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Question

Discuss in details factors affecting drug metabolism

ANSWER

Many factors affect the rate and pathway of metabolism of drugs and the major influences can be subdivided into internal (physiological and pathological) and external (exogenous) factors as indicated below; INTERNAL FACTORS: genetics, species , age, sex, race, hormones while EXTERNAL FACTORS include diet and environment.

INTERNAL FACTORS

1. GENETIC VARIATION:

* Slow and fast acetylators of INH (Autosomal Recessive)
* Atypical pseudocholinesterase for SCh (Autosomal Recessive)

1. *SPECIES DIFFERENCE: It has been observed in both phases – PHASE - I & PHASE - II. In Phase - I, qualitative and quantitative variations of enzymes have been observed.*

* *Human livers contain less cytochromeP-450 per gram of tissue than do the liver of other species.*
* *Human liver is 2 percent of body weight whereas rat liver is approximately 4 percent of their body weight.*
* *In men, amphetamine and ephedrine are predominantly metabolized by oxidative deamination, whereas in rat aromatic oxidation is the major route in Phase-II reactions.*
* *In pigs the phenol is excreted mainly as glucoronide whereas sulphate conjugate dominates in cats.*

1. *AGE: The drug metabolism rate in the different age differs.*

* *Neonates have low microsomal enzymes. Eg: Chloramphrenicol causing Grey baby syndrome.*
* *Elderly have reduced hepatic flow and metabolizing enzyme system declines.*

1. *SEX: Metabolic differences between females and males have been closely observed for certain compounds. Metabolism of Diazepam, caffeine, and paracetamol is faster in females than in males while oxidative metabolism of lidocaine, chordiazeperoxide are faster in men than in females. Several studies has shown that women on contraceptive pills metabolize a number of drugs at a slow rate.*
2. *RACE: Chinese have high alcohol dehydrogenase, low aldehyde dehydrogenase.*
3. *HORMONAL IMBALANCE: Higher level of one hormone may inhibit the activity of few enzymes while inducing that of others. Adrenolectomy, thyroidectomy alloxan-induced diabetes in animals showed impairment in the enzyme activity with subsequent fall in the rate of metabolism.*

*EXTERNAL FACTORS*

* 1. *DIET: The enzyme content and activity is altered by a number of dietary components. Generally*
* *Low protein diet decreases and high protein diet increases the drug metabolizing ability as enzyme synthesis is promoted by protein diet and also raise the level of amino acid for conjugation with drugs.*
* *Fat free diet depresses cytochrome P-450 levels since phospholipids which are important components of microsomes become deficient.*
* *Starvation results in decreased amount of glucoronides formed than under normal conditions.*
* *Grapefruit inhibits metabolism of many drugs and improve oral bioavailability*
  1. *ENVIRONMENT: The effects of environmental factors alter not only relative activities of the cytochrome P-450 in liver microsomes but also the activities of other drug-metabolizing enzymes and that the relative effects of the environmental factors of these enzymes may differ depending on the animal species or the animal strain.*