NAME: Osuagwu Oluomachi Joline

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Department: MBBS

### Discuss in details the factors that affect drug metabolism.

###  Answer

### 1. Age Differences

In neonates (upto 2 months) and in infants (2 months to 1 year), the microsomal enzyme system is not fully developed. So, many drugs are metabolized slowly. For e.g: caffeine has a half-life of 4 days in neonates in comparision to 4 hrs in adults. The drug metabolic rate in the different age groups differs mainly due to variations in the enzyme content, enzyme activity and haemodynamics. In elderly persons, the liver size is reduced, the microsomal enzyme activity is decreased and hepatic blood flow also declines as a result of reduced cardiac output, all of which contributes to decreased metabolism of drugs. For example, chlomethiazole shows a high bioavailability within the elderly, therefore they require a lower dose while Children (between 1 year and 12 years) metabolize several drugs much more rapidly than adults as the rate of metabolism reaches a maximum somewhere between 6 months and 12 years. As a result they require large mg/kg dose in comparison to adults.

**2. Species and Strain 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. Species difference have been observed in both Phase-I and Phase-II reactions. In Phase-I reactions, both qualitative and quantitative variations in the enzyme and their activity have been observed. Qualitative differences among species generally result from the presence or absence of specific enzymes in those species. Quantitative differences result from variations in the amount and localization of enzymes, the amount of natural inhibitors, and the competition of enzymes for specific substrates. Human liver contains less cytochrome P-450 per gram of tissue than do the livers of other species. For example, rat liver contains approximately 30 to 50 nmol/g of Cytochrome P450, whereas human liver contains 10 to 20 nmol/g. For instance, species differences in many conjugation reactions have also been observed. Often, these differences are caused by the presence or absence of transferase enzymes involved in the conjugative process. E.g, cats lack glu-curonyltransferase enzymes and, therefore, tend to conjugate phenolic xenobiotics by sulfation instead. 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 capabilities.

**3. Hereditary or Genetic Factors**

Some families have faster body metabolism rate than others with some genetic disorders also affecting metabolism. Many of these genetic or hereditary factors are responsible for the large differences seen in the rate of metabolism of some drugs.

**4. Sex Differences**

The rate of metabolism of xenobiotics also varies according to gender in some animal species. Men generally have faster metabolisms than women, for instance, [nicotine](https://www.pharmacologicalsciences.us/nicotine.html) and aspirin seem to be metabolized differently in women and men, such variations are generally observed following puberty. So, sex related differences in the rate of metabolism could probably be due to sex hormones.

Studies carried out on rats indicated that adult male rats metabolize several foreign compounds at a much faster rate than female rats (e.g., N-demethylation of aminopyrine, hexobarbital oxidation, glucuronidation of o-aminophenol). Apparently, this sex difference also depends on the substrate, because some xenobiotics are metabolized at the same rate in both female and male rats. Also, sex differences in drug metabolism appear to be species dependent. Rabbits and mice, for example, do not show a significant sex difference in drug metabolism.

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### 5. Hormonal Factors:

Higher levels of one hormone may inhibit the activity of few enzymes while inducing that of others. Adrenolectomy, thyroidectomy and alloxan-induced diabetes in animals showed impairment in the enzyme activity with subsequent fall in the rate of metabolism. A similar effect was also observed in the pituitary growth hormone and stress related changes in ACTH levels.

**6. Disease**

There are many disease states that affect the metabolism of drugs. Some of them are cirrhosis of liver, alcoholic liver disease, cholestatic jaundice, diabetes mellitus, acromegaly, malaria, various bacterial and viral infections, etc. It can be seen that major effects are seen in the disease affecting liver as liver is quantitatively the important site for metabolism. The possible cause in the effect of metabolism due to diseases may be: Hypoalbuminaemia (leading to lower plasma binding of drugs). For example: glycine conjugation of salicylates, oxidation of Vitamin D and hydrolysis of procaine are impaired in kidney diseases, altered hepatic blood flow , decreased enzyme activity in liver.

**7. Environmental Factors** Several environmental agents influence the drug metabolizing ability of enzymes. Halogenated pesticides such as DDT & polycyclic aromatic hydrocarbons contained in cigarette smoke have enzyme induction effect. Organophosphate insecticides & heavy metals such as mercury, tin, nickel, cobalt & arsenic have enzyme inhibition effect. Also an environmental change such as increased heat or cold forces the body to work harder to maintain its normal temperature and increases body metabolism rate.

8. **Diet.**

Food affects metabolism. What and how we eat has a big influence on your body metabolism rate. Dietary deficiency of vitamins like Vitamin A, B2, B3, C and E and minerals such as Fe, Ca, Mg, Zn retard the metabolic activity of enzymes. Grapefruit inhibits metabolism of many drugs and improve their oral bioavailability. Fat free diet depresses cytochrome P-450 levels since phospholipids, which are important components of microsomes become deficient. Low protein diet decreases and high protein diet increases the drug metabolizing ability as enzyme synthesis is promoted by protein diet and also raises the level of amino acids for conjugation with drugs.

**9.** **Body size.**

Those with bigger bodies have a larger body mass rate because they have larger organs and fluid volume to maintain.

**10. Pregnancy**

Pregnancy is known to affect hepatic drug metabolism. Physiological changes during pregnancy are probably responsible for the reported alteration in drug metabolism. These include elevated concentrations of various hormones such as estrogen, progesterone, placental growth hormones and prolactin. For example, in women, the metabolism of promazine and pethidine is reduced during pregnancy. It was also confirmed by the study in animals.