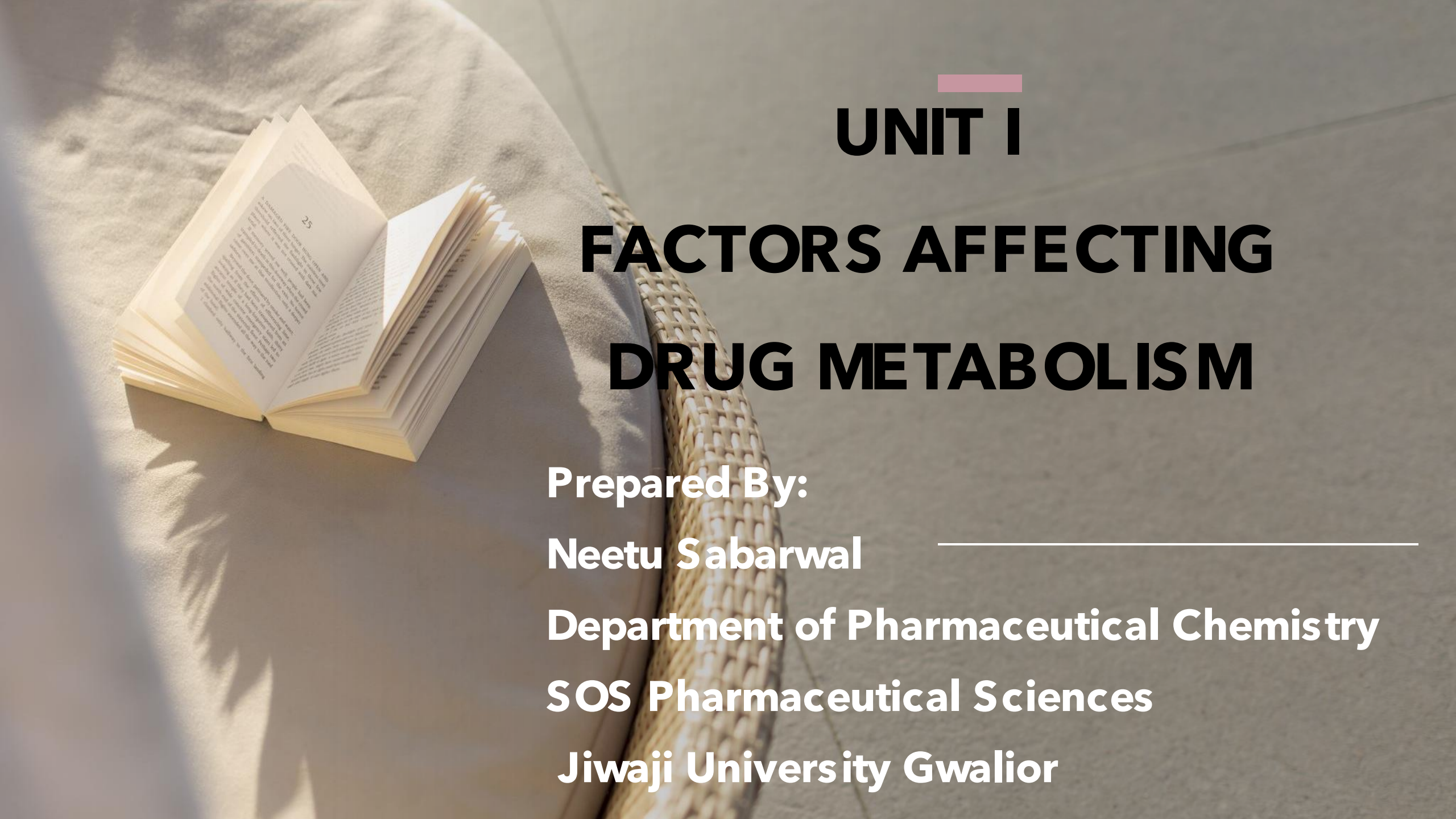

UNIT I

FACTORS AFFECTING DRUG METABOLISM

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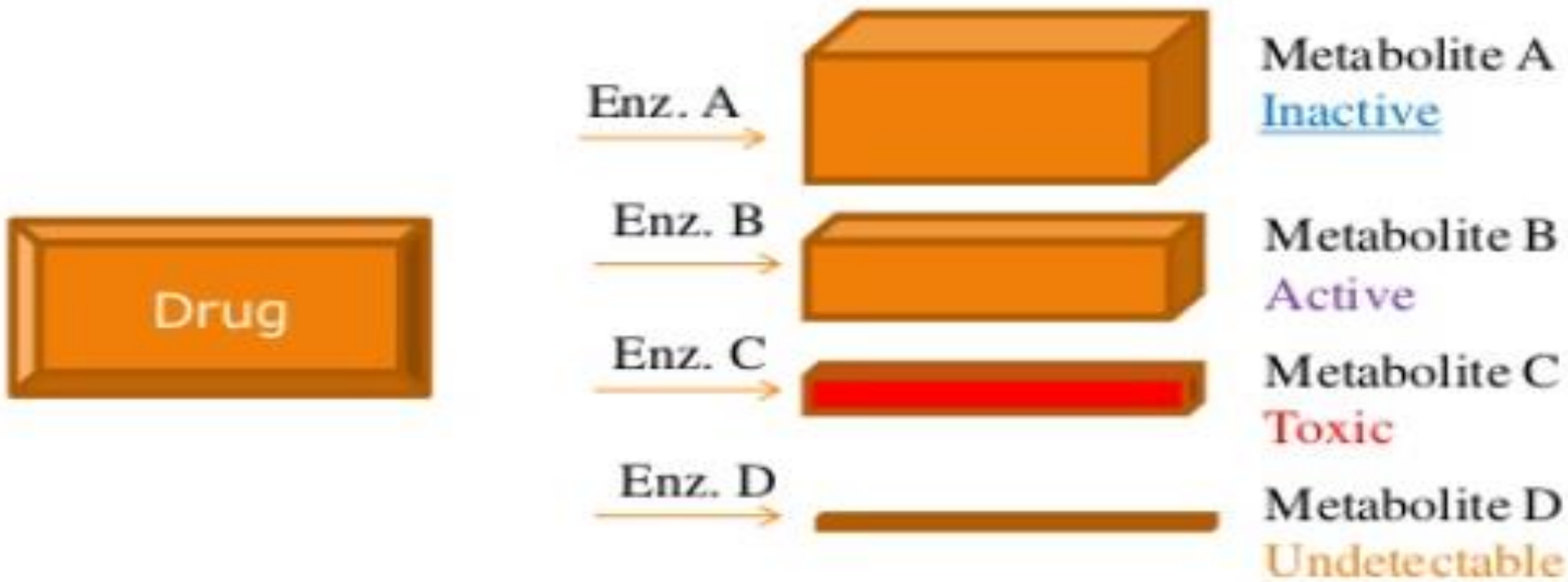
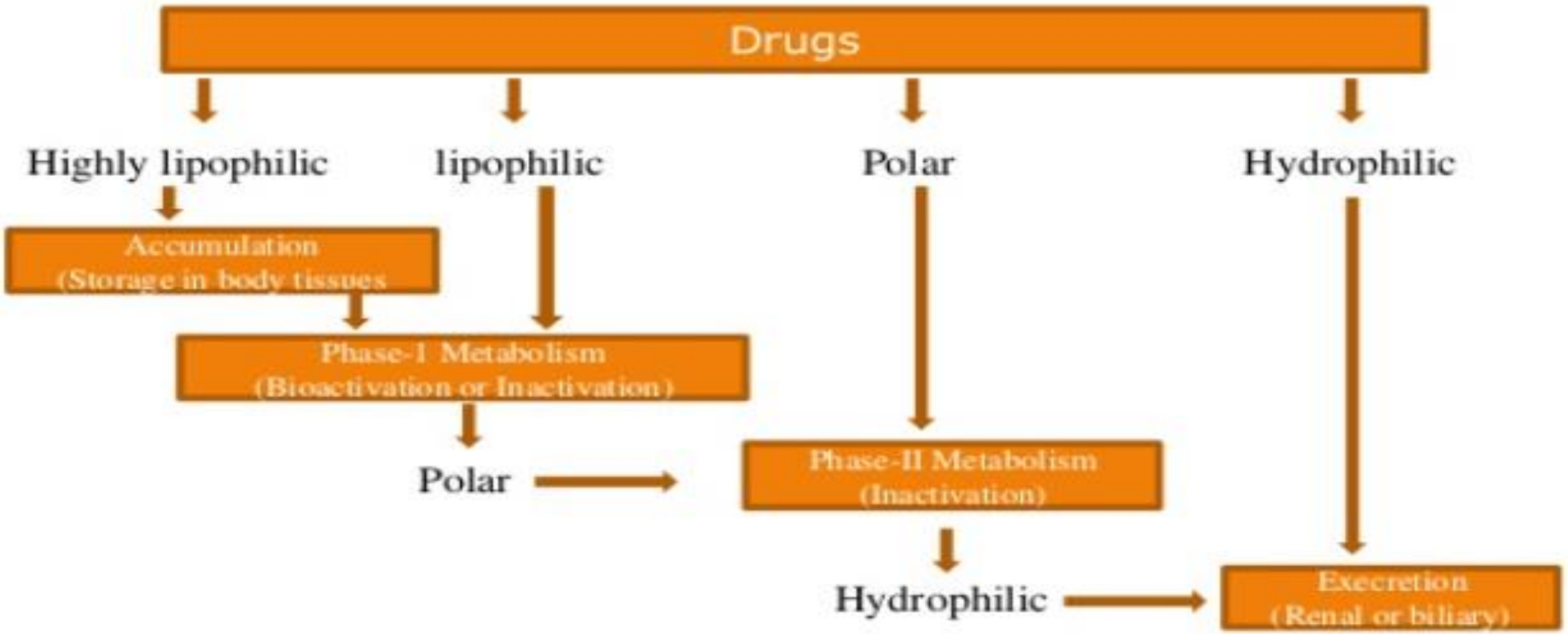
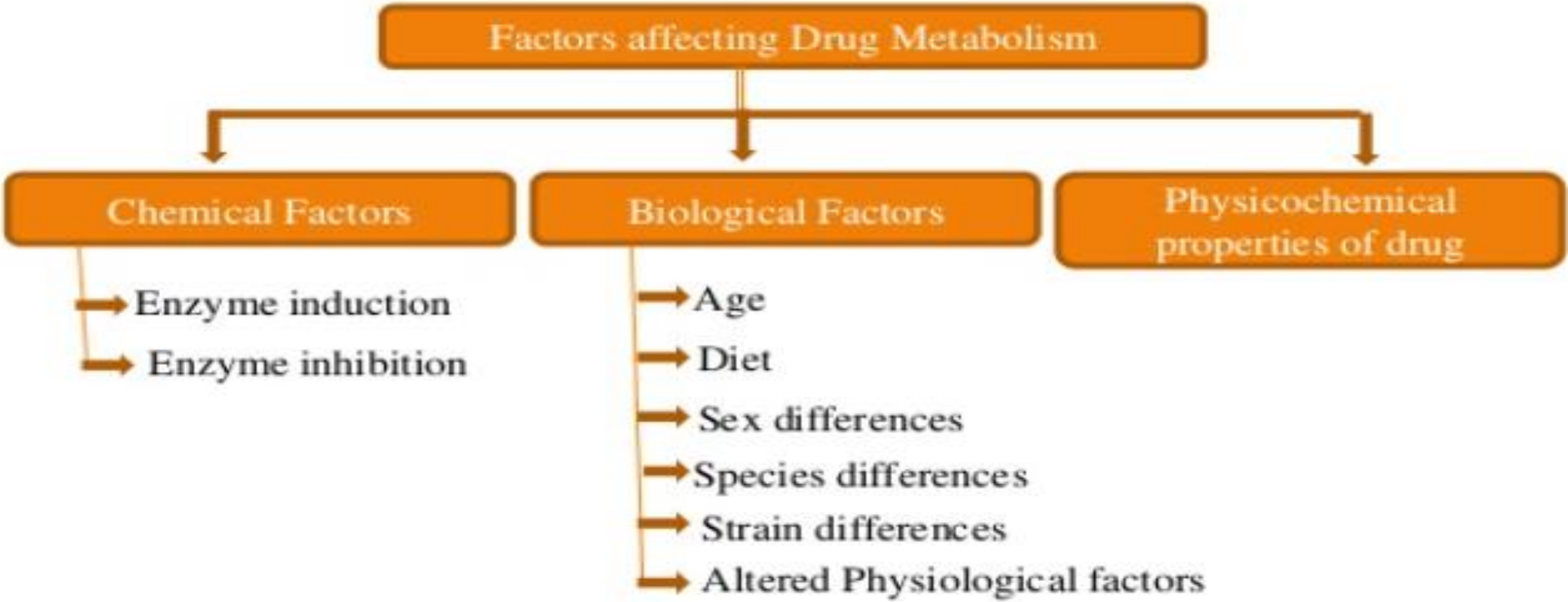
Definition

Drug metabolism is a biochemical modification of pharmaceutical substances usually through specialized enzymatic activity.


Drug
Enz. A
Metabolite A
Inactive
Enz. B
Metabolite B
Active
Enz. C
Metabolite C
Toxic
Enz. D
Metabolite D
Undetectable

Mechanism


Drugs
Highly lipophilic
lipophilic
Polar
Hydrophilic
Accumulation
(Storage in body tissues
Phase-I Metabolism
(Bioactivation or Inactivation)
Polar
Phase-II Metabolism
(Inactivation)
Hydrophilic
Execretion
(Renal or biliary)


Factors affecting Drug Metabolism
Chemical Factors
Biological Factors
Physicochemical properties of drug
Enzyme induction
Enzyme inhibition
Age
Diet
Sex differences
Species differences
Strain differences
Altered Physiological factors

1. Chemical Factors

a) Enzyme induction:

The phenomenon of increased drug metabolizing ability of enzymes by several drugs and chemicals is called as enzyme induction and the agents which bring about such an effect are called enzyme inducers.

Mechanisms of enzyme induction:

- Increase in both liver size and liver blood flow
- Increase in both total and microsomal protein content
- Increased stability of enzymes
- Increased stability of cytochrome P-450
- Decreased degradation of cytochrome P-450
- Proliferation of smooth endoplasmic reticulum

Consequences of enzyme induction include:

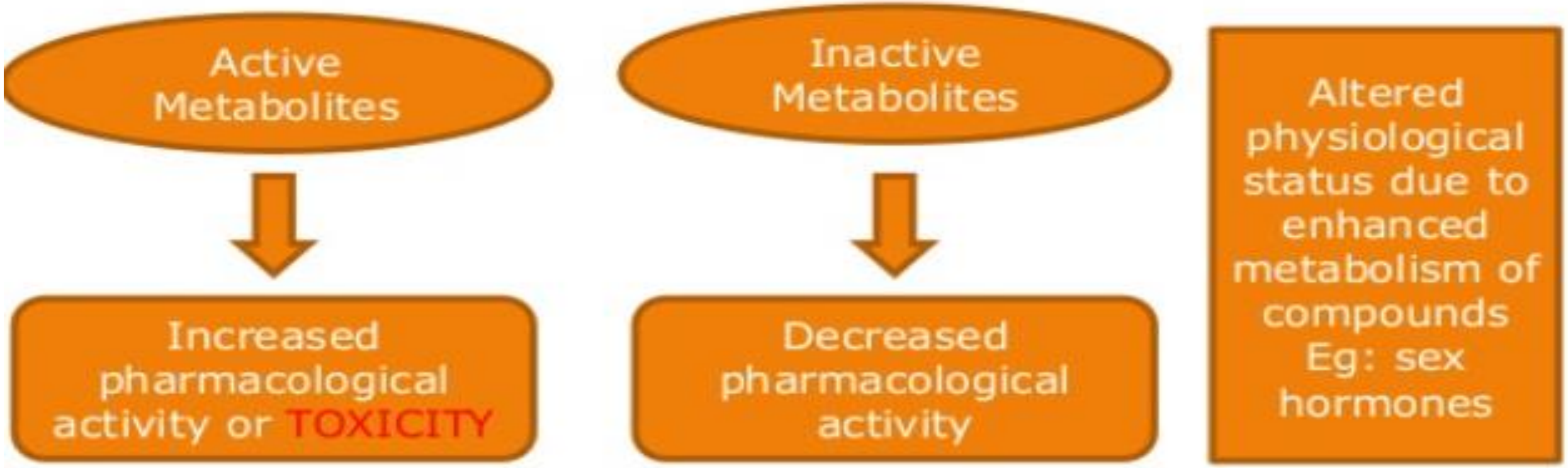
- Decrease in pharmacological activity of drugs
- Increased activity where the metabolites are active

Chemical Factors

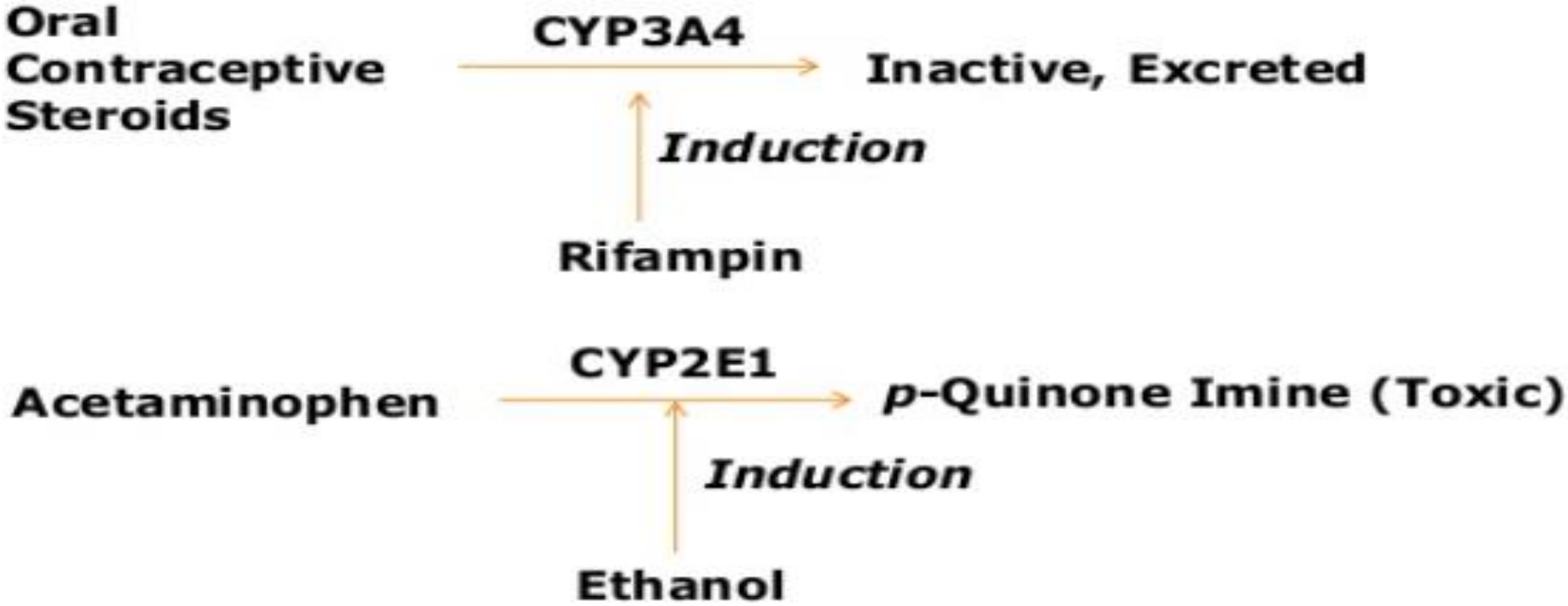
Enzyme induction

It is the phenomenon of *incresed drug metabolising ability* of enzymes by several drugs and chemicals.

Consequences



Examples of enzyme induction



b) Enzyme inhibition

A decrease in the drug metabolizing ability of an enzyme is called as enzyme inhibition. The process of inhibition may be direct or indirect.

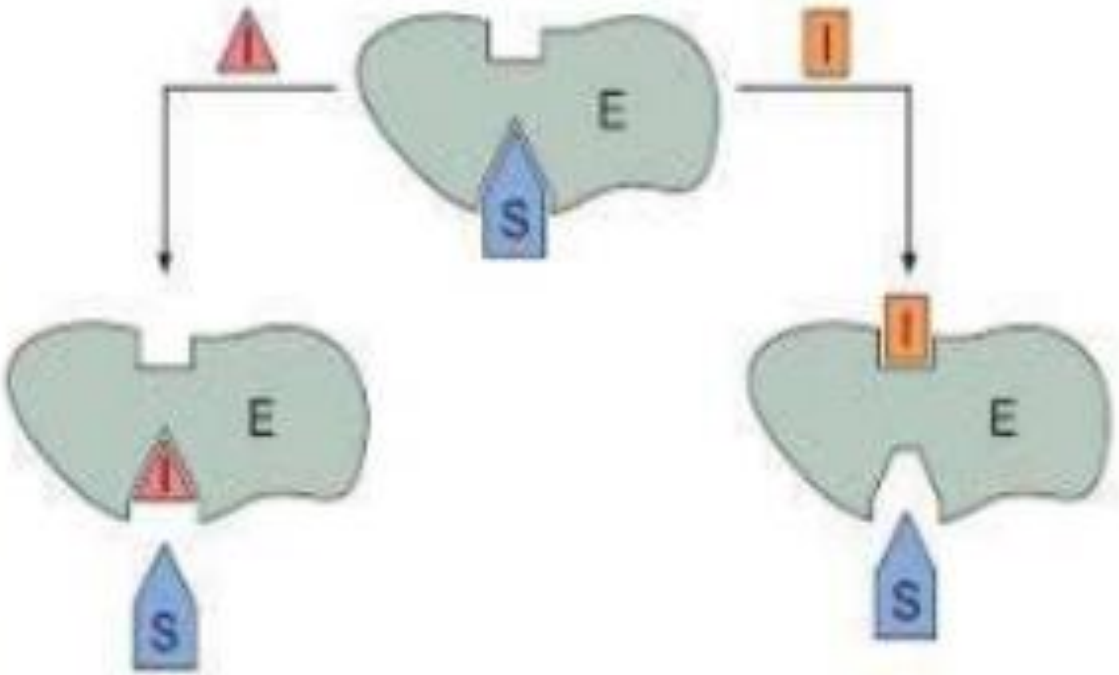
1) Direct inhibition: It may result from interaction at the enzymic site, the net outcome being a change in enzyme activity. Direct enzyme inhibition can occur by one of the following mechanisms:
    i. Competitive inhibition: occurs when structurally similar compounds compete for the same site on an enzyme.
    ii. Non-competitive inhibition: occur when a structurally unrelated agent interacts with the enzyme and prevents the metabolism of drugs.
    iii. Product inhibition: occurs when the metabolic product competes with the substrate for the same enzyme.
2) Indirect inhibition: it is caused by one of the following mechanism:
    i. Repression: it may be due to fall in the rate of enzyme synthesis or rise in the rate of enzyme degradation.
    ii. Altered physiology: it may be due to nutritional deficiency or hormonal imbalance.

Enzyme inhibition

It is a decrease in the drug metabolising activity of an enzyme.

The process of inhibition may be:

Direct inhibition



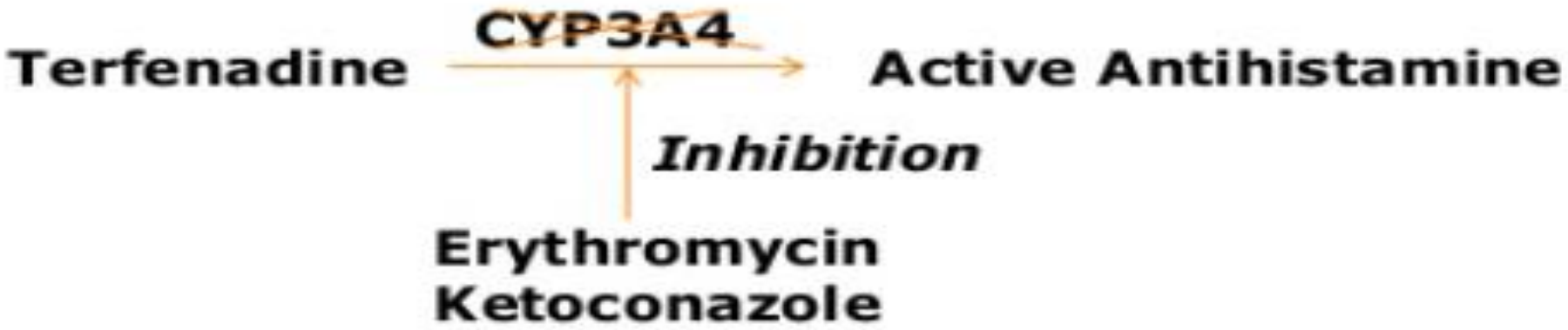
Competitive inhibition

Non-competitive inhibition

Indirect inhibition

- Repression → Decrease in the enzyme content
- Altered physiology → Due to nutritional deficiency or hormonal imbalance

Examples of enzyme inhibition



Consequences of Inhibition

- Increase in the plasma concentration of parent drug
- Reduction in metabolite concentration
- Exaggerated and prolonged pharmacological effects
- Increased likelihood of drug-induced toxicity

Enzyme inhibition is more important clinically than enzyme induction esp. for drugs with narrow therapeutic index.

Eg: anticoagulants,antiepileptics,hypoglycemias,etc.

Biological factors

Age

Neonates and infants (upto 1 year)

Microsomal enzyme system is not fully developed

Many drugs metabolised slowly

Half life of caffeine

In neonates: 4 days

In adults: 4 hours

Children (1 to 12 years)

Rate of metabolism reaches maximum

Require large mg/kg dose than adults

Half life of theophylline in children is 2/3rd of that in adults

Elderly

Reduced liver size

Reduced hepatic blood flow

Reduced enzyme activity

Decreased metabolism of drugs

2. Biological factors

a. Age

The drug metabolic rate in the different age groups differs mainly due to variations in the enzyme content, enzyme activity and haemodynamics.

- In neonates (upto 2 months) and in infants (2 months to 1 year), the microsomal enzyme system is not fully developed. So, many drugs are metabolized slowly. For eg: caffeine has a half-life of 4 days in neonates in comparision to 4 hrs in adults.[7&1]
- Children (between 1 year and 12 years) metabolize several drugs much more rapidly than adults as the rate of metabolism reaches a maximum somewhere between 6 months and 12 years. As a result they require large mg/kg dose in comparison to adults.
- In elderly persons, the liver size is reduced, the microsomal enzyme activity is decreased and hepatic blood flow also declines as a result of reduced cardiac output, all of which contributes to decreased metabolism of drugs. For example, chlomethiazole shows a high bioavailability within the elderly, therefore they require a lower dose.

b. 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 raiss the level of amino acids for conjugation with drugs.
- 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, Zn retard the metabolic activity of enzymes.
- Starvation results in decreased amount of glucuronides formed than under normal conditions.

Diet

Enzyme content and activity is altered by dietary components

Protein diet

Enzyme synthesis is promoted

Increased drug metabolising activity

Fat free diet

Depresses cytochrome P-450 levels

Decreased drug metabolising activity

grapefruit

Inhibit metabolism of some drugs Eg: Terfenadine

Vitamins and minerals

Vitamin A, B_2,B_3,C & E

Ca, Fe, Mg & ZN

Retard metabolic activity of enzymes

c. Sex difference

Since variations between male and female are observed following puberty. So, sex related differences in the rate of metabolism may be due to sex hormones. Such sex differences are widely studied in rats where male rats have greater drug metabolizing capacity. In humans, women metabolize benzodiazepines slowly than men. Several studies have shown that women on contraceptive pills metabolize a number of drugs at a slow rate. [5]

Studies in animals

Male rats have greater drug metabolising capacity

Studies in humans

Women metabolise benzodiazepines **slowly** than men

Women on **contraceptive pills** metabolise some drugs **slowly**

. **Species difference**

Species difference have been observed in both Phase-I and Phase-II reactions. In Phase-I reactions, both qualitative and quantitative variations in the enzyme and their activity have been observed. Qualitative differences among species generally result from the presence or absence of specific enzymes in those species. Quantitative differences result from variations in the amount and localization of enzymes, the amount of natural inhibitors, and the competition of enzymes for specific substrates.

Human liver contains less cytochrome P-450 per gram of tissue than do the livers of other species. For example, rat liver contains approximately 30 to 50 nmol/g of Cytochrome P-450, whereas human liver contains 10 to 20 nmol/g. Furthermore, human liver is 2 percent of body weight, whereas rat liver is approximately 4 percent.[8]

Similarly,In men, amphetamine and ephedrine are predominantly metabolized by oxidative deamination, whereas in rats aromatic oxidation is the major route in Phase-II reactions.

Similarly in pigs, the phenol is excreted mainly as glucuronide whereas its sulphate conjugate dominates in cats.

Species differences

Differences are mainly quantitative but there are some qualitative differences too

Examples

In Phase-I reactions

Metabolism of amphetamine and ephedrine

By aromatic oxidation

By oxidative deamination

In Phase-II reactions

- Variations are mainly qualitative.

Glucuronide conjugation is an important route of metabolism in mammals, birds, reptiles, and amphibians, but not in fish.

In mammals, cats lack the ability to conjugate phenols with Glucuronic acid but it dominates in pigs

Strain difference

Just as the difference in drug metabolising ability between different species is attributed to genetics, the differences are observed between strains of same species also. It may be studied under two headings:

Pharmacogenetics: A study of inter-subject variability in drug response is called pharmacogenetics. The inter-suject variations in metabolism may either be monogenetically or polygenetically controlled. A polygenetic control is observed in twins.

In identical twins (monozygotic), very little or no difference in metabolism of halothane, phenylbutazone, dicoumaral and antipyrine was detected but large variations were observed in fraternal twins (dizygotic)[8]

Ethnic variations: Differences observed in the metabolism of drug among different races are called ethnic variations. Such variations may be monomorphic or polymorphic.

Example: Approximately equal percent of slow and rapid acetylators are found among whites and blacks whereas the slow acetylators dominate Japanese and Eskimo population.[9]

Strain differences

Pharmacogenetics
(Study of *intersubject* variability in drug response)

Metabolism of phenylbutazone, antipyrine

In monozygotic twins

Very little or No difference

In dizygotic twins

Large difference

Ethnic variations
(variation among different races)

Acetylation of isoniazid

Whites and blacks

Equal percent of slow and rapid acetylators found

Japanese and Eskimo

Slow acetylators dominate

Altered physiological factors

. Pregnancy

Pregnancy is known to affect hepatic drug metabolism. Physiological changes during pregnancy are probably responsible for the reported alteration in drug metabolism. These include elevated concentrations of various hormones such as estrogen, progesterone, placental growth hormones and prolactin.[11]

For example: in women, the metabolism of promazine and pethidine is reduced during pregnancy.

It was also confirmed by the study in animals. In pregnant Sprague-Dawley rats, hexobarbital biotransformation indicated unchanged or slightly elevated microsomal enzyme activity compared to normal rats.[10]

ii. Disease states

There are many disease states that affect the metabolism of drugs. Some of them are cirrhosis of liver, alcoholic liver disease, cholestatic jaundice, diabetes mellitus, acromegaly, malaria, various bacterial and viral infections, etc. It can be seen that major effects are seen in the disease affecting liver as liver is quantitatively the important site for metabolism. The possible cause in the effect of metabolism due to diseases may be:

- Decreased enzyme activity in liver
- Altered hepatic blood flow
- Hypoalbuminaemia (leading to lower plasma binding of drugs). [2]

For example: glycine conjugation of salicylates, oxidation of Vitamin D and hydrolysis of procaine are impaired in kidney diseases.

Hormonal imbalance

Higher level of one hormone may inhibit the activity of few enzymes while inducing that of others. Adrenolectomy, thyroidectomy and alloxan-induced diabetes in animals showed impairment in the enzyme activity with subsequent fall in the rate of metabolism. A similar effect was also observed in the pituitary growth hormone and stress related changes in ACTH levels.

Altered Physiological factors

Pregnancy

Diseased states

High levels of steroid hormones

Maternal drug metabolising ability is reduced

Liver disease (hepatitis, jaundice etc)

Reduction in hepatic drug metabolising ability

Renal disease

Oxidation of Vit.D. Conjugation of salicylates are impaired

CCF, MI

Decrease in blood flow to liver

THANK YOU