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Factors and Barriers that Affect Drug Metabolism

Nitin Pandey*

Department of Clinical Embryology, Kasturba Medical College, Manipal, Karnataka, India

Perspective

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For Correspondence: Nitin Pandey, Department of Clinical Embryology, Kasturba Medical College, Manipal, Karnataka, India
E-mail: Pandey@gmail.com

DESCRIPTION

The metabolic breakdown of pharmaceuticals by living organisms, usually through specialised enzyme systems, is known as drug metabolism. Xenobiotic metabolism (from the Greek xenos "alien" and biotic "associated to living creatures") refers to the metabolic pathways that change the chemical structure of xenobiotics, which are molecules that are foreign to an organism's normal biochemistry, such as any medicine or poison. These biotransformation routes are found in all major groupings of organisms and are thought to be of ancient origin. These reactions are frequently used to cleanse hazardous substances (although in some cases the intermediates in xenobiotic metabolism can themselves cause toxic effects).

Pharmaceutical drug metabolism is an important part of pharmacology and medicine. The duration and strength of a drug's pharmacologic action, are determined by its rate of metabolism. Multidrug resistance in infectious diseases and cancer chemotherapy is influenced by drug metabolism, and the actions of some medications as substrates or inhibitors of xenobiotic metabolism enzymes are a major cause of dangerous drug interactions. These pathways are especially essential in environmental research, because microorganisms' xenobiotic metabolism determines whether a pollutant is broken down during bioremediation or persists in the environment. Xenobiotic metabolism enzymes, notably glutathione S-transferases, are extremely significant in agriculture because they can cause pesticide and herbicide resistance.

There are three stages to drug metabolism. Enzymes like cytochrome P450 oxidases incorporate reactive or polar groups into xenobiotics during phase I. In phase II processes, these changed molecules are conjugated to polar compounds. Transferase enzymes, such as glutathione S-transferases, catalyse these processes. Finally, the conjugated xenobiotics may be processed further in phase III before being recognised by efflux transporters and pumped out of the cells. Lipophilic substances are frequently converted into hydrophilic metabolites, which are more easily eliminated, during drug metabolism.

The exact compounds to which an organism is exposed will be largely unpredictable, and may vary significantly over time; these are major characteristics of xenobiotic toxic stress. The major challenge confronting xenobiotic detoxification systems is that they must be able to remove an almost infinite number of xenobiotic compounds from the complex mixture of chemicals involved in normal metabolism. An innovative mix of physical barriers and low-specificity enzymatic systems has evolved as a solution to this problem.

To limit access to their internal environment, all organisms use cell membranes as hydrophobic permeability barriers. The uptake of useful molecules is mediated by transport proteins that specifically select substrates from the extracellular mixture. Polar compounds cannot diffuse across these cell membranes, so the uptake of useful molecules is mediated by transport proteins that specifically select substrates from the extracellular mixture. Because most hydrophilic compounds are not recognised by any specialised transporters, this selective absorption prevents them from entering cells. Hydrophobic substances, on the other hand, cannot be controlled as they pass through these barriers, therefore organisms cannot use membrane barriers to keep lipid-soluble xenobiotics out.

The presence of a permeability barrier, on the other hand, suggests that organisms have evolved detoxification systems that take advantage of the hydrophobicity seen in membrane-permeable xenobiotics. As a result, these systems overcome the challenge of specificity by having such broad substrate specificities that they can metabolise practically any non-polar molecule. Because useful metabolites are polar and generally contain one or more charged groups, they are omitted.

Because these species are formed from regular cellular constituents and usually share their polar features, the mechanisms indicated above cannot detoxify the reactive by-products of normal metabolism. Due of the small amount of these molecules, specialised enzymes can detect and eliminate them. The glyoxalase system, which eliminates the reactive aldehyde methylglyoxal, and the different antioxidant systems that eliminate reactive oxygen species are examples of these particular detoxification mechanisms.

Drug metabolism can be influenced by a variety of physiological and pathological variables. Age, individual variation (e.g., pharmacogenetics), enterohepatic circulation, diet, and other physiological factors can all affect drug metabolism. In general, prenatal, neonatal, and geriatric humans and animals absorb medications more slowly than adults. Some of the diversity in pharmacological action is due to genetic variation (polymorphism). Individual diversity in N-acetyltransferases (engaged in Phase II processes) provides a group of people who acetylate slowly (slow acetylators) and those who acetylate quickly (quick acetylators), split around 50:50 in the Canadian population. Because slow acetylators are more prone to dose-dependent toxicity, this variation could have significant effects. Individuals' cytochrome P450 monooxygenase system enzymes can also differ, with impairments affecting 1%–30% of people depending on their ethnic origin.

The drug's metabolism is influenced by its dose, frequency and methods of administration, tissue distribution, and protein binding. Drug metabolism can also be influenced by pathological conditions such as liver, renal, or cardiac disease. Drug metabolism can be anticipated in virtual patient populations using *in silico* modelling and simulation methodologies before clinical trials in humans. This can be used to identify people who are most likely to have an unpleasant reaction.