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**COURSE: BIOCHEMISTRY**

**ASSIGNMENT: Discuss in details the factors affecting drug metabolism. Dr. (Mrs) Owolabi**

**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 and external factors (i.e. diet and environment). These are, of course, purely arbitrary divisions and much interaction exists between the various factors (hormonal, sex and age influences) – such interactions will be pointed out where they are important. The factors to be discussed here are listed below:

**INTERNAL:** species, genetic, age, sex, hormones, disease

**EXTERNAL**: diet and environment

**FACTORS AFFECTING DRUG METABOLISM: INTERNAL FACTORS**

**SPECIES DIFFERENCES**

Species differences in drug/xenobiotic 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).

**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 is also being found for other species, including man. Such differences are referred to as genetic polymorphism. It has been recognised for a long time that large variations in drug metabolism occur in man and that discrete genetic sub-populations are present in the human population. One such sub-population is the group of ‘isoniazid slow acetylators’. Another aspect of genetic control of drug metabolism is the appearance of racial differences. Differences between the metabolism of propranolol in Negro and Caucasian populations exist as do differences in the glucuronidation of paracetamol between Caucasians and Chinese. Clear indications of the genetic nature of these differences has again come from molecular biology with differences noted in the genes for CYP2D6 and CYP2C9 (amongst others) in Polynesians of the South Pacific and Japanese, respectively. African and Afro-American populations have also been shown to have genetic differences in drug metabolism. Genetic differences within a population can affect the rate at which drugs are metabolised and there is convincing evidence to support a direct genetic control of some oxidative and conjugative reactions.

**AGE**

It has long been recognised that the young, and particularly the new born, 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.

**Mechanism of control of sex differences**

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’. Although this still holds true, the mechanism by which perinatal androgens exert this effect is now well established and it is accepted that there is no direct effect of the androgen on the liver. The perinatal androgen ‘imprints’ a pattern of growth hormone secretion from the pituitary gland and it is this male or female pattern of growth hormone secretion that gives the sex differences in drug metabolism. Sex differences in drug metabolism are of great importance when dealing with rats, mice and some farm animals (e.g. goats) but seem to be of less importance in a clinical context.

 **HORMONAL CONTROL OF DRUG METABOLISM**

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. In this section it is intended to expand this idea to include all endocrine organs and to further examine the role of the pituitary, adrenal and sex glands and consider the thyroid and pancreas in terms of their effects on drug metabolism.

**THE EFFECTS OF DISEASE ON DRUG METABOLISM**

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. 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. Disease states that affect drug metabolism includes: Cirrhosis of the liver, Alcoholic liver disease, Cholestatic jaundice, Liver carcinoma, Endocrine disorders, Diabetes mellitus, Hypo- and hyperthyroidism, Acromegaly, Pituitary dwarfism, Infections, Bacterial, Viral, Malaria, Inflammation, etc.

**FACTORS AFFECTING DRUG METABOLISM: EXTERNAL FACTORS**

There are, however, 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.

**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 (dietary factors) but the effects on drug metabolism can be profound. The environment is replete with substances that can affect drug metabolism and reviewers have different views concerning what constitutes an environmental factor. Many include dietary factors in this category and one should not be confused by these differences in nomenclature. It should also be realised that there are a large number of environmental chemicals that could potentially affect drug metabolism; the representative examples of a number of groups of compounds discussed here are only a small part of this. Those chemicals to be considered in this section are: Heavy metals: lead, mercury, cadmium, gadolinium. Industrial pollutants: tetrachlorodibenzodioxin (TCDD), solvents, polychlorinated biphenyls (PCBs). Insecticides, herbicides: parathion, mirex. Motor vehicle exhaust.

**DIETARY FACTORS**

In discussing dietary factors, 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 and is discussed in Section 4.6), 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.