

Drugs' organism-internal fate and examination methods

2nd phase metabolic reactions

The reactive groups of the metabolite originating from the original drug, or from during the 1st phase metabolic transformation, along with the suitable molecules of the organism, can be conjugated, hereby compounds that are highly soluble in water (hydrophil) originate. The reaction takes place with the suitable endogenous compounds, that is glucuronic acid, glutathion, amino acid, and methyl, sulphate, or acetyl groups, which serves certain endogenous donors, and catalyzes specific enzymes.

While the 1st phase metabolic transformations don't serve unanimously inactive metabolites, up until the 2nd phase metabolic reactions, they lead to inactive conjugations, disregarding the exception of two types. The effect of the drug generally ceases during the conjugation, except for morphine-6-glucuronid forming from morphine, which is more efficient than the original compound. The second kind of exception, when the conjugation forms further, for example, with hydrolysis, results in toxic compounds. In this instance an example is isoniazid (INH) acetylation to N-acetyl-INH, which – through hydrolysis – gives isonicotinic acid and hepatotoxic acetylhydrazin.

Glucuronid conjugation

The glucuronide conjugation is possible with several groups of the parent compound or the metabolite, on the other hand, the source of glucuronid conjugation, the glucose, is available in the organism in large amounts.

The SH, NH₂, as well as the OH groups are suitable for this transformation. The UDP glucuronic acid (uridin-diphosphate-glucuronic acid) forming from UDP-glucose serves the related glucuronic acid. Different UDP-glucuronyl-transferase (UDPGT) isoenzymes catalyze the differently structured drugs' (and their metabolites) glucuronid conjugations. They have identified close to 20 human UDPGTs, and these can be connected to two gene families.

Sulphate conjugation

This is the most frequent metabolic transformation besides the glucuronid conjugation. The activated sulphate components are 3'-phosphoadenosin-5'-phosphosulphate, while the catalytic enzyme is the sulphate transferase. Sulphate conjugations are compounds that are highly soluble in water, and quickly evacuate from the organism. The sulphate transferase, that is, the sulphate conjugation, is saturable.

Amino acid conjugation

Aside from the most common glycine-conjugations, glutamine, ornithine, and taurine conjugations are also known. ATP is required for the process. On glycine-conjugation, glycine itself is the reagent, the transferase enzyme is acetyl-CoA-glycyl-transferase. Energy (ATP) is also required for the process.

Glutathion-conjugation

The glutathion (GSH) conjugation from three amino acid (Gly-Cys-Glu) takes place in microsome and in cytosome. The glutathion-S-transferase enzyme catalyzes the glutation connection, and this conjugation plays a basic role in the excretion of the reactive electrofil compounds (for example, epoxids) from the organism. The reactive compounds containing electrofile oxygen are generally side-products of the oxidative biotransformation, and are capable of reacting with nucleofile compounds, such as for example, proteins. The cells hereby suffer damage, which can lead to injuries and necrosis. The GSH then transforms the reactive oxygen containing side-products originating from the organism, by both enzymatic and non-enzymatic non-reactive metabolite. At the same time, the glutathion conjugation is a precursor for origination of the mercapturic acid (N-acetylcisteine) by-products. The origination of the GSH by-products is limited however. In such instances when the drug ends up in the organism in too high quantities (for example, acetaminophen overdose), the cells' GSH reserve is exhausted, and the reactive electrofil side-products can link covalently to the other cells' proteins, hereby causing cell damage.

Clinical importance of metabolism, problems

The most decisive step of metabolic xenobiotics and organism side-effects, in every day language „detoxication”, usually lies in the concept that as a maximum it relates to one side of the process, namely that it prompts the transformation of the by-products suitable for the elimination of the injected drugs, but does not mean the process of activation – the transformation of de-facto pro-drugs.

During the two opposing types of processes – inactivation and activation – the physical-chemical property and polarity of the drug molecules is modified, and with this possibility of their organism-internal movements is changed.

Presystemic metabolism

More commonly called the „first-pass effectus”, that is, the preventative transformation of the product taken through the mouth, during absorption, arriving into the circulation. The calculable value is the so-called absolute bio-serviceability percentage; the attainable plasma level proportion by enteralis-parenteralis ingestion. Looking at the phenomenon, long known and in experience with this consequence for the concerned drugs, their *oral dosage* is „uncertain” - it is suggested to apply the given effective agent by other ingestion methods.

Hepaticus transformation

From a clinical viewpoint the most studied area of this exceptionally complex process is also microsomic oxidation, the role of the cytochrom family, and the influence on the applied drug therapy.

Even though the different isoenzymes have characteristic – often regio- or stereoselective – specificity related to the structure of the substrate, remarkable overlaps can be found between the drug families that are the substrates of these isoenzymes.

CYP3A4/5 isoenzymes dissolve more than a half of applied drugs; benzo-diazepines, calcium channel-blockers, the statins, non-sedative antihistamines, HIV protease inhibitors, cyclosporine and the related macrolide type immune-suppressive structures, and propulsive cisapride, so that only from the point of view of the problems of the latter ones, we should mention the most important ones. By volume, the CYP 2 family and C and D base family concern few drugs, but their importance is not smaller than the former. CYP2E1 is especially interesting in the dissolving of alcohol, regarding its role played in the paracetamol metabolism, and because of the activation of carcinogen nitrosoamines. The important ascertainment in relation to these enzymes is that a small change in the protein structure of the enzyme greatly changes the activity of the enzyme, the substrate specification, that is, the drug-metabolismic effect.