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ASSIGNMENT TITLE: XENOBIOTICS

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QUESTION: Discuss, in detail, the factors affecting drug metabolism.

ANSWER: Drug metabolism in body is to allow for biotransformation of such drugs which are non-polar into polar compound or metabolites and to excrete the drug or xenobiotics. Drug metabolism occurs in two phases which are phase I and phase II which are known as the functionalization and conjugation reactions respectively.

FACTORS AFFECTING DRUG METABOLISM

We have the i) internal factors and ii) external factors

1. Internal factors: We have internal factors such as species, age, sex, genetic make-up, diseases and hormones. All these factors affect the xenobiotic-metabolizing enzymes.
 - a) Species: Activities of these enzymes differ among species such as action of hexobarbitone on mouse, rat, dog and man. Hexobarbitone is a drug for inducing sleep. As the table shows below, we see that each species has its own sleeping time, half-life and metabolism units. This just shows that how different species break down drugs or xenobiotics are different.

Species	Sleeping time(min)	Hexobarbitone $t^{1/2}$	Hbt metabolism(units)
Mouse	12±8	19±7	16.6
Rat	90±15	140±54	3.7
Dog	315±105	260±20	1
Man		≈360	?

- b) Age: Some drugs metabolize faster due to age difference. Drug metabolic rate indifferent age group differs mainly due to variations in enzyme content, enzyme activity and haemodynamics. For an adult, you take two tablets of paracetamol but for a child or baby, you have to break down a tablet into the lowest point that the doctor or pharmacologist thinks is advisable for the baby to use. This is because the rate at which adults metabolize paracetamol is higher than that of a child. Neonates have low microsomal enzymes. Elderly have reduced hepatic flow.
- c) Sex: In 1932, Nicholas and Baron discovered that half of total hexobarbitone given to male mice is given to female mice. Males have a larger drug metabolism capacity than females. Some differences may be due to sex hormones.
- d) Diseases: Disease such as cirrhosis of the liver can affect the activities of drug-metabolizing enzymes. People with diseases, mainly liver diseases may have a hard time breaking down xenobiotics as it is metabolized in the liver. It leads to decrease in drug metabolism. Thyroid disease: hyperthyroid increase metabolism and hypothyroid decrease metabolism. Cardiac disease can slow blood flow to liver and therefore decrease metabolism.
- e) Hormones: we have some that induce or inhibit drug metabolism. For example, testosterone and estrogen play a leading role in metabolism. For example, steroid hormones interact with drug-metabolizing enzyme.
- f) Genetics/strain: Gender and race differences in enzyme activity can affect drug metabolism. The difference that can be used is in the rate of acetylation. Rapid acetylators have more hepatic acetyl N-transferase than the slow acetylators. 90% of Eskimos are rapid acetylators. Egyptians and mediterraneans are slow acetylators. 70% of middle-eastern populations, 50% of Caucasians and 25% of Asians are slow acetylators. The rate of acetylation is clinically important in terms of therapeutic response and toxicity. Also, genetic factors also affect the rate of oxidation.

2. External factors: we have diet and environment.

- a) Diet: enzyme content and activity is altered by a number of dietary

components.

- Low protein diet decreases and high protein diet increases drug metabolizing activity.
- Fat free diet depresses cytochrome p-450 levels since phospholipids which are important components of microsomes become deficient.
- Grapefruit inhibits metabolism of many drugs and improve their oral bioavailability.
- Dietary deficiency of vitamins like vitamin A, B2, B3, C and E and minerals such as Fe, Ca, Mg and Zn retard the metabolic activities of enzymes.
- Exposure to other drugs particularly alcohol also affect metabolism of certain drugs.

b) Environment: there are some environmental chemicals that affect metabolism.

- Halogenated pesticides such as DDT and polycyclic aromatic hydrocarbons contained in cigarette smoke have enzyme induction effect.
- Organophosphate insecticides and heavy metals such as mercury, nickel, cobalt and arsenic inhibit drug metabolizing ability of enzymes.
- Xanthines and flavones in food
- Other environmental factors that may also influence drug metabolism are temperature, altitude, pressure, atmosphere e.t.c.