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MEDICINE AND SURGERY

MEDICAL BIOCHEMISTRY

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. The factors affecting drug metabolism can be classified under two subtopics, they are:

1. Internal factors
2. External factors

INTERNAL FACTORS: They include; species, genetic, age, sex, hormones, disease

1. Species differences: 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). Some examples of each of these cases are given below.

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| --- | --- | --- | --- |
|  | Sleeping time (min) | hexobarbitone half life (min) | Hexobarbitone metabolism |
| Mice | 12+/- 8 | 19+/- 7 | 16.6 |
| Rat | 90+/- 15 | 140+/-64 | 3.7 |
| Dog | 315+/- 105 | 260+/- 20 | 1 |
| man |  | 360 |  |

The table above indicates that the overall oxidative metabolism of hexobarbitone varies widely between species and is inversely related to the half-life and duration of action of the drug. This direct relationship between metabolism, half-life and action of a drug, however, does not always hold true. In this case, however, this would seem to indicate that man metabolises hexobarbitone at a slower rate than the dog and that the rate of elimination of the drug from the body is dependent on the metabolism of the drug. Other species differences in phase 1 metabolism can be seen for caffeine where the formation of paraxanthine is highest in man and lowest in monkey, whereas theophylline production is highest in monkey and lowest in man.

1. GENETIC DIFFERENCES: 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. The marked strain differences in the mouse have also been extended to include differences in the induction of drug metabolism. Using two strains of mouse it was shown that one responds to treatment with 3-methylcholanthrene (3-MC, a polycyclic hydrocarbon inducer of aryl hydrocarbon hydroxylase) whilst the other (strain DBA) does not. Cross breeding of the strains has shown that the inheritance of inducibility is an autosomal dominant(ahd) trait and accounted for by the presence of the Ah receptor. The biochemical mechanism of this induction is discussedIn man the possibility of showing a pure genetic inﬂuence on drug metabolism is hampered by interfering inﬂuences from environmental sources as it is impossible to keep humans in controlled conditions of environment, diet, etc., during their lifespan. It has, however, been possible to show probable genetic effects on drug metabolism that have subsequently been proved using molecular biological techniques.
2. 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.

* Development of phase 1 metabolism: The activity of phase 1 drug metabolism may develop in many different ways between birth and adulthood and, indeed, may start developing at different times during gestation. The pattern of development varies according to the species and sex of the animal and on the substrate being investigated (and, thus, the particular form being studied)
* Development of phase 2 metabolism: The development of phase 2 metabolism is of considerable importance as excretion of drugs and other xenobiotics is mainly in the form of conjugates – the conjugation reactions being generally regarded as the true ‘detoxiﬁcation’ reactions. Changes in the ability of the body to conjugate drugs therefore leads to large changes in toxicity of the drugs. The balance between phase 1 and phase 2 metabolism during development is also of great importance. As with the phase 1 metabolism, phase 2 routes of metabolism are poorly represented in the foetal and neonatal animal and mainly develop perinatally.

1. HORMONES: 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 developmental control and sexual dimorphism.

* Pituitary gland: The pituitary gland controls the release of hormones from the other endocrine organs, 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.
* Adrenal glands: The adrenal glands have already been discussed in terms of glucocorticoid control of development of drug metabolism. 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.

1. EFFECT OF DISEASE : Many disease states have been shown to affect the way in which the body clears drugs. It can be seen that the major effects are observed with diseases affecting the liver. Other diseases, however, such as infections and endocrine disorders, are also important when looking at drug metabolism.

* Cirrhosis: In cirrhosis parts of the liver are replaced by ﬁbrous tissue and the number of functional hepatocytes is reduced. It is therefore not unexpected that drug metabolism is impaired in this condition and, indeed, the oxidative metabolism of chlordiazepoxide to its primary metabolite, desmethylchlordiazepoxide, is slower in cirrhotic patients. This appears to be true also for the conversion of diazepam to desmethyldiazepam. Oxazepam and lorazepam metabolism, however, which is purely glucuronidation, is not affected by cirrhosis.
* Alcoholic liver disease: Chronic alcohol administration can lead to a condition similar to that of cirrhosis with large portions of the liver replaced by ﬁbrous masses following the death of the hepatocytes. Before this stage is reached, however, alcohol administration can markedly affect drug metabolism in different ways.

Acute ethanol exposure → chronic ethanol exposure → alcoholic cirrhosis.

* Viral hepatitis: Little is known of the effects of viral hepatitis but what information is available suggests that this condition causes a decrease in hepatic drug metabolism. Chlordiazepoxide clearance is decreased in viral hepatitis, as is the clearance of meperidine (pethidine). Clearance of lignocaine is unaffected by viral hepatitis whereas tolbutamide exhibits an enhanced clearance in this condition. One study of patients with hepatitis A showed a marked decrease in the activity of CYP2A6 (related to 7-hydroxylation of coumarin).
* Hepatoma: A hepatoma is a cancerous growth derived from the liver parenchymal cells. The drug-metabolising capacity of the tumour cells, however, is very much less than the corresponding normal cells. This is a typical loss of differentiated function in de-differentiated cells.

EXTERNAL FACT0RS: They include; diet and environment.

1. DIET: Here, two major groups of substances can be distinguished: the macronutrients (e.g. protein, carbohydrate and fats, making up the bulk of the diet) and micronutrients (vitamins and minerals, essential in small quantities). Dietary factors can also be said to include alcohol (which provides a large number of calories), non-nutrients (such as colourants, antioxidants and ﬂavour components) and the components of tobacco smoke. Although the latter is not strictly a dietary factor, it is taken intentionally and has similar effects to some of the other non-nutrients in the diet.

**Macronutrients:**

* Protein: The normal proportion of protein in the diet is about 20% – animals kept on a diet containing this amount of protein show normal development of drug-metabolising enzymes. The decrease in drug metabolism is partially due to decreases in overall microsomal protein and partially to speciﬁc effects on the enzymes still remaining.
* Fat: 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)
* Carbohydrate: 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.
* Vitamins: Vitamins are an essential part of the diet and are needed for the synthesis of proteins and lipids, both of which are vital components of the drug metabolizing enzyme system. Therefore changes in vitamin levels, particularly deﬁciencies, cause changes in drug-metabolising capacity. The vitamins involved in drug metabolism are vitamins A,B,C,E, and K.
* 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. As is seen, most mineral deﬁciencies lead to a fall in drug metabolism.

1. 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. The environment is replete with substances that can affect drug metabolism. It should also be realised that there are a large number of environmental chemicals that could potentially affect drug metabolism; these chemicals include

* Heavy metals: Exposure of the human population to heavy metals can be related to occupation (cadmium from zinc smelting), diet (such as cadmium in 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 vegetables) or other phenomena (e.g. lead in water from lead pipes). Acute lead toxicity in rats, however, is associated with reduced drug-metabolising capacity.
* Industrial pollutants: There are literally thousands of industrial pollutants that, in experimental animals, have been shown to affect drug metabolism. Three important and well-studied industrial pollutants will be discussed in detail to illustrate the general principles; these are 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), industrial solvents of the benzene and chlorinated hydrocarbon types, and polychlorinated biphenyls
* Solvent: 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 that affect drug metabolism the most are the benzene derivatives (benzene, toluene and the xylenes) and the chlorinated hydrocarbons (chloroform, trichloroethylene and dichloromethane).