MINISTRY OF HEALTH OF THE RUSSIAN FEDERATION VOLGOGRAD STATE MEDICAL UNIVERSITY DEPARTMENT OF PHARMACEUTICAL AND TOXICOLOGICAL CHEMISTRY

LECTURE 2

TOXICOLOGIKAL CHEMISTRY

Biotransformation of xenobiotic in the body. Metabolites and toxicity. Lethal synthesis. Introduction to secondary metabolism.

> Maria Petrovna Paramonova Assistant professor, PHD

The term "**metabolism**" includes a description of all stages (*absorption, distribution, accumulation, biotransformation* and *elimination*) of the toxicant in the body.

Biotransformation is the metabolic transformation of endogenous and exogenous chemicals (toxicants) into more polar (hydrophilic) compounds.



The biotransformation of xenobiotics takes place in the liver.

Enzymes for the biotransformation of xenobiotics are present in the microsomes, in the cytosol and a small part - in the mitochondria, the nucleus and lysosomes.

There are two stages of biotransformation





The first phase of metabolism is the biotransformation stage, during which polar functional groups are added to the compound molecule, or groups that are in the hidden are released form

There are 3 types of **first phase reactions**:

- oxidation,
- reduction,
- Hydrolysis

https://youtu.be/oONqmNRWU0o

Reactions of the second phase of biotransformation or conjugation reactions:

- glucuronidation,
- -sulfation,
- -acetylation,
- -methylation,
- -conjugation with:
 - a) glutathione

b) amino acids (glycine, taurine and glutamic acid). https://www.youtube.com/watch?v=v6_qb_M89qQ

Oxidation reaction

Cytochrome P450 catalyzes oxidation reactions:

- -hydroxylation of aliphatic and aromatic hydrocarbons
- -epoxidation of double bond;
- -oxidation of heteroatoms (O-, S-, N-, Si-)
- -N-hydroxylation;
- -dealkylation of heteroatoms (O-, S-, N-, Si-),
- -oxidative group transfer;
- -breaking the ester bond;
- -dehydrogenation.

$\mathsf{RH} + \mathsf{O}_2 + \mathsf{NADPH} + \mathsf{H}^+ \rightarrow \mathsf{ROH} + \mathsf{H}_2\mathsf{O} + \mathsf{NADP}^+$

Epoxidation and hydroxylation of aromatic compounds



Monoamine oxidase - oxidative deamination of primary, secondary and tertiary amines

$$RCH_2NH_2 \longrightarrow RCH=NH \xrightarrow{H_2O} R-C \xrightarrow{O} + NH_3$$

oxidation of alcohol by alcohol dehydrogenase



Hydrolysis

$$R-C \xrightarrow{>0} X \xrightarrow{H_2O, E} R-C \xrightarrow{>0} + HX$$

OH
$$X = OR', SR', Cl, NR'_2$$

Reduction

 $R-C_6H_4-N=N-C_6H_4-R1 \xrightarrow{H,E} R-C_6H_4-NH_2 + H_2N-C_6H_4-R1$

 \mathbb{O}^{NO_2} $\overset{\mathrm{H}}{-}$

$$\begin{array}{c} \mathbf{O} \\ \mathbf{R} - \mathbf{C} - \mathbf{H} \end{array} \xrightarrow{\mathbf{H}, \mathbf{E}} \mathbf{R} - \mathbf{C} \mathbf{H}_2 \longrightarrow \mathbf{H} \\ \end{array}$$

$$H, E$$

R-S-R1 H, E
R-S-R1

$$\begin{array}{ccc} \mathbf{O} & \mathbf{H}, \mathbf{E} & \mathbf{OH} \\ \mathbf{R} - \mathbf{C} - \mathbf{R}\mathbf{1} & \xrightarrow{\mathbf{H}, \mathbf{E}} & \mathbf{R} - \mathbf{C} - \mathbf{R}\mathbf{1} \end{array}$$

Восстановление хинонов -

НАДФН-хинонокси, флавопротеины цито

Reactions of the second phase of biotransformation

Glucuronidation





Sulfation



Methylation and Acetylation





Conjugation with: glutathione



Factors influencing the metabolism of toxicants.

- **1. Genetic factors and intraspecific differences** (possible genetic defects of enzymes, studies them pharmacogenetics).
- 2. Physiological:-age and development of enzyme systems;sex differences;-hormonal background;-pregnancy;nutrition;- pathological conditions, diseases;-long-term use of medications.
- **3. Environmental factors**:-stress;-ionizing radiation;stimulation of metabolism by foreign compounds;-inhibition of metabolism by foreign compounds.

Lethal synthesis

Biotransformation of xenobiotics is usually detoxification process, that is, aimed at reducing toxicity.

However, in some cases, **xenobiotics in the body transform into more toxic compounds**. This process called "lethal synthesis"

1. Oxidation of methanol to formaldehyde and formic acid



Formaldehyde and formic acid are highly toxic compounds. They cause poisoning and irreversible blindness

2. Oxidation of ethanol



3. Ethylene glycol oxidation



Thalidomide





https://www.youtube.com/watch?v=bjsz4UxDeiQ

Еще один пример «летального синтеза» – образование из малотоксичного паратиона (тиофоса) в организме путем замещения атома серы на атом кислорода параоксона – мощного ингибитора холинэстеразы, хотя сам паратион антихолинэстеразной активностью не обладает в опытах *in vitro*:



В процессе О-дезалкилирование фенацетина образуется парацетамол и ацетальдегид:



Путем О-дезалкилирования в организме происходит превращение кодеина в морфин (более токсичное соединение).



Нетоксичная фторуксусная кислота в организме подвергается синтезу, в результате которого образуется токсичная фторлимонная кислота. Она блокирует цикл трикарбоновой кислоты, подавляя фермент аконитазу. Потеря энергии в результате остановки цикла Кребса сопровождается клеточной дисфункцией и смертью.





Secondary metabolism

Secondary metabolism – postmortem metabolic processes. After death, the transformation of poisonous substances occurs according to a different mechanism because the enzymes of a living organism become inactive

In the postmortem period occurs :

- Irritation of poisonous substances;
- Formation of products of putreficative decomposition of tissues.



Putrefaction (a specific strong odor)

Factors affecting decomposition of bodies:

- The pH of the soil
- Activity of cellular enzymes
- Activity of bacterial enzymes
- Humidity, temperature
- Oxygen availability

Types of postmortem changes:

• <u>1. Putrefaction</u> - low oxygen availability (In the graves).



- **During the <u>putrefaction</u> of proteins**: mercaptans (organic sulfur compounds); organic acids; amines putrescine cadaverine- ptomaine are formed.
- **During the <u>putrefaction</u> of carbohydrates** organic acids, aldehydes, ketones, carbon monoxide are formed.
- **During the <u>putrefaction</u> of fats** higher alcohols that oxidize to aldehydes and acids are formed.

2. Тление (dry decay)

- The corpse is in the air at low humidity
- Occurs faster due to dehydration, insects and mold fungi.
- Less poisonous substances are formed

<u> 3. Жировоск (adipocere)</u>

Жировоск (*adipocere*) – твердая мылообразная или творожистая масса

Formation of adipocere :



4. Мумификация (mummification):

Мумификация (mummification) – complete drying of corpses.

- Dry air, high temperature and oxygen availability
- The corpse is drying up
- The volume and mass of the corpse decreases
- Brown skin similar to parchment.
- For adults the process takes 3-6 month , for newborns-3-4 weeks .
- Poisons persist for a long time

The nature of the transformation depends on the nature of the poisons:

- Organic poisons decompose faster than inorganic
- Metal ions decompose to ions with a lower oxidation number .
- Arsenic, sulfur and phosphorus to volatile compounds
- Arsenic and talium persist 8-9 years, antimony –
 5 years, mercury-a few months

Образование «трупных ядов»:

Secondary metabolism of ornithine and lysine



Secondary metabolism of tryptophan:



Secondary metabolism of phenylalanine, tyrosine, histidine:



Secondary metabolism of orotic acid:

