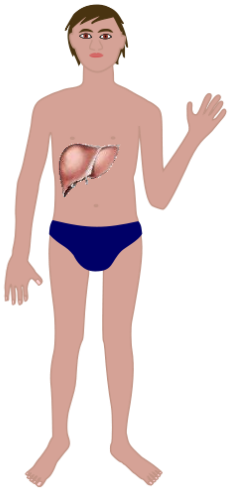
A central aspect of pharmacokinetics (what the body does to a drug) is drug metabolism, defined as the process by which drugs are altered to facilitate their removal from the body. Ultimately, the body needs to find a way to get rid of the chemical that was just put into it.



Goal of drug metabolism: Inactivate and make drugs water soluble so they leave the body.

Drug metabolism is mostly enzyme-mediated. This means that it does not happen spontaneously – there are proteins in the body that process the drug and facilitate removal. Drug metabolism occurs primarily (but not exclusively) in the liver. It also occurs in target organs (where the drug is affecting the body) such as the lungs, kidney, and the heart. Usually, metabolism inactivates the drug so that it can be removed from the body. But, there are instances when metabolism can convert the drug to a more active form. When this occurs, the drug is said to be a pro-drug and the metabolite is called an active metabolite.

There can be **considerable variation** between individuals' ability to metabolize drugs. This can be due to many factors including the presence of other drugs, certain foods, or dietary supplements, genetics, age, disease conditions, and environmental conditions.

There are two general phases of drug metabolism: phase 1 and phase 2. Phase 1 introduces reactive and polar functional groups onto the drugs. The enzymes involved in phase 1 metabolism include **cytochrome P450 enzymes (CYPs),** monoamine oxidases, alcohol and aldehyde dehydrogenases, and several others. Phase 2 enzymes conjugate those reactive and polar groups with groups that increase solubility (things that are easy to get out of the body). The groups include **glucuronide**, glutathione, glycine, sulfate, acetate, and methyl. Once this group is on the drug, it is very water soluble, and gets easily shuttled into the urine and passed out of the body. Phase 1 metabolism by CYPs and phase 2 conjugation to a glucuronide is one of the most common drug-metabolism combinations.

There are many drugs that alter the normal action of drug metabolizing enzymes. Some drugs **induce** CYPs. This is typically due to the production of the new protein (drug metabolizing enzyme). When there is more drug metabolizing present, the metabolism of all drugs by that enzyme will be increased and you will get a reduced (or no effect) from the drug. St. John's Wort is an example of a dietary supplement that induces CYP3A4. When St. John's Wort is taken together with some prescription medications (amitriptyline, cyclosporine, digoxin, fexofenadine, indinavir, methadone, midazolam, nevirapine, simvastatin, theophylline, warfarin, and some oral contraceptives to name a few), there can be decreased blood concentrations of medications. Conversely, some drugs **inhibit** CYPs. This is the cause of many drug interactions and adverse effects. When an enzyme is inhibited, it is essentially blocked from working and cannot metabolize anything. This will cause a buildup of drugs in the body and eventual toxicity. An example of this is grapefruit juice, or more specifically, a compound in grapefruit juice called dihydroxybergamottin. Dihydroxybergamottin inhibits CYP3A4 and renders it unable to metabolize anything effectively.

Next time, we will explore a pharmacodynamic term: dose-response. Stay tuned!

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