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COURSE: MEDICAL BIOCHEMISTRY

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1) DISCUSS IN DETAILS THE FACTORS AFFECTING DRUG METABOLISM

Drugs can be metabolized by different pathways and many factors can determine which pathway is used by which drug and to what extent a particular drug is bio-transformed 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 and external factors (i.e. diet and environment).

FACTORS AFFECTING DRUG METABOLISM

A. INTERNAL FACTORS: species, genetic, age, sex, hormones, disease
B. EXTERNAL FACTORS: diet and environment

A) INTERNAL FACTORS

1. **Species differences**: in drug/xenobiotics metabolism have been known for many years but have become topical due to the necessity to relate metabolism of drugs in animal systems to that in man during routine drug testing and the advent of simpler test systems (e.g. isolated liver cells) which allow a closer investigation of interspecies variability. Species differences can be found for both phase 1 and phase 2 metabolism and can be either quantitative (same metabolic route but differing rates) or qualitative (differing metabolic routes)
2. **Genetic differences:** It has been noted above that significant differences in drug metabolism are found between species – it is equally true, however, that such differences exist within species. This is most easily seen in the inbred populations of rats and mice used in many studies but are also being found for other species, including man. Such differences are referred to as genetic polymorphism.

   The classical example of strain differences in drug metabolism is that of hexobarbitone metabolism in the mouse. There is up to a 2.5-fold difference in sleeping time between one strain of mouse and another and the values for the animals in the inbred groups are close to each other whereas the outbred group shows a wide variation in sleeping time. This is clear evidence for a genetic .control of drug metabolism.

3. **Age:** It has long been recognised that the young, and particularly the newborn, and the old of many animals are more susceptible to drug action. Studies on the development of drug-metabolising capacity have indicated that this increased sensitivity of neonates may be related to their very low or, at times, unmeasurable drug-metabolising capacity which subsequently develops in a species-, strain-, substrate- and sex-dependent manner until adult levels of enzyme activity are achieved. The decrease in drug-metabolising capacity in old age also appears to be dependent on these factors although other specific factors may be involved.
4. **Hormonal control:** Hormones play a major role in the control of drug metabolism and, in particular, the hormones of the pituitary, adrenal and testes are involved in this control. The endocrine glands such as the thyroid gland, pancreas, and pregnancy equally play a role.

- **The pituitary gland**: controls the release of hormones from the other endocrine organs (except in the case of the pancreas where other influences are more important) and thus any effects exerted by the endocrine organs will be mimicked by the pituitary gland. Direct effects of pituitary hormones, such as growth hormones, have also been seen. Other direct effects on hepatic drug metabolism are seen with adrenocorticotrophic hormone (ACTH), luteinizing hormone (LH), follicle-stimulating hormone (FSH) and prolactin. The pituitary gland, therefore, occupies a central role in the hormonal control of drug metabolism.
- **Sex glands:** Sex glands in this context refer to the endocrine glands, the testes (in the male) producing androgens and the ovaries (in the female) producing estrogens and progestins. The effects of these hormones on drug metabolism are, as would be expected, mainly related to sex differences, although progestins (e.g. progesterone) have been implicated in the induction of CYP3A4 in women. Sex differences in drug actions were first noted by Nicholas and Barron in 1932 that saw that female rats required only half the dose of barbiturate needed by male rats to induce sleep.
  In 1958 it was proposed that androgens were the regulators of the sex differences.
  Thus the presence or absence of androgens in the perinatal period determines whether an animal is male or female with respect to drug metabolism – a process known as ‘imprinting’.
- **The adrenal glands**: are however, also thought to be involved in the regulation of drug metabolism in the adult period. Adrenalectomy has been shown to reduce the phase 1 microsomal metabolism of a number of xenobiotics, whereas glucocorticoid replacement therapy can reverse the effect of adrenalectomy.
- **Thyroid gland:** In the human, the thyroid gland has also been implicated in the control of drug metabolism. For the limited number of substrates used (antipyrine, paracetamol and aspirin), thyroidectomy always decreases their apparent metabolism. The mechanism of thyroid control of drug metabolism is

unclear but may involve changes in cytochrome P450, although not all changes in enzyme activity are correlated with changes in cytochrome P450.

- **The pancreas:** produces and secretes one hormone of particular relevance to the control of drug metabolism, i.e. insulin. This is produced by the cells of the endocrine pancreas. Diabetes mellitus (a reduction in the amount or action of insulin caused by genetic abnormalities or chemically by means of streptozotocin) causes marked changes in hepatic phase 1 and 2 metabolism.
- **Pregnancy:** is a natural condition when the hormonal balance of the female body is grossly altered. The oestrous (menstrual) cycle ceases and there are large changes in blood levels of peptide and steroid hormones. It is relevant, therefore, to discuss the effects of pregnancy on drug metabolism under the heading of Hormonal Control. In the rat, pregnancy causes a general decrease in drug metabolism.

5. **Diseases:** Many disease states have been shown to affect the way in which the body clears drugs and these are listed in Table 4.12. It can be seen that the major effects are observed with diseases affecting the liver. This is hardly surprising as the liver is quantitatively the most important site of drug biotransformation. Other diseases, however, such as infections and endocrine disorders, are also important when looking at drug metabolism. Drug metabolism can be reduced in the following:
   - Liver cirrhosis
   - Alcoholic liver disease
   - Viral hepatitis
   - Hepatoma

     As has been seen, diseases of various types generally decrease the liver's ability to metabolise drugs (with the notable exception of chronic ethanol exposure). The possible reasons for this decreased capacity are listed below:
     1. Decreased enzyme activity in liver
     2. Altered hepatic blood flow (intra/extrahepatic shunting)
     3. Hypoalbuminaemia (leading to lower plasma binding of drugs).
6. **Non-hepatic diseases:** Other non-hepatic diseases should also be considered in terms of their influence on drug metabolism and these particularly include the hormonal diseases such as hyperthyroidism, pituitary insufficiency (dwarfism), adrenal insufficiency, pituitary, thyroid or adrenal tumours, diabetes, and the genetic abnormalities of sexual development. All of the above-mentioned disease states have been shown to influence drug metabolism.

B) EXTERNAL FACTORS

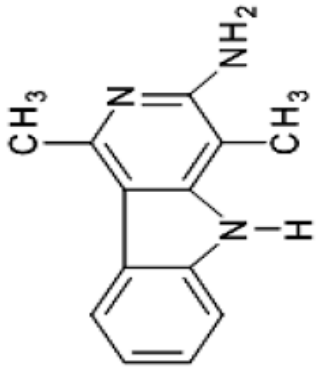
There are other factors, from outside the body that can also have a profound influence on drug metabolism. The body can be exposed to these factors by design (e.g. substances taken as food, alcohol and tobacco smoke) or by accident (air, water and food contaminants or pollutants).The first group will be

referred to as dietary factors and the second group as environmental factors.

1) **Dietary factors:** this can be grouped into macronutrients, micronutrients, alcohol, non-nutrients and components of tobacco smoke.
   - **Macronutrients:** this includes protein, carbohydrate, fats which make up the bulk of the diet.
     1. Protein: Drug metabolising capacity decreases with decrease in protein due to decrease in microsomal protein effect on the enzymes.
     2. Lipids: are required by the drug-metabolising enzymes as membrane components and, possibly, for specific interactions and certain lipid components can also act as inhibitors of drug metabolism (e.g. steroids).
     3. Carbohydrates: seem to have few effects on drug metabolism, although a high intake of glucose in particular can inhibit barbiturate metabolism, and thus lengthen sleeping time. Glucose excess has also been shown to decrease hepatic cytochrome P450 content and to lower biphenyl-4-hydroxylase activity.
     4. Starvation and re-feeding: In humans the effects of starvation and re-feeding are also somewhat confusing, with the clearance of paracetamol (acetaminophen), chloroquine and metranidazole all decreased whereas in malnourished children, aspirin clearance may be enhanced.
   - **Vitamins:** are essential parts of the diet and are needed for the synthesis of proteins and lipids, both of which are vital components of the drug metabolising enzyme system.
     1. Vitamin A: Retinoids (vitamin A and its metabolites) have been found to have profound effects on drug metabolism. The effects of the retinoids depend on whether they bind to the retinoic acid (RAR) or retinoid X (RXR) receptors. Vitamin A deficiency is also seen to cause a fall in circulating androgen levels but androgen treatment has no effect on circulating vitamin A levels.
     2. Riboflavin (vitamin B2): A deficiency of riboflavin, therefore, would be expected to reduce NADPH-cytochrome P450 reductase content and thus decrease drug-metabolising capacity.
     3. Vitamin C (ascorbic acid): In man, excess vitamin C ingestion decreases the ability of the gut to conjugate estrogens with sulfate.
     4. Vitamin E: Deficiencies of vitamin E reduce drug-metabolising capacity when assayed with a variety of substrates.
   - **Minerals:** Minerals are the elements needed in the diet to maintain good health and normal physiological function. Those which have been shown to affect drug metabolism are iron, calcium, magnesium, zinc, copper, selenium and iodine. Most mineral deficiencies lead to a fall in drug metabolism. However, iron is an exception to this rule.
     1. Iron deficiency increases drug metabolism and excess inhibits drug metabolism.

2. Calcium and magnesium deficiency decreases drug metabolism. However, the onset of the effect of calcium deficiency takes longer.
3. Excess copper and copper deficiency has the same effect as it reduces the ability to metabolise drugs in some cases.
4. Zinc deficiency reduces drug metabolism and excess zinc has some toxological effect.
5. Selenium deficiency impairs the ability of the liver to respond to phenobarbitone treatment. In the presence of selenium a 3.65-fold induction is seen but this falls to 2.64-fold in selenium-deficient animals. Selenium deficiency has also been shown to markedly inhibit expression of the estrogen sulfotransferase gene in the rat (to less than 10% of control).

- **Non-nutrients:** The most notable group of these substances naturally occurring in food which affect drug metabolism are the pyrolysis products – chemicals formed by the cooking (literally burning) of the food. The pyrolysis products that are formed in meat and fish, particularly when fried or charcoal-broiled, have been isolated as breakdown products of amino acids, mainly tryptophan. All these are potential mutagens or carcinogens. It is found that feeding charcoal-broiled beef to rats induces the metabolism of phenacetin in the intestines, thus lowering bioavailability of the drug. A fall is also seen in plasma concentrations of phenacetin and theophylline in humans fed on a charcoal-broiled beef diet.



- **Tobacco smoking:** Although not strictly a food component, tobacco smoke is inhaled deliberately and, thus, is a self inflicted effector of drug metabolism. Tobacco smoking can be thought of as a different way of ingesting pyrolysis products (from the burning of the plant materials in tobacco) with the lungs the first site of interaction rather than the intestine as in the case of charcoal-broiled meat. The most common effect of tobacco smoking is an increase in biotransformation of drugs – an effect very similar to that seen for ingestion of charcoal-broiled meat.

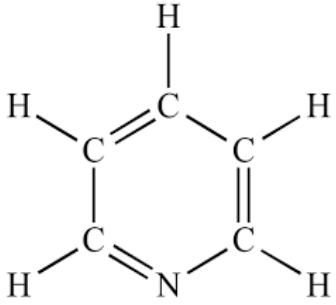
ENVIRONMENTAL FACTORS: Environmental factors are those influences in our

surroundings that can affect drug metabolism; no conscious act is required to be influenced by them but the effects on drug metabolism can be profound. It should also be realised that there are a large number of environmental chemicals that could potentially affect drug metabolism;

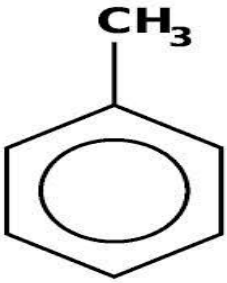
1) **Heavy metals:** Exposure of the human population to heavy metals can be related to occupation (cadmium from zinc smelting), diet (such as cadmium in vegetables) or other phenomena (e.g. lead in water from lead pipes). Most exposure is low level and long term and so cumulative exposure becomes important. Chronic exposure of rats to lead in the diet has little effect on drug metabolising capacity but does induce cytochrome P450 levels. The increased level of cytochrome P450 indicates that lead induces a form of enzyme that does not metabolise any of the substrates so far tested – different substrates may show induction of drug-metabolising capacity. Acute lead toxicity in rats, however, is associated with reduced drug-metabolising capacity. The situation found in human subjects was similar but only young children exhibited the inhibition of drug metabolism during acute lead toxicity.
2) **Industrial pollutants:** There are literally thousands of industrial pollutants that, in experimental animals, have been shown to affect drug metabolism;
   a) TCDD: TCDD is a polycyclic compound (Figure 5.10) with a rigid planar structure. It is a precursor for a number of herbicides. TCDD causes marked induction of the metabolism of polycyclic hydrocarbons and of the enzymes UDP-glucuronosyltransferase, -aminolevulinic acid synthetase and glutathione -S-transferase; it can thus affect both phase 1 and 2 metabolisms.
   b) Solvents: are in very widespread use in industry (and in the home). Serious concern is now being expressed about their effects on the body. The two groups of solvents of most interest in the study of drug metabolism are the benzene derivatives (benzene, toluene and the xylenes) and the chlorinated hydrocarbons (chloroform, trichloroethylene and dichloromethane).

      The aromatic hydrocarbons, therefore, seem to be phenobarbitone-like inducers of drug metabolism and are active by inhalation, thus indicating that workers in those industries using such solvents (e.g. the paint industry) may have induced drug metabolism as a result of solvent exposure.

      The chlorinated hydrocarbons, in contrast to the aromatic hydrocarbon as discussed above, do not always cause induction of drug metabolism.

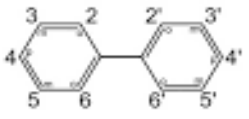


Benzene

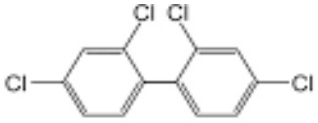


Toluene

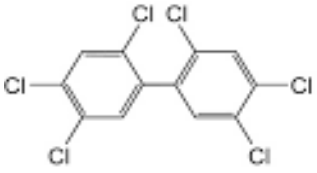
c) Polychlorinated biphenyls (PCBs): The polychlorinated biphenyls (PCBs) are a large group of compounds used in various manufacturing industries. Structurally the compounds can be split into two distinct groups: the planar and non-planar types. These two groups of compound have different effects on drug metabolism. The planar PCBs induce hepatic drug metabolism similar to polycyclic hydrocarbons whereas the non-planar PCBs exhibit induction of drug metabolism of the phenobarbitone type.



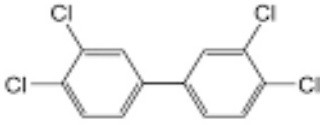
Generalized structure of PCB



2,2',4,4'-Tetrachlorobiphenyl
(PCB-47)



2,2',4,4',5,5'-Hexachlorobiphenyl
(PCB-153)



3,3',4,4'-Tetrachlorobiphenyl
(PCB-77)

d) Pesticides of various types are prevalent environmental contaminants in air, water and food. Again, there are many different chemical types of herbicides, insecticides etc., and only a few will be discussed here with respect to their effects on drug metabolism. The compounds to be discussed are mirex, kepone, malathion, parathion and DDT.

Mirex and kepone are structurally similar insecticides. There is an indication that both of these compounds are specific inducing agents.

Malathion and parathion are well-known, phosphothionate-type insecticides which are converted in vivo and in vitro to the corresponding phosphates,

malaoxon and paraoxon. These insecticides are inhibitors of drug metabolism both in vivo and in vitro, probably due to competitive inhibition of the cytochrome P450-dependent reaction that also metabolises the insecticides.

Pesticides can, therefore, be inducers or inhibitors of drug metabolism.

e) Motor vehicle exhaust Similar to tobacco smoke, the exhaust from a two-stroke petrol engine contains thousands of compounds including alkanes and cyclic hydrocarbons such as benzene, toluene and xylene as well as polycyclic aromatic hydrocarbons. It is little surprise that this potent mixture can induce drug metabolism.