**BIOCHEMISTRY: XENOBIOTICS**

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**Assignment: Discuss in details the factors affecting drug metabolism.**

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 a form of biotransformation present in all major groups of organisms. These reactions often act to detoxify poisonous compounds and make them more polar for excretion.

**FACTORS AFFECTING DRUG METABOLISM**

1. **Internal factors:**
2. Species
3. Diseases
4. Sex
5. Hormones
6. Genetics
7. Age
8. **External factors**
9. Diet
10. Epigenetics (Environment)

**INTERNAL FACTORS**

1. **Species**: Examples of species differences in drug biotransformation are numerous, continuously investigated, and encountered in both phases of biotransformation. An interesting observation is that they may involve the same route, but differ in the rate along that particular pathway (i.e. quantitatively different) or they may adopt different pathways. It should be noted as well that there is not always a direct relationship between metabolism, half-life and action of a drug. Selected examples. An interesting quantitative species difference in phase I metabolism is known for caffeine, both in terms of total metabolism and metabolite production. Thus, the total metabolism is highest in humans, decreasing in the order - monkey, rat and rabbit. While there are no significant differences in the formation of theobromine, marked differences have been recorded for the other two metabolites, paraxanthine and theophylline, with paraxanthine formation highest in humans and lowest in monkey, whereas the reverse obtains for theophylline.

 An interesting aspect is the way caffeine biotransformation reactions proceed in higher plants, the variability of caffeine catabolism again being dependent on species and to a greater extent, on the age of different tissues investigated. As an example, it was reported that in young tea leaves, theophylline is re-utilized for caffeine biosynthesis, while in aged leaves of Coffea arabica, it undergoes further metabolism resulting in 7-methylxanthine accumulation. Other species of Coffea have been proven to convert caffeine to methyluric acids. Obviously, these cases exemplify qualitative differences, as well as species- and age-dependence.

1. **Diseases:** Drug metabolism is a highly complex process involving the cooperative function of drug transporter proteins and drug-conjugating and -metabolizing enzymes, as well as targeted programs of gene activation and the proteasomal degradation pathway. The transport and metabolism of drugs in intestine and liver mediates the systemic delivery of therapeutic compounds, protects the body from drug toxicity, and initiates droves of signaling cascades that collectively work to maintain the body’s homeostatic conditions. The multifaceted nature of drug homeostasis requires a high level of regulation on multiple levels, and thus a disturbance in homeostatic conditions can have major detrimental effects on patient health. There are several disease states (inflammation/diabetes/morbid obesity/cancer) that can profoundly alter key drug transport and/or drug metabolic pathways in liver and intestine.

The liver and intestine are the primary sites of drug metabolism in the body and therefore disease states that alter hepatic and intestinal regulatory pathways are potentially lethal. Nuclear receptor proteins (NRs) are the primary regulators of the expression of genes encoding drug metabolizing enzymes and several key drug transporter proteins.

1. **Sex:** On average, men are larger than women. Body size differences results in larger distribution volumes and faster total clearance of most medications in men compared to women. Greater body fat in women (until older ages) may increase distribution volumes for lipophilic drugs in women. Total drug absorption does not appear to be significantly affected by sex although absorption rates may be slightly slower in women. Bioavailability after oral drug dosing, for CYP3A substrates in particular, may be somewhat higher in women compared to men. Bioavailability after transdermal drug administration does not appear to be significantly affected by gender; nor does protein binding. Renal processes of glomerular filtration, tubular secretion, and tubular reabsorption appear to be faster in men compared to women whether considered on a mg/kg basis or total body weight basis. Algorithms to estimate glomerular filtration rate incorporate sex as a factor; some also include weight. For hepatic processes, drugs metabolized by Phase I metabolism (oxidation, reduction, and hydrolysis via cytochrome P450's 1A, 2D6, 2E1), Phase II conjugative metabolism (glucuronidation, conjugation, glucuronyltransferases, methyltransferases, dehydrogenases) and by combined oxidative and conjugation processes are usually cleared faster in men compared to women (mg/kg basis). Metabolism by CYP2C9, CYP2C19, and N-acetyltransferase, appear to be similar in men and women (mg/kg). Clearance of p-glycoprotein substrates appear to be similar in men and women. In contrast, total clearance of a number of CYP3A substrates appear to be mildly or moderately faster (mg/kg) in women compared to men. The clinical significance of reported differences warrants consideration.
2. **Hormones:** The term "hormone" is used in its broad sense and includes products of the major endocrine glands (i.e., thyroid, adrenals, gonads, and pancreas) and compounds that are not classically considered hormones, such as neurogenic amines, cytokines, interleukins, and eicosanoids. In addition, we comment on the effects on CYP expression of states associated with profound hormonal changes, such as pregnancy, malnutrition, obesity, diabetes mellitus, systemic inflammation, and conditions of altered extracellular fluid volume or osmolality. Available data are limited and are derived primarily from in vitro and animal studies. Moreover, the picture is obscured by conflicting results among studies and the complexity of the regulation of the expression and activity of elements of the CYP system. While the clinical significance of hormonal effects on the CYP system remains to be determined, we anticipate that such effects will be most pertinent to drugs with a narrow therapeutic range. Further research is needed to determine the scope and significance of these effects in view of rapid advances in the field of pharmacogenomics and the ever-increasing number of drugs available for therapeutic use.
3. **Genetics:** The study of genetic variations in drug response is called pharmacogenetics when studying an individual gene, or pharmacogenomics when studying all genes. A person's genotype is his or her genetic makeup. The term can pertain to all genes or to a specific gene. The phenotype is a person's outward physical appearance or function resulting from the interaction between the genotype and the environment. Genetic polymorphisms are naturally occurring variants in gene structure that occur in more than 1 percent of the population. Polymorphisms may influence a drug's action by changing its pharmacokinetics or its pharmacodynamics.
4. **Age:** With aging, there are changes in all these areas; some changes are more clinically relevant. The metabolism and excretion of many drugs decrease, requiring that doses of some drugs be decreased. Toxicity may develop slowly because concentrations of chronically used drugs increase for 5 to 6 half-lives, until a steady state is achieved. For example, certain benzodiazepines (diazepam, flurazepam, chlordiazepoxide), or their active metabolites, have half-lives of up to 96 h in older patients; signs of toxicity may not appear until days or weeks after therapy is started.

Despite an age-related decrease in small-bowel surface area, slowed gastric emptying, and an increase in gastric pH, changes in drug absorption tend to be clinically inconsequential for most drugs. One clinically relevant exception is calcium carbonate, which requires an acidic environment for optimal absorption. Thus, increases in gastric pH—which may be age-related (such as with atrophic gastritis) or drug-related (such as with proton pump inhibitors)—can decrease calcium absorption and increase the risk of constipation. Thus, older adults should use a calcium salt (e.g., calcium citrate) that dissolves more easily in a less acidic environment. Another example of altered absorption with increased gastric pH is early release of enteric-coated dosage forms (e.g., enteric-coated aspirin, enteric-coated erythromycin), increasing the risk of GI adverse effects.

**EXTERNAL FACTORS**

1. **Diet**: Foods can enhance, delay, or decrease drug absorption. Foods impair absorption of many antibiotics. They can alter metabolism of drugs; eg, high-protein diets can accelerate metabolism of certain drugs by stimulating cytochrome P-450. Eating grapefruit can inhibit cytochrome P-450 34A, slowing metabolism of some drugs (eg, amiodarone, carbamazepine, cyclosporine, certain Ca channel blockers). Diets that alter the bacterial flora may markedly affect the overall metabolism of certain drugs. Some foods affect the body’s response to drugs. For example, tyramine, a component of cheese and a potent vasoconstrictor, can cause hypertensive crisis in some patients who take monoamine oxidase inhibitors and eat cheese.

Nutritional deficiencies can affect drug absorption and metabolism. Severe energy and protein deficiencies reduce enzyme tissue concentrations and may impair the response to drugs by reducing absorption or protein binding and causing liver dysfunction. Changes in the GI tract can impair absorption and affect the response to a drug. Deficiency of Ca, Mg, or zinc may impair drug metabolism. Vitamin C deficiency decreases activity of drug-metabolizing enzymes, especially in the elderly.

Many drugs affect appetite, food absorption, and tissue metabolism (see Table: Effects of Some Drugs on Nutrition). Some drugs (e.g., metoclopramide) increase GI motility, decreasing food absorption. Other drugs (e.g., opioids, anticholinergics) decrease GI motility. Some drugs are better tolerated if taken with food.

Certain drugs affect mineral metabolism. For example, diuretics, especially thiazides, and corticosteroids can deplete body K, increasing susceptibility to digoxin-induced cardiac arrhythmias. Repeated use of laxatives may deplete K. Cortisol, desoxycorticosterone, and aldosterone cause marked Na and water retention, at least temporarily; retention is much less with prednisone, prednisolone, and some other corticosteroid analogs. Sulfonylureas and lithium can impair the uptake or release of iodine by the thyroid. Oral contraceptives can lower blood zinc levels and increase copper levels. Certain antibiotics (e.g., tetracycline) reduce iron absorption, as can certain foods (e.g., vegetables, tea, and bran).

1. **Environment:** Although various kinds of environmental factors may alter the activity of cytochrome P-450 enzymes in liver micromes, their effects on the pharmacokinetics of drugs and other foreign compounds in living animals may not be as great as might be predicted from assays of these enzymes in vitro. Indeed, the effects will depend on the relative importance of excretory and metabolic mechanisms in the elimination of the drug, the relative importance of various metabolic reactions in different tissues, the extraction ratio of the drug by the liver, and in some instances on the route of administration of the drug. Moreover, the effect of the various environmental factors on the pharmacologic and the toxicological actions of the drug will depend on whether these actions are caused by the parent foreign compounds or by one or more of their metabolites. It may also be important that the environmental factors may alter not only relative activities of the cytochrome P-450 in liver microsomes but also the activities of other drug-metabolizing enzymes and that the relative effects of the environmental factors of these enzymes may differ depending on the animal species or the animal strain. Indeed, a given factor may increase the pharmacologic effects of a drug metabolite in one animal species but decrease it in another. For these reasons, it frequently is not possible to predict the effects of environmental factors on drug action in living animals solely from in vitro rates of metabolism of model substrates.