

Factors affecting drug metabolism

Age differences

- ❖ Age related differences in drug metabolism is quite apparent in the newborn.
- ❖ In new born babies deficiency of oxidative and conjugative enzymes are responsible for reduced metabolic capability.
- ❖ e.g. Oxidative (Cytochrome P450) metabolism of tolbutamide appears to be low in newborn.
- ❖ The ability of infants to conjugate chloramphenicol with glucuronic acid appears to be responsible for gray baby syndrome.

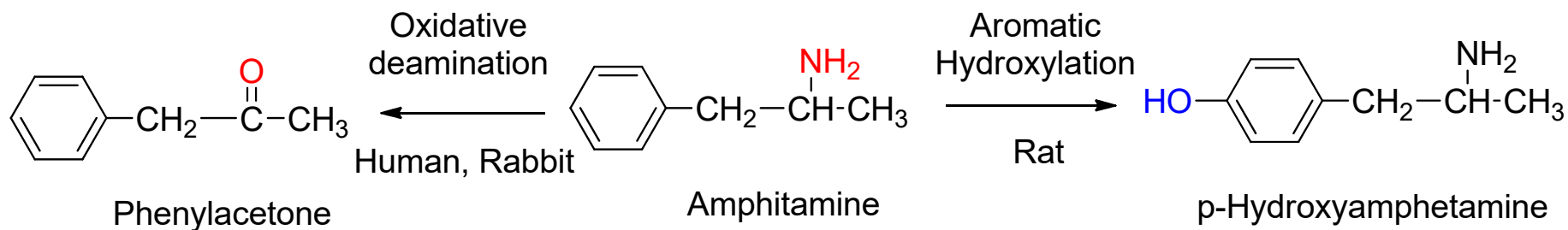
Species and strain differences

The metabolism of many drugs and xenobiotics are often species dependant.

❖ Metabolism of amphetamine occurs by two different pathway i.e. Oxidative deamination or aromatic hydroxylation.

❖ In human, guinea pig, and rabbit deamination appears to be the predominate pathway.

❖ However in rat, aromatic hydroxylation appears to be more important.



Hereditary or genetic differences

- ❖ Marked difference in metabolism of several drugs in human occurs due to genetic factors.
- ❖ Genetic factors influence the rate of oxidation of phenytoin, phenylbutazone, nortriptyline etc.
- ❖ The rate of oxidation of these drugs varies widely among different individual.

Gender differences

- ❖ The rate of metabolism of drugs also varies due to gender difference in animals.
- ❖ Adult male rat metabolize several drugs at much faster rate than female rat.
- ❖ e.g. N-demethylation of aminopyrin, oxidation of hexobarbital, glucuronidation of o-aminophenol.

Enzyme induction

- ❖ The activity of hepatic enzymes such as cytochrome P-450 can be increased by exposure to diverse drugs , pesticides etc.
- ❖ The process by which the activity of these drug metabolising enzymes is increased is termed enzyme induction.
- ❖ e.g. Phenobarbital can increase the metabolism of cortisol, Vitamin D in human.

❖ Phenobarbital induces the **glucuronyltransferase enzyme**, thereby enhances the conjugation with glucuronic acid.

❖ Other chemicals such as **polycyclic aromatic hydrocarbons** and pesticide may induce certain **oxidative pathway** and thereby alter drug response.

Enzyme inhibition

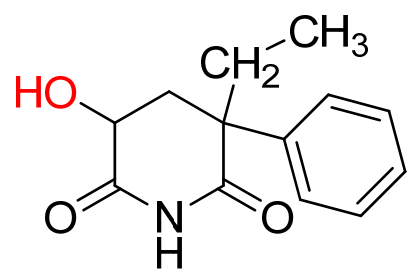
- ❖ Several drugs and food material can inhibit drug metabolism. With decreased drug metabolism, a drug often accumulated leading to prolonged duration of action and serious adverse effect.
- ❖ Enzyme inhibition can occur by diverse mechanism such as inactivation of drug metabolising enzymes, interference with protein synthesis and hepatotoxicity leading to impairment of enzyme activity.

❖ e.g. Phenylbutazone inhibits the metabolism of warfarin. This can lead to increased hemorrhage in patient on both warfarin and phenylbutazone therapy.

❖ Similarly the metabolism of phenytoin is inhibited by chloramphenicol and isoniazid.

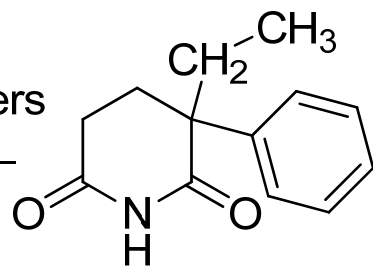
Stereochemical aspects

- ❖ Many drugs are often administered as racemic mixture in humans. The two enantiomer present in the racemic mixture may differ in pharmacological activity.
- ❖ The individual enantiomers of racemic mixture also may be metabolised by different pathway.
- ❖ e.g. In dogs the (+) enantiomer of sedative hypnotic glutethimide is hydroxylated primarily at α to the carbonyl to yield 5-hydroxyglutethimide, whereas the (-) enantiomer undergoes aliphatic hydroxylation of its C-2 ethyl group.



5-Hydroxyglutethimide

(+)-Enantiomers



Glutethimide

(-)-Enantiomers

