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QUESTION

Discuss in details the factors affecting drug metabolism.

ANSWER

Drug metabolism is the metabolic breakdown of drugs by living organisms, usually through specialized enzymatic systems. More generally, xenobiotic metabolism is the set of metabolic pathways that modify the chemical structure of xenobiotics, which are compounds foreign to an organism’s normal biochemistry, such as any drug or poison. These pathways are form of biotransformation present in all major groups of organisms, and are considered to be ancient origin.

FACTORS AFFECTING DRUG METABOLISM

The duration and intensity of pharmacological action of most lipophilic drugs are determined by the rate they are metabolized to inactive products. The cytochrome P450 monooxygenase system is the most important pathway in this regards. In general, anything that increases the rate of metabolism of a pharmacologically active metabolite will decrease the duration and intensity of the drug action. The opposite is also true. However, in case 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. Various physiological and pathological factors can also affect drug metabolism. Physiological factors that can influence drug metabolism includes age, individual variation (e.g. pharmacogenetics), sex, intestinal flora etc. in general, drugs are metabolized more slowly in fetal, neonatal and elderly humans and animals than in adults. Genetic variation 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 and those who acetylate slowly and those who acetylate quickly, split roughly 50:50 in the population of Canada. This variation may have dramatic consequences, as the slow acetylators are more prone to dose dependent toxicity. Cytochrome P450 monooxygenase system enzymes can also vary across individuals, with deficiencies occurring in 1-30% of people, depending on their ethnic background.

Pathological factors can also influence drug metabolism, including liver, kidney or heart diseases. In silico modeling and simulation methods allow drug metabolism to be predicted in virtual patient populations prior to performing clinical studies in human subjects. This can be used to identify individuals most at risk from adverse reaction.