C. 3 & 4

Drug Transport & Distribution in blood

See: www.veterinarypharmacon.com

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- Drug substances and most exogenous or endogenous compounds (e.g. hormones, bilirubin, etc.), bind in the body to:
  - plasmatic or
  - tissular proteins.

They will result in large complexes that cannot cross the biological membranes.

The biologic membranes

- are functional units, of 5 to 8 nm. thick

Composed mainly by:

lipoproteic and phospholipidic complexes,

They have a perpendicular orientation on the membranal surface thus forming a hydrophobic chain.

Proteins are incorporated into the membranes as globular molecule groups, providing the contact of the average extra- and intra- cellular environment.

Individual lipidic molecules have the ability to move laterally, ensuring the membrane's specific flexibility & fluidity.

In the middle of aqueous channels we can find the globular molecules, which can open and close, depending on the electric resistance, allowing the exchange of substances.

- In blood, drugs can be found under two forms:
  - free and
  - coupled.

The coupled form is reversible, fixed on the plasmatic proteins (or to the sanguine elements).

- Generally, the drugs have three main caracteristics:
  - one part of the active substance is linked and one part is free;
  - the link is reversible;
  - only unlinked substances can pass biologic membranes

Drugs bind to proteins by interacting with the:

- **ionisant,**
- **polar** or
- **non-polar groups,**

generating the following bonds:

a) covalent bonds
(electrons are shared between two atoms; this kind are sparse and much more common for the toxic drugs)

b) ionic bonds (energy = cca.5 Kcal/mol)
(accomplished between oppositely charged electric ions. Such a bond is proportional with the task size and square of the distance between the centers of particles)

c) hydrogen bonds (energy = cca.0,5 Kcal/mol)
(which are achieved when two atoms come very close. These are weak links with low energy, forming less stable complexes).

Factors

that influence drug transport

Chemical structure:

It is very important for the drug coupling and transport because is influencing the affinity of the organic molecules for proteins.

For example: phenylbutazone, oxphenbutazone, dicoumarinic derivatives, long-active sulphonamides, some penicillins, salicylates, etc. are binding heavily on the plasmatic proteins.

Changes in the chemical structure of drugs can cause large differences in terms of coupling to plasma proteins.

Bounding of some drugs to plasmatic proteins

(After: Dobrescu, 1977))

Species	% of drug bound to blood proteins			
	Penicillin G	Cloxacillin	Sulphadiazin	Sulphafurasol
Human	49	7	67	16
Horse	59	30	-	-
Rabbit	65	22	45	18
Rat	-	-	55	16
Mouse	-	-	93	69

Drug binding

for the transport

It is accomplished with a preference on the proteins, because they are the only peptide chains with a large contact surface compared to other blood proteins.

Theoretically, each molecule can carry approx. 100 positive or negative charges.

Drugs bind to groups consisting of amino acid
residues of albumin, surface oriented:

- R –COO-,
- R –O-,
- R –S-,
- R –NH 3+

In solution they interact with polar

Ions have a different affinity depending on the nature of the group to which they refer, for example:

- **Mn** (for the sulfhydryl groups),
- **Zn, Cd** (for the imidazole groups).

The anion affinity order seems to be:

bicarbonates <
acetates <
chlorures <
citrates <
nitrates.

The amount of the drug coupled to protein is determined by:

- the concentration of the drug;
- drug affinity and
- capacity up to saturation of these coupling sites.

Serum albumin provides:

a) some coupling places for the basic drugs;

b) for the binding of acid drugs , there are no more than two primary (usually only one) **coupling sites** .

Globulins

Compared to albumins, they have a relatively small importance for drug coupling.

Very few drugs have an affinity for them.

It is well known that thyroxine and cortisol have a

high affinity for the α-globulins, but with relatively

low coupling capacity.

When the coupling capacity is saturated, the exceeding drug is fixed to the albumins.

Globulins such as transferrin and ceruloplasmin bind

Lipoproteins α and β

Bind with liposoluble substances such as:

cholesterol, vitamin A, D, E, K, and steroids.

Gamma globulins

Bind with very few drugs and they are specifically

set only antigens.

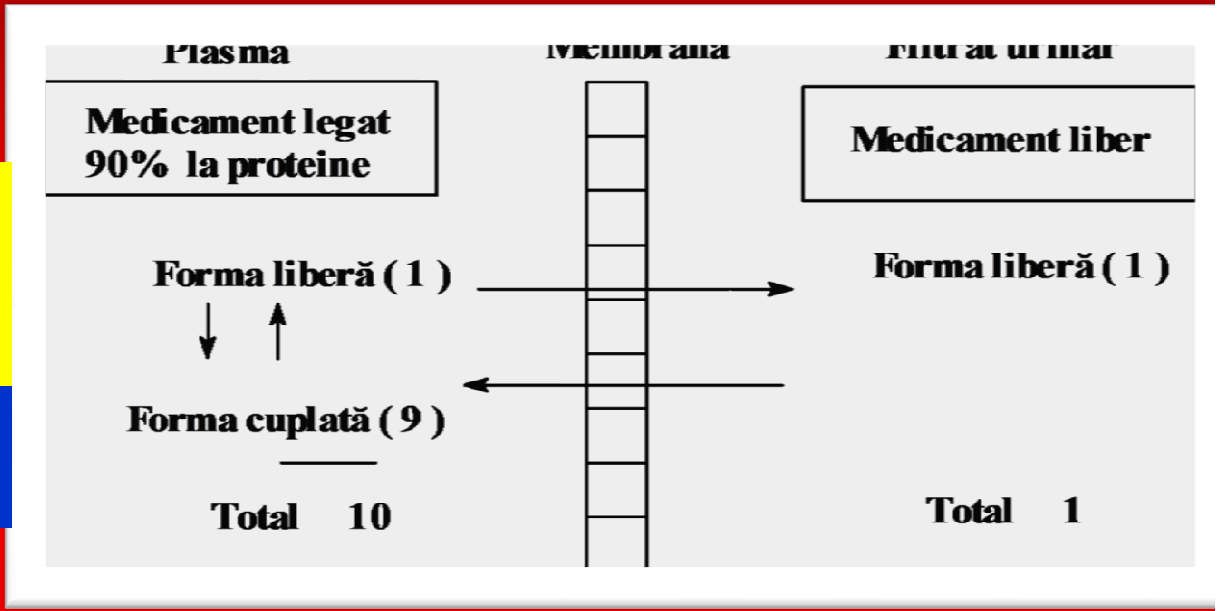
Relationship between coupling to protein and the action du

(After: Mihăilescu, 1980)

Pharmacodynamic group	Drug	Plasma protein binding(%)	Complete elimination	Action duration
Cardiotonics	Digitalin	95	2-3 weeks	1-2 weeks
	Strophantin	0	1-3 days	1-2 days
Antiinflamatory	Phenilbutasone	98	7-10 days	1-2 days
	Acetylsalicylic Ac.	64	15-30 hours	6-8 hours

Free and coupled fraction drug kinetics
(After: Dragomir, 1978)

Serum albumin	Secondary effects (%)	Without Secondary effects (%)
< 2,6	53	47
> 2,6	15	85



hypoproteinemia & alterations of albumin - globulin *ratio* =
- rapid saturation of the coupling capacity
- massive increase of the unbound,
- the danger of side effects or intoxications

Biotransformation increases with the amount of free drug in plasma.

Drugs extensively coupled to plasma proteins are

slowly eliminated (e.g. digitalin, phenylbutazone) and though, they will have a long action duration.

Protein binding is a dynamic and reversible process

Saturation of plasma protein binding capacity and increased free fraction, leads to a quicker metabolism and elimination of the drug, resulting in an equilibrium between the two factions.

The states of hyperproteinemia and alterations of the albumin - globulin *ratio* have as a result:

- **a faster saturation coupling capacity,**
- **a massive increase of the unbound fraction,**
- **danger of the side effects or of poisoning.**

For example,

- in newborn animals, plasma proteins are reduced.

For this reason, the unbound fraction of the drugs, is higher than in adults, a fact which explains the sensitivity of newborns and the risk of poisoning.

- in pregnant females, a large part of the plasma protein's ability to couple endogenous compounds is occupied, a fact that will increase the unbound fraction in the blood.

Among substances there is a competition for the coupling sites.

Some acidic drugs compete for the same binding sites on plasma proteins.

Sometimes movement may be therapeutically advantageous, sometimes in contrast, toxicities occur.

Corticosteroids present in plasma are circulating coupled to a specific globulin, named transcortin.

Anti-inflammatory substances (such as, phenylbutazone or salicylic acid derivatives) are able to move the corticosteroids, accomplishing the therapeutic effect.

Stages

of drug diffusion

Circulatory, the absorbed drug is able to access all body compartments in different concentrations.

Phases of diffusion

- **begin** with the **vascular wall crossing** and
- **end** with **drug penetration to the site of action,**

a phase, also known as the **drug distribution phase.**

Blood represents a central compartment responsible for the distribution of drugs, while representing a **small**

proportion compared to the other two great diffusion compartments (intra- and extra-cellular) of the body.

In addition to these three compartments, there are also a number of special sections whose accessibility is regulated by key barriers as:

- CNS blood-brain barrier,
- fetal placental-aqueous humor and
- Inner's ear endolymph.

Histo-morphologic features

The morphological boundary between blood plasma and the extracellular compartment is represented by the vascular endothelium.

There are three main endothelial types:

1) high active transport by pinocytosis
This form of endothelium is present in almost all organs and allows rapid transfer of substances in both directions;

2) Fenestrated epithelia
Endocrine organs and intestinal capillaries constituting this type of endothelium. This allows the exchange of substances very quickly.
Here, the renal glomerule capillary endothelium can be also included.

3) Endothelia that have no transport activity by pinocytosis and present the so called *Zonulae ocludentes*

(or. tight junctions),

- **continuous type connections between cells,**

preventing the intercellular exchange of substances,

- **the blood-brain barrier basis is located in the CNS.**
- **it is also met in the case of peripheral nerves.**

From a kinetic standpoint, the plasma compartment and the extracellular compartment are considered as a unit.

The fact that membranes are composed of a double
lipid layer is of particular importance to the phenomenon of distribution, since membranes are impermeable to water-soluble substances.
Only few substances in the body are distributed in proportion to the percentage that represents each compartment.
Most pharmacons and toxins have a complicated behavior, as additional phenomena can be induced
depending on the nature of the molecule.

Physico-chemical factors

involved in drug distribution

Pharmacon solubility

is a significant feature for drug distribution, absorption

and elimination.

Substances can be divided into three groups:

a) Strictly water-soluble compounds

- **hardly absorbed after the p.o. administration**
- **after i.v. administration they are distributed only in the extracellular compartment, being easily eliminated by the kidney.**

In this group, there are few substances (e.g. the osmotic diuretics).

b) Strictly fat-soluble compounds

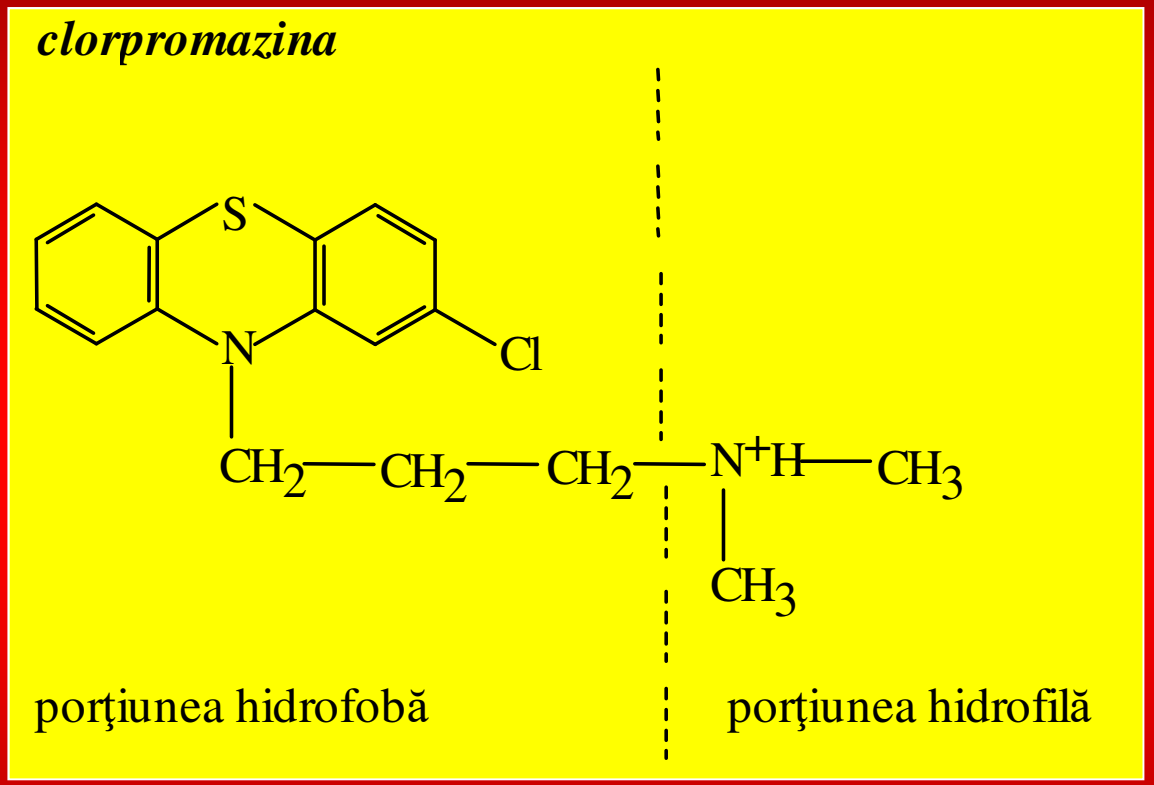
are placed in body fat, where the partition coefficient, water / octenol is in function, especially in the neutral fat of the fat cells (e.g. chlorinated hydrocarbons).

c) Amphiphilic compounds

A molecule is considered amphiphylic, when it presents:

- a hydrophilic part and
- a hydrophobic part, positioned close to one another.

in the case of larger distances between these components, they will enter the surfactants category.



Amphiphilic character of chlorpromazine

(After: Kuschinsky, 1989)

Amphiphylic substances accumulate properly in the interphase (i.e. where the aqueous phase meets the lipid phase).

This is the case for all cellular membranes:

- either plasmalemma or
- intracellular membranes (e.g. mitochondria, nucleus, ER, lysosomes).

This accumulation has already been demonstrated for membranes in the case of numerous drugs and is of practical importance (i.e. the *ratio* of the cell and plasma concentration can reach values of 150 or higher.)

Therefore, amphiphylic drugs are found only in a very small extent in the neutral lipids of the fat cells, because they are not lipophilic.

Since most of the drugs are weak acids or bases they are found as unionized forms (in case of a biological pH).

The size of the dissociation constant is, therefore, important for the distribution phenomenon.

Another phenomenon that depends on the hydrophobic drug molecule and plays an important role in drug distribution (and in drug interactions) is the coupling to plasma proteins and to the extracellular fluids, based on the hydrophobic interactions

Since the drug came into use, there are many factors that tend to decrease its active concentration.

These phenomena are mainly determined by:

- storing drugs in the body;
- binding to proteins;
- dilution in the body fluids.

A drug is able to leave the vascular space by:

- diffusion through the lipoid membranes,
- the large size pores (4nm) or
- the capillary wall fenestrations.

These "openings" allow passage of albumins , so that

all, even the biggest drug molecules (e.g. dextrin

70,000 Da.) can quickly get out of the vascular bed.

Balance will occur

- rapidly in: heart, liver, kidney and brain
- slowly in: skin, bones and fat stores.

Even after the passing of sufficient time to achiev equilibrium, there are differences in drug concentrations in different parts of the body. For this reason all molecules, even the greatest a able to distribute the ECL.

The speed of drug plasma balancing, achieved

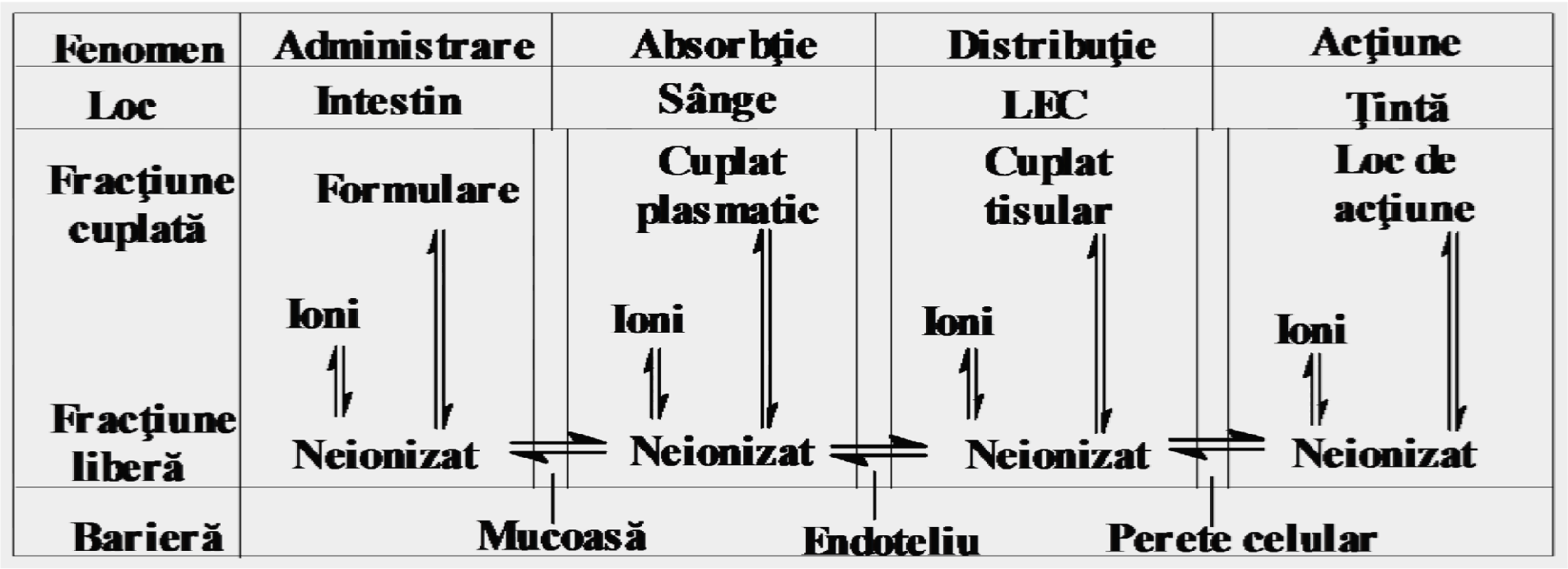
concentrations and ECL depend on:

- **the degree of vascular tissue infusion.**

Unionized lipid-soluble fraction is shown as being in **balance** between the different compartments.

Although there is a balance between the concentrations of uncoupled substances from each

compartment, the total drug concentration may differ significantly between the compartments. There may be also significant differences in pH between compartments which will cause different ratios between the unionized and ionized fraction.



Equilibrium diagram of a drug that is found in a compartment disposed in and between the different body fluid compartments.

In this example, the drug was orally administered, and its growth is monitored until it reaches the site of action (Brander, 1991).

E.g. significant pH difference between compartments

is important: e.g. stomach pH = 2/ECL (pH = 7).

A weak acid with pKa = 4, will be almost exclusively

in a non-ionised state in the stomach, while in the CEL will be mainly in the ionized state.

Generally the acidic drugs, tend to accumulate in the

phases where the pH is high, and the alkaline drugs

tend to concentrate in areas with low ph.

The distribution of the available binding site in compartments also affects the total amount of the drug present in each compartment when there is balance between them.

Because of the coupling, variations in concentration

between the two compartments may appear, even if the pH has the same value and thus the concentration of the unionized drug is the same in both compartments.

Another factor that can cause an uneven distribution

of the drug between compartments is the presence

of an active transport mechanism suitable to the

membrane that separates them (e.g. that is

Coupling influence

of drugs on the proteins

A variable proportion of an absorbed drug, can be

reversibly coupled to plasma proteins.

Active drug concentration in the uncoupled fraction, is able to leave the plasmatic space and reach the action site.

Between the coupled and the free fraction, an equilibrium is forming.

When the free substance leaves the circulation, the coupled fraction will be released, in order to restore balance.

Protein couplings reduce the loss of substance rate
in plasma, to the extent that it lowers the free plasma concentration fraction.

This will decrease the concentration gradient on which the drug diffusion occurs.

It will reduce the loss rate of the drug through the

kidneys (because only the free fraction is filtered).

When a drug is **actively excreted,** coupling to protein **does not confer protection** (e.g. penicillin is excreted almost entirely in the first renal pass).

The practical consequence of coupling to plasma proteins is that **the toxicity and efficacy** of the drugs that are coupling, are greatly intensified in a substantial portion of the proteins in the case of hypoproteinemia.

The unbound fraction concentration of a drug coupled in a large proportion may be increased when administering a higher affinity drug for the same coupling sites.

Drug coupling in blood, most commonly, but not

exclusively, occurs with the serum albumins, but can also be held by :

- **figurate elements or ,**
- **α -1 acid glycoproteins.**

Albumin is able to achieve the following couplings:

- high affinity - low capacity or
- high capacity - low affinity.

Concentration assessment of:

- unbound and
- total concentration

is feasible in experiments where the total drug concentration is gradually increased.

Studies of this type provide information on:

- the number of coupling sites on an albumin molecule and about,
- the value of the coupling constant affinity.

This is important when searching for a suitable dose

for an antimicrobial drug.

Diffusion

in the body's hidric regions

In adult animals, body water can be found in percentages of:

- **70-75%** of the body weight (depending on the age and species), being included in fluid or distribution

regions, separated by tissue barriers with a variable

component.

In each of these compartments, a drug reaches

steady state surprisingly quickly.

In terms of drugs distribution, the body is divided into

three major areas:

- blood plasma (intravascular), approx.. 4-5% of bw.;
- extracellular (intercellular), approx. 15-20% of bw.,

which bathes the cells (ECL)

- intracellular approx.. 50% of body weight (ICL).

Also known, is the:

- intestinal luminal space, approx.. 25-30% of

The drug distribution volume

Is the part of the total body water in which a drug can be successfully diffused.

Solubility and diffusion in the aqueous phase

are medicinal properties that give the drug the

ability to come into contact with the first membrane.

The degree to which a specific dose of a medicine will be diluted, depends on the number of compartments it can penetrate in the body.

Since the elimination mechanisms cause a lowering of the plasma level, drugs tend to revert back from the distribution volume in the plasma.

Transcellular fluids

are separated from the interstitial fluid that surrounds

the cells by an epithelium.

Transcellular fluids are considered to be:

- **liquids from the intestinal lumen,**
- **urinary tract**
- **CNS**
- **Glands**
- **joints and body cavities.**

When drugs diffuse in these fluids, they must overcome all these spaces.

The capillary wall is a membrane which has a different permeability for different drugs.

Its penetration will depend on the:

- liposolubility,
- physiological state and
- molecular size.

The more liposoluble the drugs are, the easier they
will penetrate the capillary walls.
Substances coupled with plasmatic proteins
cannot diffuse transcapillary, until after they get
back into free form.
Passing through the capillary wall is influenced by
the capillary permeability changes, under the
influence of some drugs or tissular

Drugs that can cross cell membranes are distributed into the intracellular space, or in the constitution water (representing about 50% of the body weight).

All drugs with a low molecular weight (incl. acids)

will be filtered at a glomerular level, according to

their plasma concentration.

In the frame of this mechanism, are involved an active process which lacks specificity towards its substrate and a high capacity transport

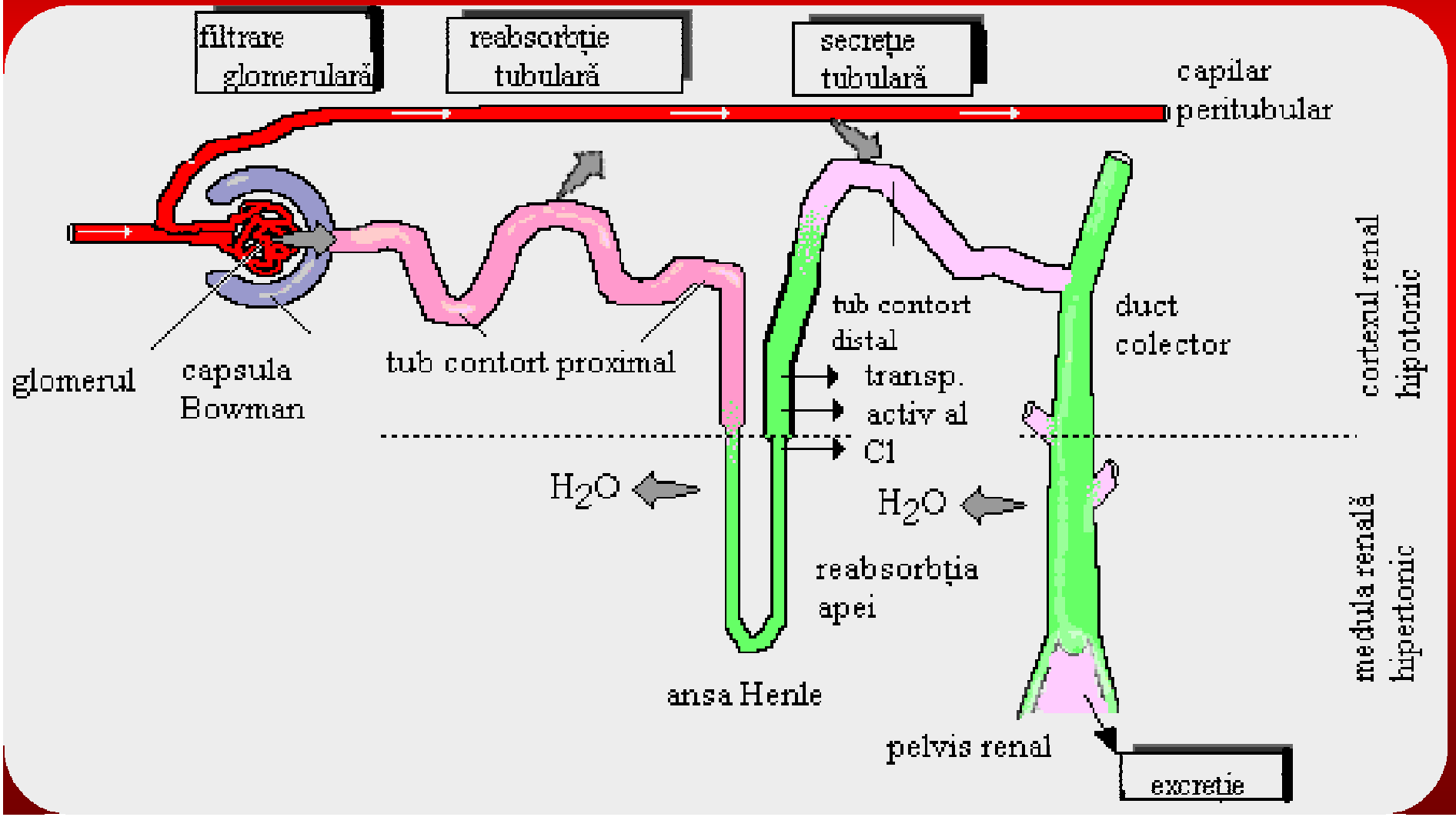
Acidic active substances will also be transported

by this mechanism, which may lead to:

- the fact that distribution and renal elimination will not be adjusted **only by** the physico-chemical parameters, but will be determined, also by the **active transport processes.**

Proximal portion of the nephron representation: active resorption mechanisms, absorption and secretion of acids in the drug distribution

(After: Kuschinsky and Lillmann, 1989)



Not only the kinetic behavior of drugs is influenced

by modifications to the acid transport mechanism,

but also the kinetic behavior of the body's own substances versus some medicines.

A good example is the uric acid: which is filtered in

the glomerule, and then, quantitatively reabsorbed.

Any reduction in acid secretion capacity, due

The role of cell membranes

These components are important from a functional

point of view (membranes of organelles,cytoplasmatic ones and plasmatics) represent about 80% of the cell's drymatter.

Plasmatic membrane

Works as an interface between the cell and the ECL

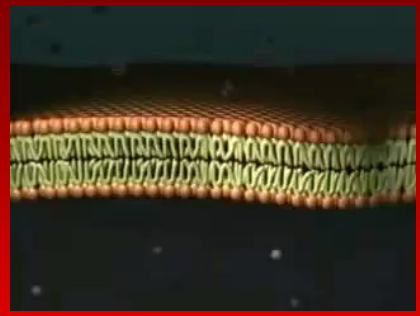
(extracellular fluid) and possesses qualities and

properties that allow the transfer from and

Phospholipid fluidity in double layer explains the surface mobility of the cell components (e.g. of the receptors).

This vision of cell membranes is known as the **fluid mosaic model** and it is fully compatible with the known behavior of the medicines at membrane level.

Biological membranes behave as punctured lipidic



The diffusion mechanisms

The simplest case is that of a small water-soluble

molecule who has a passage rate controlled only by the concentration gradient.

Since water-soluble molecules larger than the urea

penetrate more slowly, it was supposed the presence of membrane pores or channels of small diameter (approx. 0.4 nm)

Because of the water passing through and its dependency on the differences in hydrostatic and osmotic pressure, this process has been called filtration.

Liposoluble drugs must cross from the aqueous ECL into the lipidic membranes and then into the aqueous phase after this barrier.

The drug is partitioned between the aqueous and

In what concerns the penetration of medicinal substances through the membranes, several mechanisms are involved:

Some of them are carried out passively without

energy sources, while others are active mechanisms

requiring energy sources.

- **Simple diffusion**

The aqueous substances pass through the aqueous

pores of the cell membranes.

- **The solvent involving ("solvent drag")**

The aqueous substances penetrate the aqueous pores of a membrane as a result of increased water

circulation.

- **Diffusion limited by electrical charges**

The polarity of membranes causes the ionized forms of the drugs, to meet electric charges barrier.

Instead, small anions (Cl-) can pass through the

positively charged aqueous channels excluding the

- **Lipidic barrier limited diffusion**

Penetrating molecules can enter into the cell, if it has an appropriate solubility, which would allow the dissolution of the membrane first, and afterwards in the aqueous phase.

- **Facilitated diffusion**

Is a selective, saturable, transport system subjected to competition between substrates.

The transported molecule is combined reversely with a carrier.

Mechanisms listed do not require energy and do not usually lead to the concentration against an electrochemical gradient.

Mechanisms that require energy are carried out
against the concentration gradient.

- **Exchange diffusion**

- in this mechanism, a specific carrier is present, and
can cross the membrane, but only under complex
form.

- **Active transport by carrier**

- is the most common mechanism, although energy
consuming.

Trough a reaction that requires energy (ATP), the

carrier is modified on one side of the membrane, to have a greater affinity for the molecule.

On this basis, it links the substance and transports it trough the membrane, then with another chemical reaction it loses the affinity and releases the substance, to finally return either empty or in combination with other substances, repeating the cycle.

Numerous active substances diffuse through this

Pinocytosis

It is a mechanism in which the cell membrane develops invaginations with the incorporation of the substance, followed by the integration as intracellular vesicles.

External substances are taken under this form and then released into the cell, after the dissolution of the vesicle.

Active transport

Is occurring when, in addition to the functions of:

selectivity, satiability and competition, the system is

also dependent on energy (as such, it is rapidly inactivated by metabolic inhibitors) and so, it is capable to transport the substrate against the concentration and the electrochemical gradients.

Relation

pH, pKa and drug diffusion

Only a few drugs are exclusively, **hydrosoluble or liposoluble.**

On the other hand, many drugs are able to solubilize both in water and fat (or other lipophilic solvents).

Molecular and biochemical aspects

- ions, if they have **sufficiently small** molecular

sizes, can cross the membranes via the hydric

channels,

- **unionized liposoluble fractions** can diffuse

through the lipidic portions of the membranes.

- the **drug ionization degree** is dependent on

the **pH** of the aqueous phase in which they are

The consequence of the partition effect on the pH -
pKa difference - on the balance of ionic diffusion, is
called ionic capture.

Only non-ionized molecules that are able to diffuse
through the lipidic membranes have a tendencyy to
equalize the concentrations on both sides of

- The presence of a **pH difference** between the two sides of the membrane, allows a drug with suitable pKa, to develop different ionization ratios for the two liquid phases.
- So, although the ionized fraction concentration levels are almost equal, **the total concentration of dissociated and undissociated** forms can be very different from one side of the membrane to the other.

Electivity for certain tissues may lead to a substance concentration with an irregular distribution.

Most of the drugs are distributed unevenly, being

able to accumulate selectively in some tissues.

PKa values o f acidic or basic drugs

(After: Brander, 1991)

Acid drugs	pK_a	Alcaline drugs	pK_a
Ampicillin	2.5	Teophillin	0.7
Aspirin	3.5	Strichnine	2.3
Phenilbutasone	4.5	Methilene blue	3.8
Sulphacetamide	5.4	Chinidin	4.4
Sulphadiazine	6.5	Piperazine	5.7
Sulphadimidine	7.4	Trimethoprim	6.4
Penthobarbital	8.1	Ampicillin	7.2
Teophillin	8.8	Strichnine	8.0
Adrenalin	10.2	Adrenalin	8.7
Ascorbic acid	11.5	Atropin	9.7

Diffusion

through barriers

In veterinary medicine, three main body barriers for drug substances are recognized, namely:

- **blood-brain (hematoencefalic),**
- **blood-ocular and the**
- **placental barrier.**

Hemato-encephalic(Blood-brain)

barrier

The blood vessels that are crossing the brain and bone marrow are lined with a specialized endothelium with cells linked together by impermeable formations named *zonulae occludentes* and no pinocytosis activity.

This barrier is placed between the plasma of the encephalon and extracellular space.

The cerebrospinal fluid barrier (CSF)

Anatomically it is placed to the level of the choroid plexus.

Drugs that are not soluble, or those that are highly ionized penetrate slowly into the forebrain, while fat-soluble agents (e.g. volatile anesthetics) penetrate this space rapidly.

The barrier exists due to the fact that the encephalon's capillaries are free of pores, which in other parts of the body facilitate the elimination of the drug out of the plasmatic area.

- Endothelial cells are accompanied by **tight junctions** of brain substance and not by the usual **gap (button) type junctions.**

- In addition, the capillaries of the encephalon are very **closely wrapped by the glial cells**. In the absence of channels, the diffusion in the brain's ECL is only easy for **fat-soluble** drugs.

- The blood-brain barrier of the newborn is inefficient compared to an adult one.

- The blood-brain barrier efficiency reduction is considered a chemical toxicity mechanism, which is still under investigation.

- The CNS is separated from the interior fluid space by the ependymal and from the outside, by the glial cells.
- both structures present intercellular spaces, which allow communication between the extracellular fluid and CSF.
- a particular interest in terms of physiology and pharmacology is given to those small areas of the brain that are not located "after" the blood - brain

Of these, the most important are:

- ***Area postrema*** **and**
- ***Eminentia mediana***

- **The limit between CSF and plasmatic network is**

represented by the surface coating.

- ***The Area postrema*** **can be regarded as an**

assembly of chemoreceptors.

Through these "sensors" the CNS can directly receive

information through the network of blood, which is important, among other things, for the function of the respiratory center.

- In the *area postrema* are positioned the vomiting chemoreceptors, and their excitement can cause the act.

In the *eminentia mediana, are placed* the neuro-secretor axons, which release prior regulator

hormones of the pituitary function.

- **These hormones are taken up by the fenestrated**

endothelium capillaries.

- **Many substances (e.g., chemotherapeutics and**

antibiotics have difficulties in their CNS penetrating

When crossing the Central Nervous System, drugs meet two main barriers:

- **blood-brain barrier,**
- **blood-cerebrospinal fluid (CSF).**

Blood-brain barrier through which the drug passes into the encephalon's extracellular fluid is constituted by the capillary walls and glial cell layers.

Blood - CSF barrier is composed mainly of the choroid plexus epithelium.

- Studies have shown that the two barriers often act as lipidic membranes.

- The intravenous drugs pass into the brain or CSF at rates proportional to their partition coefficient and its dissociation constant at a pH of 7. 4

- Among the two barriers; blood - brain and blood - CSF can pass a series of drugs, like: chloroform,

Hemato-oftalmic

barrier

The passing of drugs, through the plasma in the aqueous chamber of the eye is performed by the ciliary body epithelium.

Substances cross with difficulty, because of the eye's much lower vascularisation, compared to other
tissues.

Placentary

barrier

The placenta is placed between maternal blood and fetal circulation.

- This barrier comes from the syncytial trophoblast formed by the merger of several cells.
- In this situation, the intercellular spaces are missing, but transcellular exchanges are present.
- The placental barrier's permeability is higher than that of the blood-brain barrier.

All pharmacons that are having central effects, namely, those who cross the blood-brain barrier, enter relatively easy in the fetal circulation.

Drug effects will last longer in the newborn animals compared with adults because the specific removal mechanisms are not yet defined.

- Liposoluble drugs diffuse **easily** through the placenta

and, therefore, most anesthetics may cause **respiratory depression in the newborn**.

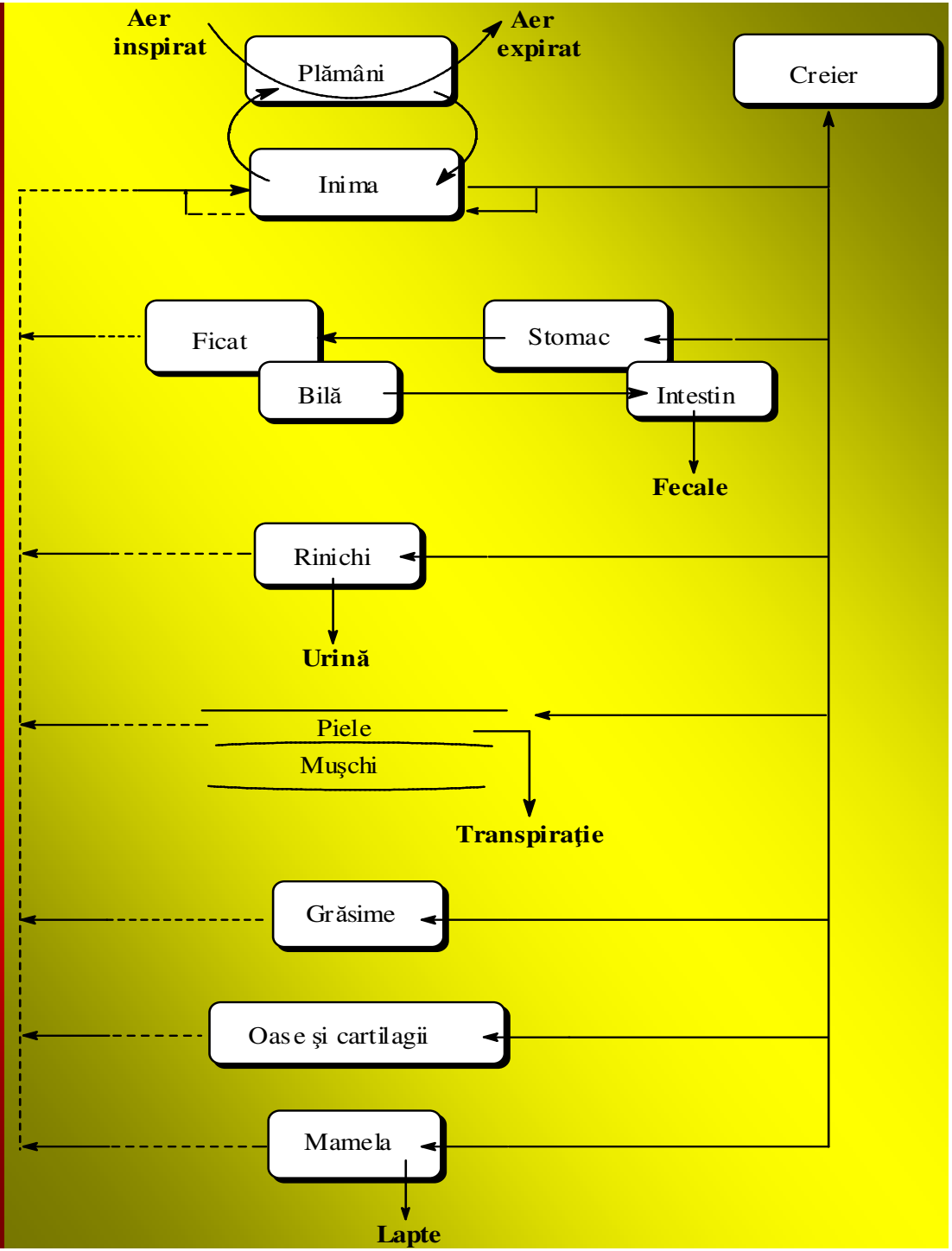
- The original concept that the placenta is an important barrier to protect the fetus from the action of medicinal substances **proved to be illusory**.

Cutaneous

barrier

- It generally prevents substances from entering in the body, which limits their effect substantially.
- the exceptions are the: liposoluble and volatile drugs (e.g. iodine, guaiacolum, eucalyptol, etc.), which can have a deep, diadermic penetration.
- most drugs, to exert their pharmacodynamic effect,must penetrate body humors from which they are directed towards farmacoceptors.
- insoluble compounds are considered as inert, from a pharmacological standpoint.

Theoretical distribution of drugs in tissues and organs
(After: Cristina, 2000)



Redistribution

of drugs

This phenomenon is illustrated for example, by the pharmacokinetics of thiopental.

When this lipophilic drug is administered I.V., it will **rapidly diffuse in the CNS** (because it is a well vascularized

and rich lipidic tissue), so the general anesthesia is rapidly induced.

- The initial equilibrium between blood and brain

will change, because the drug is more slowly

equilibrating in other tissues.

- because of this, the drug will diffuse back into the

blood from the CNS, to recreate a new blood-brain

balance.

Consequences

of uneven distribution

These mechanisms contribute to variations in drug concentration between different body areas at the moment of equilibrium.

- Drug concentration in tissues, at known established time intervals after the last administration (the so called "residue studies"), is essential to establish the withdrawal period (i.e. the time that must elapse after the last administration to slaughter for human consumption).

If the ability to attach or to seize the drug in other places than the action site (on the so-called loss sites, drug acceptor sites or silent receptors) is significant, high initial doses may be necessary.

It is possible for a pharmacon's high local concentration to produce changes (e.g. nitrofurantoin causes yellowing of the teeth), undesirable side effects (e.g. cloroquins, cause retinal dystrophies), or even accidental large values (e.g. arsenic and heavy metals, etc.).

Conclusions

Regardless of the route of administration, a medicinal product must:

- **be absorbed and leave the administration site**
- **enter into the circulatory stream and then**
- **diffuse into the body.**

A drug can be:

- **fat soluble (or liposoluble)**
- **water soluble (or hydrosoluble) and**
- **amphiphilic.**

The rate of absorption will depend primarily on the:

- **pH of the absorption surface,**
- **pKa of the drug,**
- **oil-water partition coefficient,**
- **degree of blood irrigation of the absorption area**
- **extension of the absorption area surface.**

The concentration that a drug can reach into the diffused compartments depends on the:

- pH difference between the two spaces separated by the traversed membrane
- various coupling capacities on both sides of the membrane
- the existence of an adequate transport system, or
- the existence of specific membrane barriers.

Thanks for your attention!