption in renal tubules. Drugs are reabsorbed mainly by simple diffusion. This mainly concerns lipophilic non-polar compounds, easily penetrating through biologic membranes. Polar compounds are poorly reabsorbed from the renal tubules. That is why elimination of weak acids and bases greatly depends on urine pH. Thus, when urine pH is alkaline, there is an increase in the elimination of acidic compounds (for example, salicylic acid, phenobarbital). When urine pH is

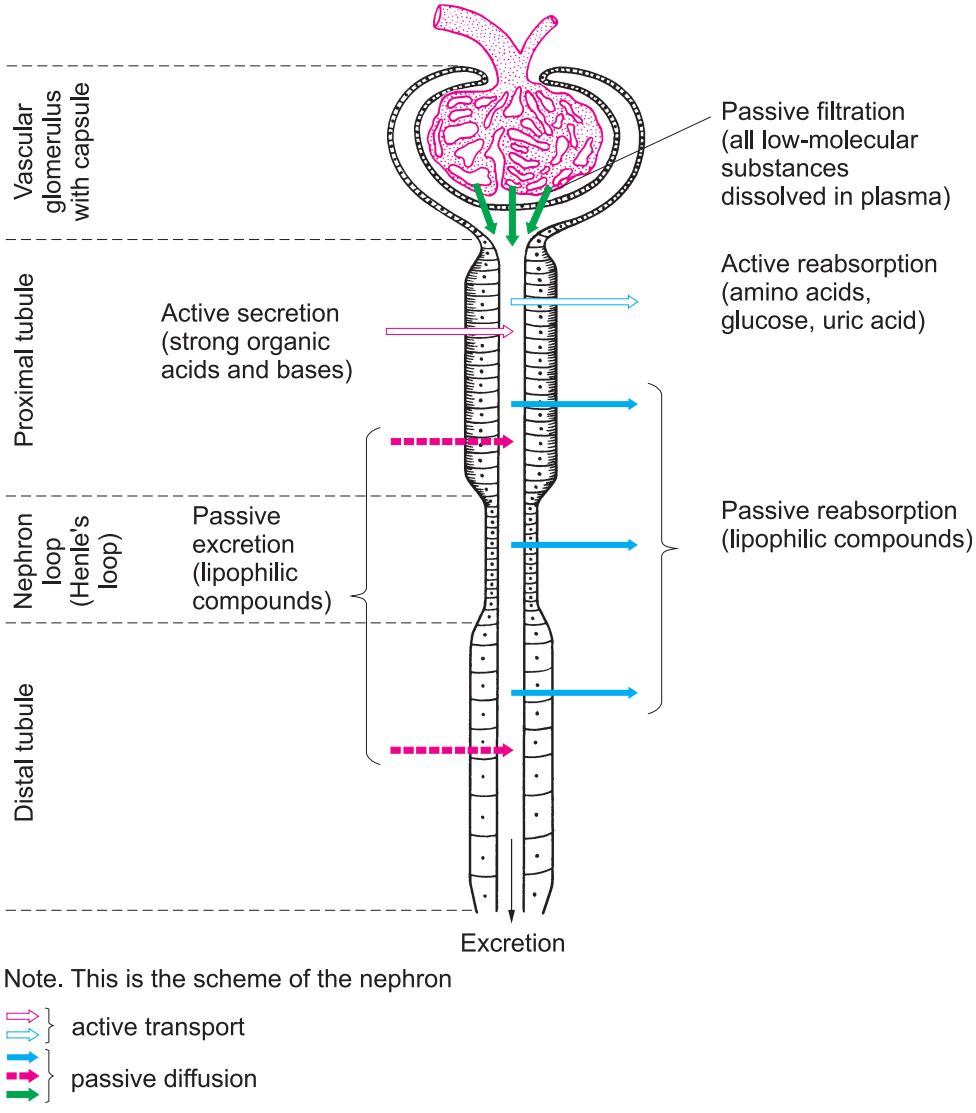


Fig. II.11. Basic processes affecting renal excretion of pharmacological substances.

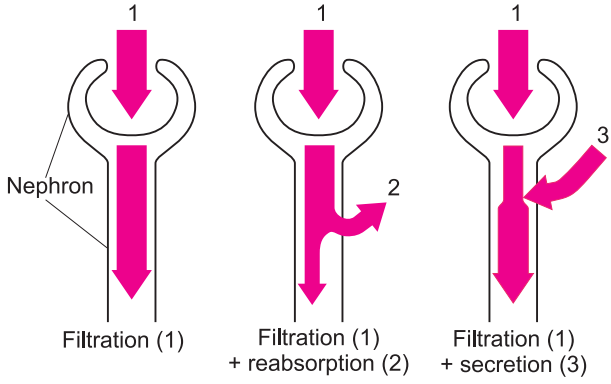


Fig. II.12. Principles of renal excretion.

acidic, elimination of bases increases (imipramine, etc.). The reason for this is the ionization of the mentioned compounds which prevents their reabsorption from the renal tubules.

Active transport is involved in reabsorption of a number of endogenous substances (amino acids, glucose, uric acid).

Significant mechanisms of the elimination of a number of drugs (tetracyclines, penicillins, phenytoin, colchicine, other) and especially products of their transformation is their transfer with bile into the intestine. A certain proportion of the drug is then eliminated with faeces, and the rest is reabsorbed. The cycle continues on, with the compound then again being eliminated into the intestine and so on (so-called hepato-intestinal circulation or hepatic recirculation; Fig. II.13).

The lungs mainly eliminate gaseous and most volatile substances (for example, inhalation anesthetics).

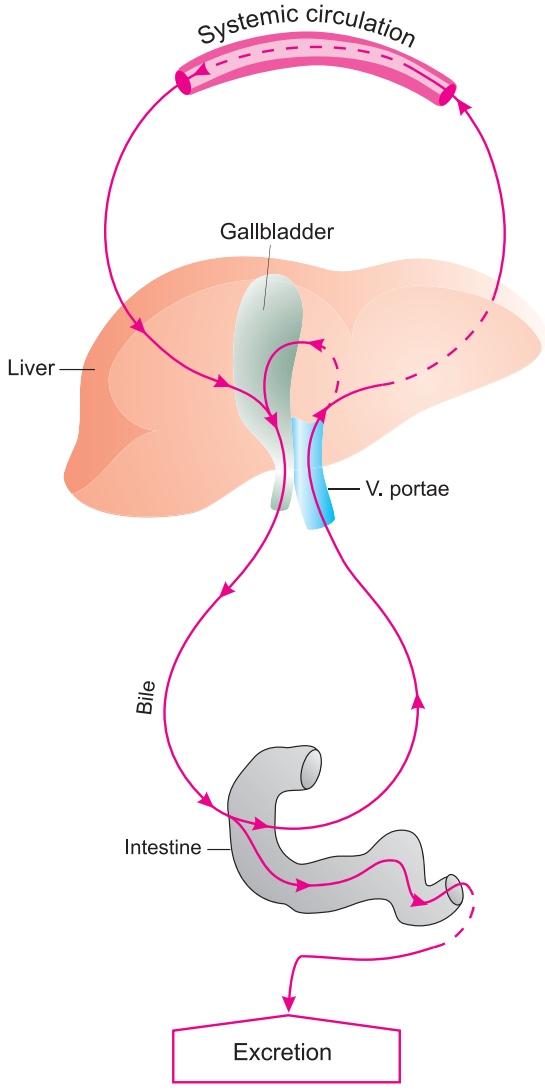


Fig. II.13. Hepato-intestinal circulation of substances.

Some drugs are eliminated by salivary glands (iodides), sweat glands (antileprotic ditophal), gastric (quinine, nicotine) and intestinal glands (weak organic acids) and lacrimal glands (rifampicin).

It has to be taken into account that during lactation a lot of substances taken by a nursing mother are eliminated via mammary glands (hypnotics, opioid analgesics, ethyl alcohol, nicotine, etc.). That is why one should be extremely cautious when administering drugs to a nursing mother. The drugs can get into the baby's body with breast milk and have unfavorable effects.

The elimination of drugs from the body occurs by excretion and biotransformation. A number of parameters are used as quantitative characteristics of elimination process: elimination rate constant (K_{elim}), «half-life» ($t_{1/2}$) and systemic clearance (Cl_T).

Elimination rate constant (K_{elim}) shows the rate of drug elimination from the body. It is defined according to the formula:

$$K_{elim} = \frac{0.693}{t_{1/2}}.$$

To define the rate of drug elimination from the body «*half-life*» (elimination half-life, $t_{1/2}$) parameter is also used. It shows the time necessary to decrease drug concentration in blood plasma by 50%:

$$t_{1/2} = \frac{0.693}{K_{elim}} = \frac{0.693 \cdot V_d}{Cl_T}$$

This parameter is used to adjust doses of drugs and intervals between the times of their administration in order to achieve stable drug concentration («steady state»). It is known that 90% of the drug is eliminated during the period that equals 4 $t_{1/2,}$ and this is considered in the dosing of the drugs. It also has to be considered that $t_{1/2}$ is defined not only by drug elimination from the body, but also by its biotransformation and storage.

Another parameter used as a quantitative characteristic of drug elimination rate is *clearance*[1] (Cl). This indicates the rate of removal of a substance from the blood (clearance) (it is measured as volume over time, or if necessary it can be expressed in relation to body mass or surface: ml/min, ml/kg/min, l/m^2/h, etc.). The parameters measured are: total (Cl_T), renal (Cl_R) and hepatic (Cl_H) clearance.

$$Cl_T = \frac{\text{Drug elimination rate}}{\text{Drug concentration in blood plasma}}.$$

Total clearance depends on such parameters as volume of distribution (V_d), «half-life» ($t_{1/2}$) and constant of elimination (K_{elim}).

$$Cl_T = V_d \cdot K_{elim} = \frac{V_d \cdot 0.693}{t_{½}}.$$

Renal clearance depends on the processes of filtration, secretion and reabsorption. It is possible to assess renal clearance by comparing drug concentration in urine and plasma (considering urine flow rate as well).

Hepatic clearance occurs via drug uptake and its further biotransformation by hepatocytes as well as drug secretion into the bile ducts.

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[1] From Latin *clarus* — clear.