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**ASSIGNMENT**

**Factors affecting drug metabolism**

Drug metabolism is the [metabolic breakdown](https://en.m.wikipedia.org/wiki/Metabolism) of [drugs](https://en.m.wikipedia.org/wiki/Drug) by living [organisms](https://en.m.wikipedia.org/wiki/Organism), usually through specialized [enzymatic](https://en.m.wikipedia.org/wiki/Enzyme) systems. More generally, xenobiotic metabolism (from the Greek [xenos](https://en.m.wikipedia.org/wiki/Xenos_%28Greek%29) "stranger" and biotic "related to living beings") is the set of [metabolic pathways](https://en.m.wikipedia.org/wiki/Metabolic_pathway) that modify the chemical structure of [xenobiotics](https://en.m.wikipedia.org/wiki/Xenobiotic), which are compounds foreign to an organism's normal biochemistry, such as any [drug](https://en.m.wikipedia.org/wiki/Drug) or [poison](https://en.m.wikipedia.org/wiki/Poison).

The rate of metabolism of pharmaceutical drugs determines the duration and intensity of a drug's pharmacologic action. Drug metabolism also affects [multidrug resistance](https://en.m.wikipedia.org/wiki/Multidrug_resistance) in [infectious diseases](https://en.m.wikipedia.org/wiki/Infectious_disease) and in [chemotherapy](https://en.m.wikipedia.org/wiki/Chemotherapy) for [cancer](https://en.m.wikipedia.org/wiki/Cancer), and the actions of some drugs as [substrates](https://en.m.wikipedia.org/wiki/Substrate_%28chemistry%29) or [inhibitors](https://en.m.wikipedia.org/wiki/Enzyme_inhibitor) of enzymes involved in xenobiotic metabolism are a common reason for hazardous [drug interactions](https://en.m.wikipedia.org/wiki/Drug_interaction).

A large number of drugs are metabolized by hepatic phase I and II reactions.

**Phase I metabolism**occurs in the [endoplasmic reticulum](https://www.sciencedirect.com/topics/medicine-and-dentistry/endoplasmic-reticulum) and involves the formation of more polar metabolites of the original compound. These reactions can involve oxidation (catalysed by [cytochrome P450](https://www.sciencedirect.com/topics/medicine-and-dentistry/cytochrome-p450) enzymes), hydrolysis, reduction, cyclization or decyclization. The polar metabolites may be directly excreted, usually in the urine, or may be converted further by phase II reactions.

**Phase II reactions**occur in the [cytoplasm](https://www.sciencedirect.com/topics/medicine-and-dentistry/cytoplasm) and commonly involve [conjugation](https://www.sciencedirect.com/topics/medicine-and-dentistry/conjugation) with sulphates, [glucuronides](https://www.sciencedirect.com/topics/medicine-and-dentistry/glucuronide), [glutathione](https://www.sciencedirect.com/topics/medicine-and-dentistry/glutathione) or amino acids and result in the formation of metabolites that are usually less toxic and more easily excreted.

The metabolism of a drug can be affected by [enzyme induction](https://www.sciencedirect.com/topics/medicine-and-dentistry/enzyme-induction), [protein binding](https://www.sciencedirect.com/topics/medicine-and-dentistry/protein-binding) and the liver extraction ratio.

Drug metabolism often converts lipophilic compounds into hydrophilic products that are more readily excreted.

**Factors affecting drug metabolism**

**Nature of the drug:** The duration and intensity of pharmacological action of most lipophilic drugs are determined by the rate they are metabolized to inactive products. In general, anything that increases the rate of metabolism (*e.g.*, [enzyme induction](https://en.m.wikipedia.org/wiki/Enzyme_induction_and_inhibition)) of a pharmacologically active metabolite will decrease the duration and intensity of the drug action. The opposite is also true (e.g. [enzyme inhibition](https://en.m.wikipedia.org/wiki/Enzyme_induction_and_inhibition)). However, in cases where an enzyme is responsible for metabolizing a pro-drug into a drug, enzyme induction can speed up this conversion and increase drug levels, potentially causing toxicity.

**Physiological and pathological factors:** Physiological and pathological factors can also affect drug metabolism. Physiological factors that can influence drug metabolism include age, individual variation ( e.g. pharmacogenetics), enterohepatic circulation, nutrition, intestinal flora, or sex differences in general, drugs are metabolized more slowly in fetal, neonatal and elderly humans and animals than in adults.

Pathological factors can also influence drug metabolism, including [liver](https://en.m.wikipedia.org/wiki/Liver), [kidney](https://en.m.wikipedia.org/wiki/Kidney), or [heart](https://en.m.wikipedia.org/wiki/Heart) diseases.

**Genetic factors:** ([polymorphism](https://en.m.wikipedia.org/wiki/Polymorphism_%28biology%29)) accounts for some of the variability in the effect of drugs. With N-acetyltransferases (involved in Phase II reactions), individual variation creates a group of people who acetylate slowly (slow acetylators) and those who acetylate quickly. This variation may have dramatic consequences, as the [slow acetylators](https://en.m.wikipedia.org/w/index.php?title=Slow_acetylators&action=edit&redlink=1) are more prone to dose-dependent toxicity.

Dose, frequency, route of administration, tissue distribution and protein binding of the drug affect its metabolism.

**Resistance and tolerance:**

**Tolerance** is a decrease in response to a drug that is used repeatedly. Resistance is development of the ability to withstand the previously destructive effect of a drug by microorganisms or tumor cells.

Examples of drugs that result in tolerance include alcohol and opioids. One mechanism responsible for tolerance is accelerated metabolism, for example, by induction of hepatic enzymes such as the [cytochrome P-450 system enzymes](https://www.msdmanuals.com/professional/clinical-pharmacology/pharmacokinetics/drug-metabolism). Generally, tolerance leads to increasing doses of a drug being required to produce the same effect. Other possible mechanisms are a decrease in binding affinity between a drug and receptor and a decrease in the number of receptors. The mechanisms responsible for drug tolerance are not always known.

Examples of resistance include the following:

* Strains of microorganisms are resistant when they are no longer killed or inhibited by previously effective antimicrobial drugs. The mechanism begins with a genetic change resulting from a mutation or gene acquisition. Because the previously effective antimicrobial drug preferentially eliminates nonresistant organisms, the resistant organisms become the predominant species.
* Tumors can become resistant if a mutation develops that confers resistance to an anticancer drug and that anticancer drug is used repeatedly, preferentially eliminating nonresistant tumor cells. For example, many patients with chronic myeloid leukemia have become resistant to the tyrosine kinase inhibitor  because of the presence of the *T315I* mutation.
* Corticosteroid resistance can affect the treatment of a number of disorders such as asthma or inflammatory bowel disease. The mechanism of this type of resistance is not fully understood but may involve a number of different factors (e.g., infection, oxidative stress, allergen exposure, inflammation, deficient vitamin D3, genetic mutations or variations).