

PRINCIPLES OF DRUG METABOLISM

- Metabolism is also known as biotransformation or detoxification. The process describes attenuation or loss of pharmacological activity of a drug, due to enzymatically controlled chemical activity or toxicity of the resulting metabolite. When a metabolite is more active than its original compound, then there is lethal synthesis. Metabolism makes the compound less lipid soluble and more polar and thus hydrophilic.
- The major site of drug metabolism is the liver where the microsomal enzyme systems of hepatocytes play important role. Other sites are the kidney, lung, intestinal mucosa, plasma and nervous tissue.
- The number of microsomal enzymes is influenced by factors such as drugs and hormones, age and sex of animal, stress, temperature, nutritional status and pathological state. This is what is referred to as enzyme induction and could result in increase in enzyme activity or reduced activity. The qualitative and quantitative differences in enzymes results in species differences in drug toxicity.

TYPES OF METABOLIC TRANSFORMATION

There are two phases in the metabolism of drugs:-

Phase 1 reaction. (Non synthetic phase).

This involves a change in drug molecule. It involves oxidation, reduction or hydrolysis. This may result in activation, change or inactivation of drug.

Phase II reaction. (Synthetic phase)

It involves formation of conjugates with drug or its metabolites formed in phase 1 reaction. The conjugate is formed with an endogenous substance such as carbohydrates and amino acids.

PHASE 1 REACTIONS

There are various processes by which compounds are metabolized under the phase 1 reactions

1) Oxidation reaction.

Reaction results in proton enriched products. There are two types.

A) Microsomal oxidation reactions take place mainly in the liver.

The following reactions are grouped under microsomal reactions

- (a) Oxidation of alkyl chains.** Alkyl compounds or alkyl side chains of aromatic compounds with carbonyl, aldehyde, carboxyl or amino groups undergo oxidation e.g.
 - i. ethanol is broken down to acetaldehyde then to acetic acid

ii. amines undergo deamination eg. 5HT to 5-hydroxytryptophan

b). oxidation of aromatic ring

eg acetanilide oxidation to acetaminophen.

c) Oxidative dealkylation.

This is either on an oxygen (O-dealkylation) or on a nitrogen (N-dealkylation)

O-dealkylation eg codeine → morphine

or phenacetin → acetaminophen

N-dealkylation- eg mephobarbital to phenobarbital

d) N-oxidation eg aniline oxidation to nitrobenzene

e) Sulfoxidation

The thioethers are oxidized to their corresponding sulfoxides derivatives eg chlorpromazine is oxidized to chlorpromazine sulfoxide.

B) Non microsomal oxidation reactions.

These are oxidation reactions catalyzed by enzyme in mitochondria, cytoplasmic plasma and other organelles.

2) Reduction reactions:-

Conversion of aldehydes to primary alcohols. eg chloral hydrate reduction to trichloroethanol, cyclic ketone reduction to alcohol.

eg progesterone - pregnandiol

Conversion of prontosil to sulfanilamide

3). Hydrolytic Reactions.

These reactions involve the break down of ester, linkages (c-o-c)

eg esters of choline, amide bonds, hydrazide and glycosides.

The ester bonds in atropine are broken to give tropine and tropic acid.

Cocaine is hydrolysed to benzoic acid and ecgonine methyl ester.

Procaine to p-amino acid (PABA) and diethyl amino ethanol.

Acetylcholine to acetic acid and choline.

PHASE II (SYNTHETIC REACTIONS)

- It is usually the last step in detoxification reactions and almost always results in loss of biological activity of a compound. It may be preceded by one or more of phase one reaction. The synthetic or conjugations involve chemical combination

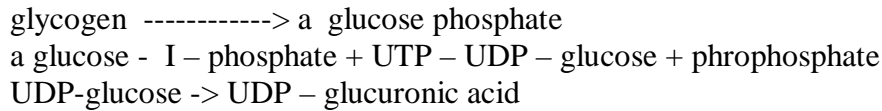
of a compound with a molecule provided by the body. The conjugating agent is usually a carbohydrate, amino acids or compounds derived from them.

- For conjugation to take place, a compound should have an appropriate group or centre eg – COOH, -OH, -NH, or –SH. A compound having none, can acquire it from the non synthetic reaction. Conjugated metabolites are in variably less lipid soluble than their parent compound.

Conjugation reactions include

a) Glucuronide Conjugation

This is the most frequently occurring conjugation. This is the conjugation of glucuronide by UDP- glucuronic acid in hepatocytes. D- glucuronic acid is derived from D- glucose in which the terminal primary alcoholic group is oxidized to carboxyl. The immediate donor of glucuronic acid for conjugation reaction is UDP- glucuronic acid which arises from breakdown to glycogen.



The glucuronide are easily secreted in urine and bile because they are highly soluble. They are broken down in the intestine by bacteria and may result in enterohepatic circulation of the drug.

Glucuronide forming capacity of cats is low.

b) Surface conjugation or ethereal sulfate formation.

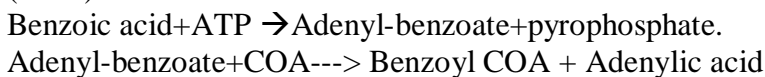
This is the transfer of sulfate groups from phosphate-adenosyl- I – phosphosulphate by sulphokinase to aliphatic or aromatic hydroxyl – containing compounds as well as amines.

Eg. Ethereal sulphates formed with hydrogen groups of phenols and catechol eg. Isoprenaline, chloramphenicol serotonin and several steroids.

c) Acylation

L-amino acids, alkyl and arylamines are combined with organic acids to form amides. In this way amines (sulfanilamide) or acids (benzoic acid, phenylacetic acid) are metabolized. The endogenous acid is usually acetic acid, the amine is glycine (in many species, glutamine (in primates only) ornithine or lysine (in birds).

Acylation involves activation of the acid by forming a derivative with co-enzyme A (COA)



The activated acid is then transferred onto the amine eg.

Salicylic acid + glycine → salicyluric acid

Phenylacetic acid + ornithine → benzoyl-ornithine

Indolylacetic acid + glutamine → indolylacetic acid glutamine.

The enzymes catalyzing these processes are in the mitochondria of the liver and the kidney.

d. Alkylation

The transfer of alkyl (methyl or ethyl) groups occurs via active methionine (s-adenosyl methionine) or ethionine (s-adenosyl ethionine) to an N or O group on the compound.

Eg N-alkylation – conversion of nicotinamide to N – methylnicotinamide;
Histamine to N-CH₃ histamine.

O-alkylation

Phenolic steroids (estradiol) and other hormones (thyroxine) and catecholamine are O – methylated.

Factors Affecting Drug Metabolism

1. Species differences eg in phenylbutazone, procaine and barbiturates.
2. Genetic differences – variation exist with species in drug metabolism.
3. Age of animal – drug metabolism is usually feeble in the fetus and in the newborn. The microsomal drug enzyme and conjugating enzymes are less active here.
4. Sex – these differences are under the influence of sex hormones.
5. Nutrition – starvation and malnutrition depress drug metabolism.
6. Pathological conditions: damage to the liver reduces drug metabolism since it's the major site of drug metabolism.

The First-pass effect

Drugs absorbed from the intestine into the portal circulation are exposed to drug metabolism before they get into systemic circulation. When large proportion of the drug is metabolized as a result of this, it is said to be subject to first pass effect.