Drug Metabolism

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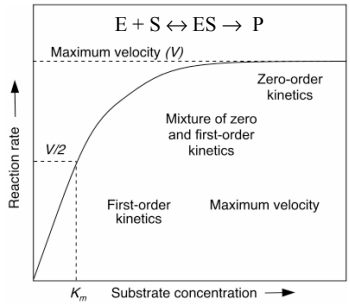
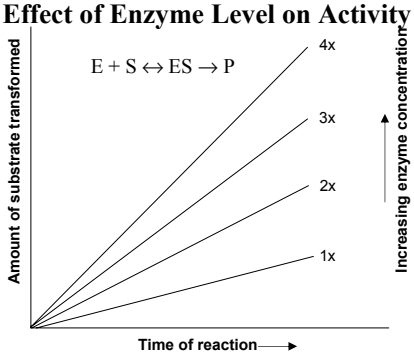
Consequences of Drug Metabolism

Drug (D)	Enzyme (E) Substrates (s) →	Metabolites (DS)
Active	MAJOR	Inactive Less Lipid Soluble more readily excreted
Inactive	MINOR	Active
Toxic		Non-toxic
Non-toxic		Toxic
Active		Equal, less or more active

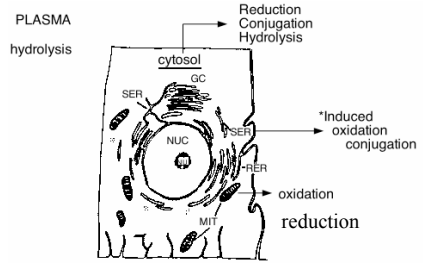
Influence of Substrate on Enzyme Activity



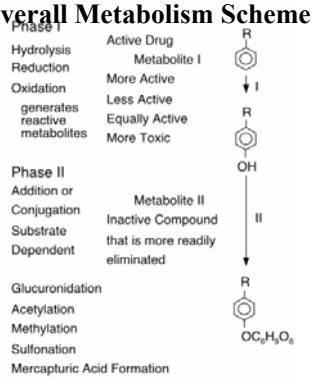
Effect of Enzyme Level on Activity



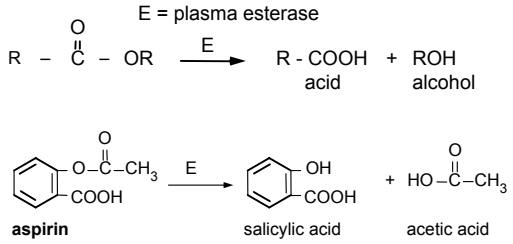
Cellular Location of Drug Metabolizing Enzymes



Overall Metabolism Scheme

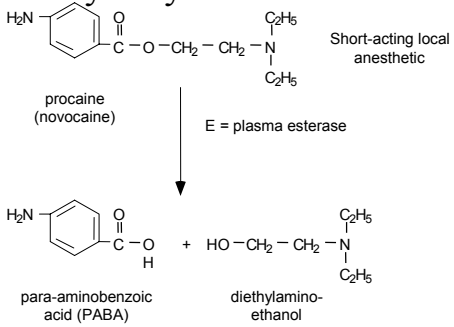


Hydrolysis of Aspirin

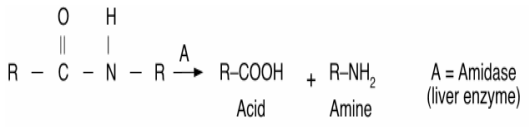


Hydrolysis of Aspirin

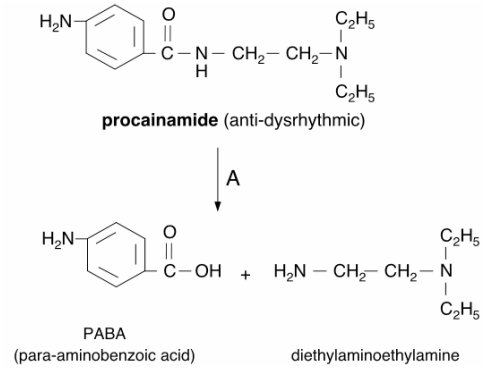
Hydrolysis of Procaine



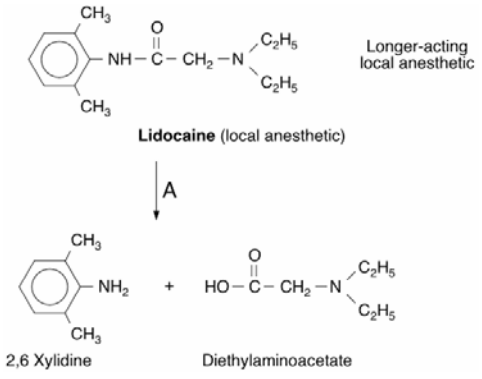
Amide Hydrolysis



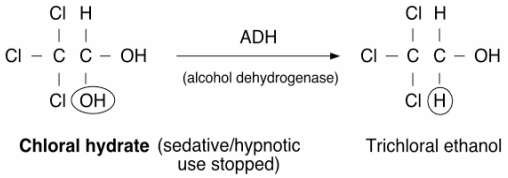
Procaine Hydrolysis



Lidocaine Hydrolysis



Reduction of Chloral Hydrate



P450-Dependent Drug Oxidation

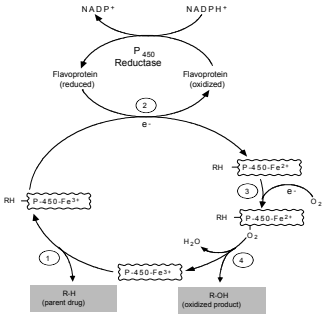
Non-specific system associated with ER

Multiple forms of CYP-P450 [enzyme]
1A2[12%] induced by Smoking and Charcoal Cooking
2B6 [20%] induced by Phenobarbital (PB) and Rifampin
2E1 [6%] induced by Alcohol and Isoniazid
3A4 [28%] induced by PB, Phenytoin, Rifampin, etc.

NADPH Cytochrome P450 reductase [enzyme]

Substrates: Oxygen, NADPH and Drug

Overall Scheme of Oxidative Metabolism



1- Substrate Binding

2- Substrate Reduction

3- Substrate Oxygenation

3- Substrate Reduction

4- Substrate Rearrangement

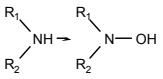
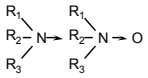
4- Product Dissociation

Regulation of Oxidative Metabolism

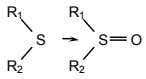
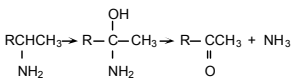
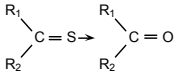
1. Level of CYP-P450 and Reductase Enzymes
   Higher in alcoholics and smokers (more drug)
   Higher with drug intake (PB etc.) [more drug]
   Lower in elderly, infants (less drug)

2. Level of substrates (drugs, oxygen and NADPH)

Examples of Oxidative Metabolism I

N-Oxidation Primary amines	$RNH_2 \rightarrow RNHOH$	Aniline chlorphentermine
Secondary amines		2-Acetylamino-fluorene, acetaminophen.
Tertiary amines		Nicotine, methaqualone

Examples of Oxidative Metabolism II

S-Oxidation		Thioridazine, cimetidine, chlorpromazine
Deamination		Amphetamine, diazepam.
Desulfuration		Thiopental.

Role of Phase I and II Reactions

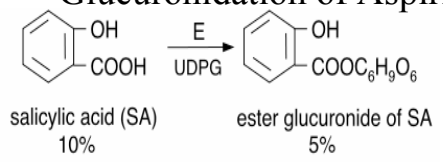
Phase I reactions usually precede Phase II reactions.

Phase I reactions produce chemically reactive sites.

Phase II reactions occur at reactive sites.

Phase II metabolites are usually inactive.

Glucuronidation of Aspirin



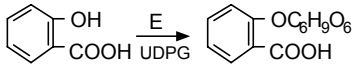
salicylic acid (SA) 10%

ester glucuronide of SA 5%

UDPG is UDP-glucuronic acid

E is glucuronosyl transferase

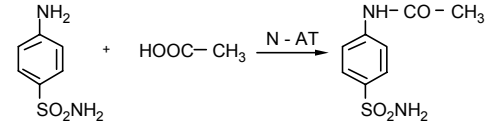
SA = salicylic acid
metabolite of aspirin



SA

ether glucuronide of SA 10%

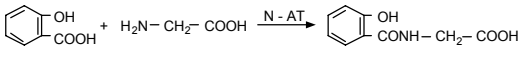
Acetylation of Sulfanilamide



Sulfanilamide Acetic Acid Acetylsulfanilamide

N-AT is N-Acyltransferase

Glycine Conjugation of Aspirin Metabolite (SA)

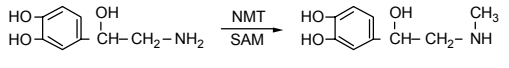


SA (salicylic acid) glycine salicyluric acid

75% major metabolite of Aspirin

Methylation Reactions

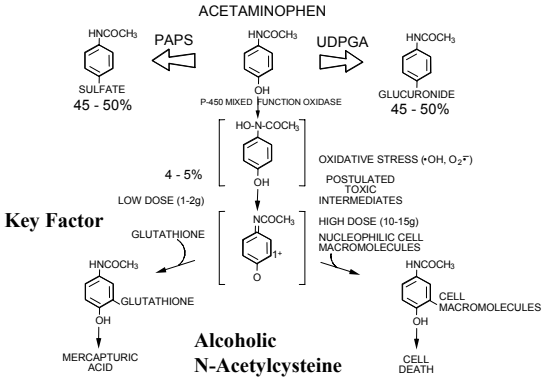
epinephrine metanephrine



norepinephrine epinephrine

O-, N-methyltransferase (OMT & NMT)
S-Adenosylmethionine (SAM)

Acetaminophen Hepatotoxicity



Key Factor

Alcoholic
N-Acetylcysteine

Factors Influencing Drug Metabolism I

Enzyme Induction (slow) increases drug clearance

Diseases: Hyperthyroidism

Drugs [many]: PB, Rifmpin, Phenytoin, etc.

Conditions: smoking, alcoholism

Higher doses of drugs are required

Only one induction period then stable level

Factors Influencing Drug Metabolism II

Enzyme Inhibition (fast) reduces drug clearance

Diseases:Hypothyroidism, Liver Disease

Drugs (many): Chloramphenicaol, Cimetidine, Disulfiram, Ethanol (acute), etc.

Conditions: Pregnancy, Aging, Newborn

Factors Influencing Drug Metabolism III

Age: low metabolism in elderly and newborn

start low and go slow with drug dose

Nutrition: high metabolism with chronic intake of alcohol and charcoal cooked food and lower with high acute alcohol intake.

Factors Influencing Drug Metabolism IV

Genetic Variations:

Isoniazid [prophylaxis of tuberculosis] produces liver injury in slow acetylators.

Succinylcholine [surgical muscle relaxant] produces prolonged respiratory depression (apnea) in patients with abnormal plasma cholinesterase which reduces the hydrolysis of succinylcholine.