Drug metabolism

Why is drug metabolism important for counselors and psychologists??

I. Definition:
- Drug metabolism is the process by which the body breaks down and converts medication into active chemical substances.
- Most drug metabolism occurs in the liver, although some processes occur in the gut wall, lungs and blood plasma.
- Only a few drugs can be excreted without being metabolized first

II. Pathways:
- The liver hepatocytes contain all the necessary enzymes for the metabolism of drugs. The main enzymes involved in metabolism belong to the cytochrome P450 group. These are a large family of related enzymes housed in the smooth endoplasmic reticulum of the cell.
- Metabolism is often divided into two phases of biochemical reaction - phase 1 and phase 2. Some drugs may undergo just phase 1 or just phase 2 metabolism, but more often, the drug will undergo phase 1 and then phase 2 sequentially.
- Let's look at aspirin as example of a drug being metabolized. Aspirin undergoes phase 1 hydrolysis to salicylic acid. In phase 2 it is conjugated with either glycine or glucuronic acid forming a range of ionized metabolites that can then be excreted in the urine.

1. Phase 1:
- Phase 1 metabolism can involve reduction or hydrolysis of the drug, but the most common biochemical process that occurs is oxidation. (Oxidation is the chemical reaction that occurs
when apples turn brown when exposed to the oxygen in air).
- Oxidation is catalysed by cytochrome P450 enzymes and results in the loss of electrons from the drug (electrons are negatively charged subatomic particles).
- The drug is now said to be oxidized and after phase 1 reactions, the resulting drug metabolite is still often chemically active.

a. Oxidation:

- Oxidation is the addition of oxygen and/or the removal of hydrogen. Most oxidation steps occur in the endoplasmic reticulum. The most important enzymes: microsomal CYP-450.
- Outside the microsomes - in liver and brain
- Alcohol dehydrogenase - in liver, kidney, lung.
- Ex: phenobarbitol.

b. Reductation:
- Add a hydrogen or remove oxygen.
- nitrazepam

c. Hydrolysis:
- Addition of water with breakdown of molecule. In blood plasma (esterases) and liver.
- Esters ---> alcohol and acid:
  - aspirin to salicylic acid.
  - Amides to amine and acid.

2. Phage 2:
- Phase 2 metabolism involves conjugation - that is, the attachment of an ionized group to the drug. These groups include glutathione, methyl or acetyl groups. These metabolic processes usually occur in the hepatocyte cytoplasm.
- The attachment of an ionized group makes the metabolite more water soluble. This facilitates excretion as well as decreasing pharmacological activity.

a. Methylation: morphine, paracetamol
b. Sulphation: nicotinic acid
c. Acetylation: sulfonamides
d. Glucuronidation: This is the main conjugation reaction in the body. This occurs in the liver. Natural substrates are bilirubin and thyroxine. Aliphatic alcohols and phenols are commonly conjugated with glucuronide. Thus hydroxylated metabolites can also be conjugated for example morphine

III. Example:
- Some drugs are administered in an inactive form called a pro-drug, like enalapril, It is the metabolite that is pharmacologically active, enalaprilat in this case, which acts as an antihypertensive agent.
- Some drug metabolites can be toxic such as those produced from paracetamol. These are are detoxified by phase 2 conjugation joining with glutathione.
- However, in an overdose situation where the dose of paracetamol is high, there is not enough glutathione to detoxify the metabolites. They accumulate causing toxicity and can result in hepatitis. As a solution, compounds are administration to boost the levels of glutathione so that
Phase 2 metabolism can take place, thus detoxifying the paracetamol metabolites fully and reducing the risk of liver injury.

**IV. Factor:**
+Race
• Age – new born jaundice: kernicterus
• Sex - hormonal
• Species - genetic differences: man, monkey
• Clinical or physiological condition
• Other drug administration
• Food: protein, carbohydrate, fat, charcoal grilled meat
• First-pass (pre-systemic) metabolism
• Enzyme induction, inhibition
• Pregnancy, Disease states
• Circadian rhythm, Substrate stereoselectivity, Pharmacologically active metabolites