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Matric. number: 17/mhs01/164

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Course: Medical Biochemistry

Discuss in details the factors affecting drug metabolism

Drugs can be metabolised by many different pathways and many factors can determine which pathway is used by which drug and to what extent a particular drug is biotransformed by a particular pathway. These factors range from the species of organism studied to the environment in which that organism lives. In order to discuss this topic, the factors affecting drug metabolism will be split into internal (i.e. physiological and pathological) factors (discussed in this chapter) and external factors (i.e. diet and environment). These are, of course, purely arbitrary divisions and much interaction exists between the various factors (cf. hormonal, sex and age influences)- such interactions will be pointed out where they are important. The factors discussed here are also not an exhaustive list and other factors that play a role in controlling drug biotransformation will be found in the Further Reading section at the end of chapter 5. The factors to be discussed here are: internal • species • genetic (strain) • age • sex • hormones • disease and external • diet • environment

**Species differences**: The metabolism of many drugs and foreign compounds is often species dependent. Different animal species may biotransform a particular xenobiotic by similar or markedly different metabolic pathways. Even within the same species, individual variations (strain differences) may result in significant differences in a specific metabolic pathway.493,494 This is a problem when a new drug is under development. A new drug application requires the developer to account for the product as it moves from the site of administration to final elimination from the body. It is difficult enough to find appropriate animal models for a disease. It is even harder to find animal models that mimic human drug metabolism.

Species variation has been observed in many oxidative biotransformation reactions. For example, metabolism of amphetamine occurs by two main pathways: oxidative deamina-tion or aromatic hydroxylation. In human, rabbit, and guinea pig, oxidative deamination appears to be the predominant pathway; in the rat, aromatic hydroxylation appears to be the more important route.495 Phenytoin is another drug that shows marked species differences in metabolism. In the human, phenytoin undergoes aromatic oxidation to yield primarily GS)(-)-p-hydroxyphenytoin; in the dog, oxidation occurs to give mainly (R)(+)-m-hydroxyphenytoin.496 There is a dramatic difference not only in the position (i.e., meta or para) of aromatic hydroxylation but also in which of the two phenyl rings (at C-5 of phenytoin) undergoes aromatic oxidation.

Species differences in many conjugation reactions also have been observed. Often, these differences are caused by the presence or absence of transferase enzymes involved in the conjugative process. For example, [cats](https://www.pharmacologicalsciences.us/cats.html) lack glu-curonyltransferase enzymes and, therefore, tend to conjugate phenolic xenobiotics by sulfation instead.497 In pigs, the situation is reversed: pigs are not able to conjugate phenols with sulfate (because of lack of sulfotransferase enzymes) but appear to have good glucuronidation capability.497 The conjugation of aromatic acids with amino acids (e.g., glycine, glutamine) depends on the animal species as well as on the substrate. For example, [glycine conjugation](https://www.pharmacologicalsciences.us/pharmaceutical-chemistry/info-xub.html%22%20%5Co%20%22Drug%20Sulfate%20Conjugation%20Pharmaceutical%20Chemistry) is a common conjugation pathway for benzoic acid in many animals. In certain birds (e.g., duck, goose, turkey), however, glycine is replaced by the amino acid ornithine.

**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.

**Age:** Age-related differences in drug metabolism are generally quite apparent in the newborn.487,488 In most fetal and newborn animals, undeveloped or deficient oxidative and conjugative enzymes are chiefly responsible for the reduced metabolic capability seen. In general, the ability to carry out metabolic reactions increases rapidly after birth and approaches adult levels in about 1 to 2 months. An illustration of the influence of age on drug metabolism is seen in the duration of action (sleep time) of hexobarbital in newborn and adult mice.489 When given a dose of 10 mg/kg of body weight, the newborn mouse sleeps more than 6 hours. In contrast, the adult mouse sleeps for fewer than 5 minutes when given the same dose.

In humans, oxidative and conjugative (e.g., glucuronida-tion) capabilities of newborns are also low compared with those of adults. For example, the oxidative (CYP) metabolism of tolbutamide appears to be markedly lower in newborns.490 Compared with the half-life of 8 hours in adults, the plasma half-life of tolbutamide in infants is more than 40 hours. As discussed previously, infants possess poor glucuronidating ability because of a deficiency in glucuronyltransferase activity. The inability of infants to conjugate chloramphenicol with glucuronic acid appears to be responsible for the accumulation of toxic levels of this antibiotic, resulting in the so-called gray baby syndrome.388 Similarly, neonatal hyperbilirubin-emia (or kernicterus) results from the inability of newborn babies to glucuronidate bilirubin.387

The effect of old age on drug metabolism has not been as well studied. There is some evidence in animals and humans that drug metabolism diminishes with old age.491,492 Much of the evidence, however, is based on prolonged plasma half-lives of drugs that are metabolized totally or mainly by hepatic microsomal enzymes (e.g., antipyrine, phenobarbital, acetaminophen). In evaluating the effect of age on drug metabolism, one must differentiate between "normal" loss of enzymatic activity with aging and the effect of a diseased liver from [hepatitis](https://www.pharmacologicalsciences.us/hepatitis.html), [cirrhosis](https://www.pharmacologicalsciences.us/cirrhosis.html), etc., plus decreased renal function, because much of the water-soluble conjugation products are excreted in the liver.

**Genetic:** Genetic variation ([polymorphism](https://en.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, split roughly 50:50 in the population of [Canada](https://en.wikipedia.org/wiki/Canada). This variation may have dramatic consequences, as the [slow acetylators](https://en.wikipedia.org/w/index.php?title=Slow_acetylators&action=edit&redlink=1) are more prone to dose-dependent toxicity.

Environment: although various kindsof environmental factors may alter the activity of cytochrome P450 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 enzymes in vitro. The effect of various environmental factors on the pharmacologic and the toxicologic actions are caused by the parent foreign compounds or by one or more metabolites. It may also be Important that the environmental factors may alter not only relative activities of the cytochrome P450 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 strain. A given factor may increase the pharmacologic effects of drug metabolite in one animal species but decrease it in another.

**Sex:** Sex is the property or quality by which organisms are classified as female or male on the basis of their reproductive organs and functions, while gender is expressed in terms of masculinity and femininity. It is how people perceive themselves and how they expect others to behave, and is largely culturally determined.

As our knowledge of medicinal drug toxicology and pharmacology is expanding it has become clear that men and women differ in response to drug treatment. Women also differ from men in response to occupational exposures[[2](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3644551/%22%20%5Cl%20%22R2),[3](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3644551/#R3)]. This is the result of the physiological differences such as body weight, length, surface area, total body water, extracellular and intracellular water as well as differences in PK/PD.  Accordingly, it is plausible that given the sex-related differences in pharmacokinetics, women are more frequently overdosed than men. This implies that at a given dose a drug reaches higher free drug concentrations or remains longer in the body in females than in males. Alternatively, females may be more sensitive to drugs than males. In this instance, free drug concentrations and duration in the body would be similar in men and women but women would respond to a greater extent. Yet, another plausible explanation might be attributed to behavior; if women take a greater number of medications than men they can increase the incidence of adverse events resulting from drug interactions.  it is also possible that sex differences between men and women result in similar rates of adverse events but women experience more severe events.