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COURSE: BIOCHEMISTRY

ASSIGNEMENT: Discuss the factors affecting drug metabolism

Many factors affect the rate and pathway of metabolism of drugs, and the major influences can be sub-divided into

Internal (physiological and pathological) and

 External (exogenous) factors as indicated below:

Internal: species, genetic (strain), sex, age, hormones, pregnancy, disease.

 External: diet, environment.

INTERNAL FACTORS

Physiological factors like:

Species/strain difference
i. The metabolism of drugs and foreign compounds is often different in different species. Even within the same species, different strains of animals may show significant differences in drug metabolism. Drug metabolism in animals may be drastically different from that in humans -> hence the need for clinical trials
ii. This is important to consider in drug development. Failure in clinical trial may be a result of a difference in drug metabolism between animal species and humans. Still controversial which animal models best reflect human metabolism.

Age: The effect of old age on drug metabolism is not well studied but there is some evidence in animals and humans that drug metabolism slows down with old age. And in new borns and infants with poorly developed enzyme systems

Sex: Some drugs (i.e. nicotine, aspirin) are metabolized differently in females and in males. Drug interactions can be significantly different in females and in males.
Example: Rifampin shortens the half-life of contraceptives in women

Pathological conditions like:

1. Impaired liver function such as hepatic cancer, cirrhosis and hepatitis may remarkably decrease the capacity of drug metabolism
b. Impaired kidney function will in general decrease the excretion of drug metabolites, thus increasing the toxicity and/or pharmacological effects from the metabolites
c. When considering the implications of over-exposure, need to look at the drug itself as well as its
metabolites. Kidney function may cause over-exposure of the body to the parent drug and its metabolites.
If the metabolites have adverse effects or toxicities, it can have negative impact on the patient

External factors

Considering diet: the kind of food individual eats can affect drug metabolism for example low protein diets have been known to reduce the availability of some enzymes. Alcohol and smoking have been known to cause negative interactions with certain drugs

Other factors like chemical interactions also play a huge roll in drug metabolism

Drug-drug Interactions inhibition VS induction of the metabolizing enzyme

Enzyme induction -> more metabolism -> larger k of elimination
i. Drug binds to the DNA sequence in the cell that enhances expression of the metabolizing enzyme
that deactivates another drug. This decreases the duration of action of the drug that is
metabolized by the induced enzyme
c. Enzyme inhibition -> less metabolism -> smaller k of elimination
i. Drug inhibits the metabolizing enzyme or decreases its expression, which results in less
metabolism of the affected drug. This can increase the risk of over-exposure or adverse effects

 Stereochemistry in Drug Metabolism EG WARFARIN

Warfarin carries a stereocenter/chiral center
Has S and R enantiomers
R enantiomer is a substrate for alcohol DH which carries out a reversible metabolism reaction
(alcohol DH AKA ketone reductase)

ADH reduces ketone group to generate a hydroxyl group, but can ONLY do so to the R enantiomer

S enantiomer is a substrate of CYP450, which hydroxylated on the aromatic ring system

The product of metabolism by ADH has another chiral center