CHEMICAL BASIS OF DRUG ACTION

Medical Chemistry is a synthetic discipline that combines all the chemical knowledge needed to understand the mechanism of action of drugs.

Medical Chemistry prepares a specialist to deal with such important issues as the development of new drugs, understanding the chemical basis of drug action, pharmacokinetics and metabolism of drugs in the body that will ensure a rational and professional pharmaceutical care of patients.

Effects of drugs depend on their physical and chemical properties. In most cases, these properties are:

- Solubility and lipophilicity;
- Acid-base properties;
- The size of the molecule and its stereo structure;
- The presence of surface activity of the molecule.

Solubility and lipophilicity of molecule

Metabolism plays a central role in the elimination of drugs and other foreign compounds (xenobiotics) from the body. A solid understanding of drug metabolic pathways is an essential tool for pharmacists in their role of selecting and monitoring appropriate drug therapy for their patients.

Most organic compounds entering the body are relatively lipid soluble (**lipophilic**). To be absorbed, they must traverse the lipoprotein membranes of the lumen walls of the gastrointestinal (GI) tract. Then, once in the bloodstream, these molecules can diffuse passively through other membranes and be distributed effectively to reach various target organs to exert their pharmacological actions. Because of reabsorption in the renal tubules, lipophilic compounds are not excreted to any substantial extent in the urine. Xenobiotics then meet their metabolic fate through various enzyme systems that change the parent compound to render it more water soluble (**hydrophilic**). Once the metabolite is sufficiently water soluble, it may be excreted from the body. The previous statements show that a working knowledge of the **ADME (absorption, distribution, metabolism. and excretion)** principles is vital for successful determination of drug regimens.

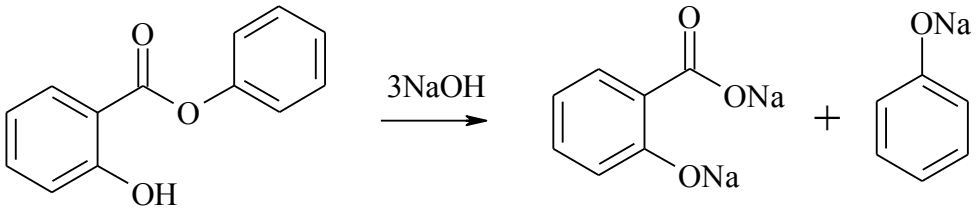
If lipophilic drugs, or xenobiotics, were not metabolized to polar, readily excretable water-soluble products, they would remain indefinitely in the body, eliciting their biological effects. Thus, the formation of water-soluble metabolites not only enhances drug elimination, but also leads to compounds that are generally pharmacologically inactive and relatively nontoxic.

Consequently, drug metabolism reactions have traditionally been regarded as **detoxication** (or detoxification) processes. Unfortunately, it is incorrect to assume that drug metabolism reactions are always detoxifying. Many drugs are biotransformed to pharmacologically active metabolites. These metabolites may have significant activity that contributes substantially to the pharmacological or toxicological effect(s) ascribed to the parent drug. Occasionally, the parent compound is inactive when administered and must be metabolically converted to a biologically active drug (metabolite). These types of compounds are referred to as **prodrugs**.

Hydrolysis of esters by digestive enzymes in the gastrointestinal tract creates pharmacologically active metabolites.

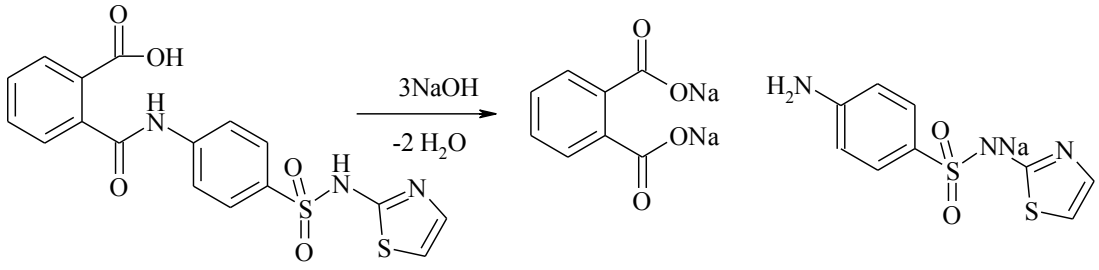
Example: chloramphenicol stearate is an ester of chloramphenicol and stearic acid, which is used in pediatrics, has antibacterial action, but unlike the bitter chloramphenicol is tasteless. The drug becomes active under intestinal lipase enzymes and micro flora action.

Example: phenyl salicylate is an ester of phenol and salicylic acid, which after oral administration is not affected by the acidic medium of the stomach but is hydrolysed in the alkaline environment of the small intestine. It is partially absorbed into the bloodstream.



Mode of its action is based on the disinfectant and bacteriostatic effect of phenol in the intestine and the urinary tract during the excretion by kidneys, and anti-inflammatory, analgesic and antipyretic effect of salicylic acid.

Example: phthalylsulphathiazole, when administered, is slowly absorbed from the digestive tract, causing a high concentration in the colon, where the influence of micro flora causes its hydrolysis. Formed sulphathiazole has a bacteriostatic effect on the pathogens of intestinal infections.



Example: hexamethylenetetramine (methenamine).

Its mechanism of action is the hydrolysis with the release of active formaldehyde that occurs only in an acidic medium. This drug affects the bacteria pathogens of urinary tract and inflammation centers with high concentration of acidic products of tissue decomposition.

$$(CH_2)_6N_4 + 6H_2O + 4H^+ \rightarrow 6HCOH + 4NH_4^+$$

In addition, it is becoming increasingly clear that not all metabolites are nontoxic. Indeed, many adverse effects (e.g., tissue necrosis, carcinogenicity, teratogenicity) of drugs and environmental contaminants can be attributed directly to the formation of chemically reactive metabolites that are highly detrimental to the body. This concept is more important when the patient has a disease state that inhibits or expedites xenobiotic metabolism. Also, more and more drug metabolites are being found in our sewage systems. These compounds may be nontoxic to humans but harmful to other animals or the environment.

Partition coefficient

The most common physicochemical descriptor is the molecule's partition coefficient in an octanol/water system. As emphasized previously, the drug will go through a series of partitioning steps: (a) leaving the aqueous extracellular fluids. (b) passing through lipid membranes, and (c) entering other aqueous environments before reaching the receptor. In this sense, a drug is undergoing the same partitioning phenomenon that happens to any chemical in a separatory funnel containing water and a nonpolar solvent such as hexane, chloroform, or ether. The partition coefficient (P) is the ratio of the molar concentration of chemical in the nonaqueous phase (usually 1-octanol) versus that in the aqueous phase. For reasons already discussed, it is more common to use the logarithmic expression.

$$P = \frac{[SOLUTE]octanol}{[SOLUTE]water} \qquad \log P_{oct/wat} = \log\left(\frac{[solute]\ octanol}{[solute]\ water}\right)$$

The difference between the separatory funnel model and what actually occurs in the body is that the partitioning in the funnel will reach an equilibrium at which the rate of chemical leaving the aqueous phase and entering the organic phase will equal the rate of the chemical moving from the organic phase to the aqueous phase. This is not the physiological situation. Note that dynamic changes are occurring to the drug, such as it being metabolized,bound to serum albumin, excreted from the body, and bound to receptors. The environment for the drug is not static. Upon administration, the drug will be pushed through the

membranes because of the high concentration of drug in the extracellular fluids relative to the concentration in the intracellular compartments. In an attempt to maintain equilibrium ratios, the flow of the drug will be from systemic circulation through the membranes onto the receptors. As the drug is metabolized and excreted from the body, it will be pulled back across the membranes, and the concentration of drug at the receptors will decrease.

Equations 1 and 2 assume that the drug is in the nonpolar state. A large percentage of drugs are amines whose pK_a is such that at physiological pH 7.4, a significant percentage of the drug will be in its protonated, ionized form. A similar statement can be made for the HA acids (carboxyl, sulfonamide. imide) in that at physiological pH. a significant percentage will be in their anionic forms. An assumption is made that the ionic form is water-soluble and will remain in the water phase of an octanol/water system.

Because much of the time the drug's movement across membranes is a partitioning process, the partition coefficient has become the most common physicochemical property. The question that now must be asked is what immiscible nonpolar solvent system best mimics the water/lipid membrane barriers found in the body? It is now realized that the n-octanol/water system is an excellent estimator of drug partitioning in biological systems. One could argue that it was fortuitous that n-octanol was available in reasonable purity for the early partition coefficient determinations. To appreciate why this is so, one must understand the chemical nature of the lipid membranes.

These membranes are not exclusively anhydrous fatty or oily structures. As a first approximation, they can be considered bilayers composed of lipids consisting of a polar cap and large hydrophobic tail.

Experimental determination of octanol/water partition coefficients is tedious and time consuming. Today, most are calculated. The accuracy of these calculations is only as good as the assumptions made by the writers of the software. These include atomic fragment values, correction factors, spatial properties, effects of resonance and induction, internal secondary bonding forces, etc. There are over 30 different software packages for calculating a molecules partition coefficient, and their accuracy varies widely.

Lipophilicity growth of drug compounds correlates with the increase in its biological activity, reduced water solubility, increase in the degree of protein binding, acceleration of metabolism, penetration through the skin, peak activity, and, in some cases, a decrease in duration of action.

Acid-base properties

Most drugs used today can be classified as acids or bases. As is noted shortly, a large number of drugs can behave as either acids or bases as they begin their journey into the patient in different dosage forms and end up in systemic circulation. A drug's acid-base properties can greatly influence its biodistribution and partitioning characteristics.

Over the years, at least four major definitions of acids and bases have been developed. The model commonly used in pharmacy and biochemistry was developed independently by Lowry and Bronsted. In their definition, an acid is defined as a proton donor and a base is defined as a proton acceptor.

GENERAL PATHWAYS OF DRUG METABOLISM

Drug metabolism reactions have been divided into two categories:

phase I (functionalization) and

phase II (conjugation) reactions.

Phase I, or functionalization reactions, include **oxidative, reductive, and hydrolytic biotransformations** (Table). The purpose of these reactions is to introduce a functional polar group(s) (e.g., OH. COOH, NH2, SH) into the xenobiotic molecule to produce a more water-soluble compound. This can be achieved by direct introduction of the functional group (e.g., aromatic and aliphatic hydroxylation) or by modifying or “unmasking" existing functionalities (e.g., reduction of ketones and aldehydes to alcohols; oxidation of alcohols to acids; hydrolysis of ester and amides to yield COOH. NH2, and OH groups; reduction of azo and nitro compounds to give NH2 moieties; oxidative N-, 0-, and 5-dealkylation to give NH2. OH. and SH groups). Although phase I reactions may not produce sufficiently hydrophilic or inactive metabolites, they generally tend to provide a functional group or “handle” on the molecule that can undergo subsequent phase II reactions.

The purpose of phase II reactions is to attach small, polar, and ionizable endogenous compounds such as glucuronic acid, sulfate, glycine, and other amino acids to the functional handles of phase I metabolites or parent compounds that already have suitable existing functional groups to form water-soluble conjugated products. Conjugated metabolites are readily excreted in the urine and are generally devoid of pharmacological activity and toxicity in humans. Other phase II pathways, such as methylation and acetylation, terminate or attenuate biological activity, whereas glutathione (GSH) conjugation protects the body against chemically reactive compounds or

metabolites. Thus, phase I and phase II reactions complement one another in detoxifying, and facilitating the elimination of drugs and xenobiotics.

Various phase I and phase II biotransformation pathways (see Table 1) are outlined, and representative drug examples for each pathway are presented. The central role of the cytochrome P450 (CYP) monooxygenase system in oxidative drug biotransformation is elaborated. Discussion of other enzyme systems involved in phase I and phase II reactions is presented in their respective sections. In addition to stereochemical factors that may affect drug metabolism, biological factors such as age, sex, heredity, disease state, and species variation are considered. The effects of enzyme induction and inhibition on drug metabolism and a section on pharmacologically active metabolites are included.

TABLE 1. General Summary of Phase I and Phase II Metabolic Pathways

Phase I or Functionalization Reactions
Oxidative Reactions
Oxidation of aromatic moieties
Oxidation of olefins
Oxidation at benzylic, allylic carbon atoms, and carbon atoms α to carbonyl and imines
Oxidation at aliphatic and alicyclic carbon atoms
Oxidation involving carbon–heteroatom systems:
Carbon–nitrogen systems (aliphatic and aromatic amines; includes *N*-dealkylation, oxidative deamination, *N*-oxide formation, *N*-hydroxylation)
Carbon–oxygen systems (*O*-dealkylation)
Carbon–sulfur systems (*S*-dealkylation, *S*-oxidation, and desulfuration)
Oxidation of alcohols and aldehydes
Other miscellaneous oxidative reactions
Reductive Reactions
Reduction of aldehydes and ketones
Reduction of nitro and azo compounds
Miscellaneous reductive reactions
Hydrolytic Reactions
Hydrolysis of esters and amides
Hydration of epoxides and arene oxides by epoxide hydrase
Phase II or Conjugation Reactions
Glucuronic acid conjugation
Sulfate conjugation
Conjugation with glycine, glutamine, and other amino acids
Glutathione or mercapturic acid conjugation
Acetylation
Methylation

Phase I

Basic regularity of metabolic oxidation

Oxidation is the most common metabolism reaction. Various reactions include the oxidation of alkanes and aromatics, epoxidation of alkenes, polycyclic hydrocarbons and halogen derivatives of benzene, dealkylation of secondary and tertiary amines, amine conversion to N-oxides, hydroxylamine and nitroso compounds, halogenated hydrocarbons dehalogenation, oxidation of organic tiophosphates and the reduction of nitroso compounds to primary aromatic amines.

Role of cytochrome p450 monooxygenases in oxidative biotransformations

Of the various phase I reactions, oxidative biotransformation processes are, by far, the most common and important in drug metabolism. The general stoichiometry that describes the oxidation of many xenobiotics (R-H) to their corresponding oxidized metabolites (R-OH) is given by the following equation:

$$O_2 + 2H^+ + 2e^- \longrightarrow O + H_2O$$

$$O + R\text{-}H \longrightarrow R\text{-}OH$$

$$O_2 + 2e^- + 2H^+ + R\text{-}H \longrightarrow R\text{-}OH + H_2O$$

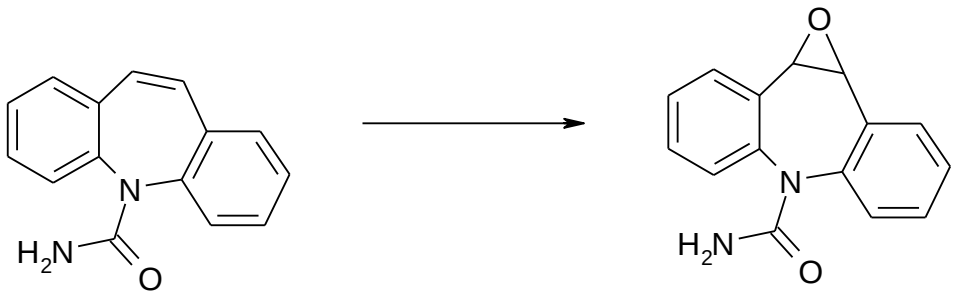
The enzyme systems carrying out this biotransformation are referred to as mixed-junction oxidases or monooxygenases. There is a large family that carry out the same basic chemical reactions. CYP refers to the cytochrome system.

During this oxidative process, one atom of molecular oxygen (0_2) is introduced into the substrate R-H to form R-OH and the other oxygen atom is incorporated into water. The mixed-function oxidase system[26] is actually made up of several components, the most important being the superfamily of CYP enzymes (currently at 57 genes) which are responsible for transferring an oxygen atom to the substrate R-H.

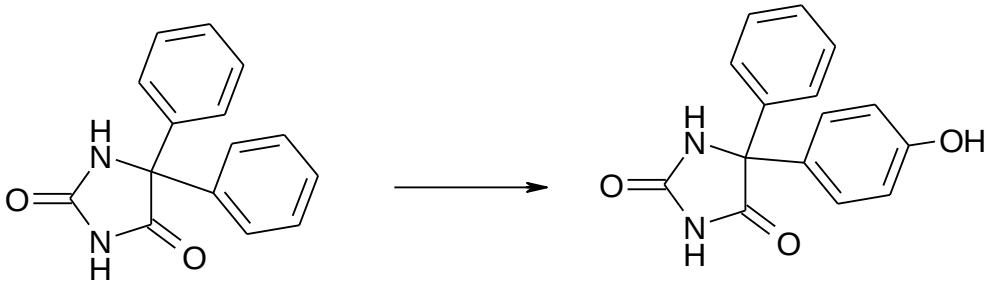
The CYP enzymes are heme proteins. The heme portion is an iron-containing porphyrin called protoporphyrin IX, and the protein portion is called the apoprotein. CYP is found in high concentrations in the liver, the major organ involved in the metabolism of xenobiotics. The presence of this enzyme in many other tissues (e.g., lung, kidney, intestine, skin, placenta, adrenal cortex) shows that these tissues have drug-oxidizing capability too. The name cytochrome P450 is derived from the fact that the reduced (Fe^{2+}) form of this enzyme binds with carbon monoxide to form a complex that has a distinguishing spectroscopic absorption maximum at 450 nm.

One important feature of the hepatic CYP mixed- function oxidase system is its ability to metabolize an almost unlimited number of diverse substrates by various oxidative transformations. This versatility is believed to be a result of the substrate nonspecificity of CYP as well as the presence of multiple forms of the enzyme. Some of these P450 enzymes are selectively inducible by various chemicals (e.g., phénobarbital, benzo[a]pyrene, 3-methyl- cholanthrene).

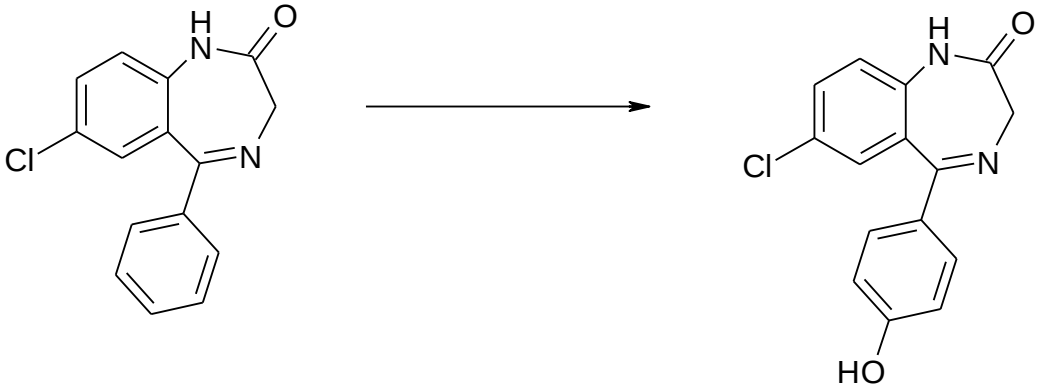
Examples of metabolic oxidation: anticonvulsant *carbamazepine*.



Phenytoin:



Diazepam:

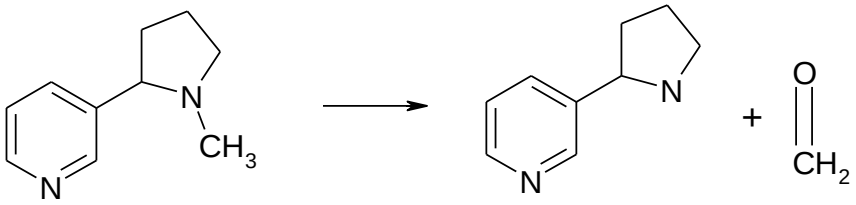


Phenobarbital:

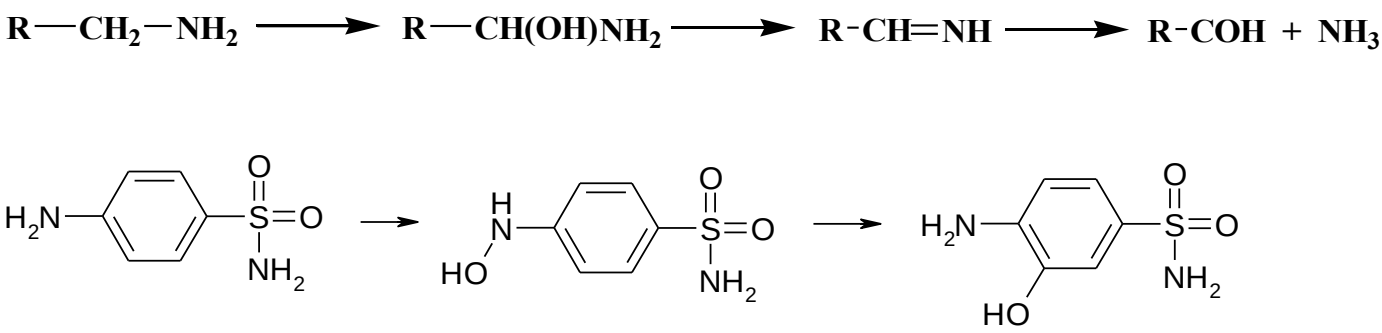
Фенобарбітал
(активний медикамент)

n-оксифенілетилбарбітурова
кислота
(неактивний метаболіт)

Nicotine:

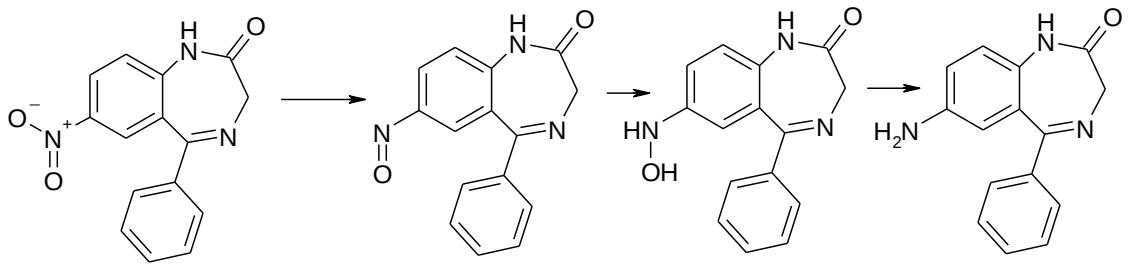


Amines:

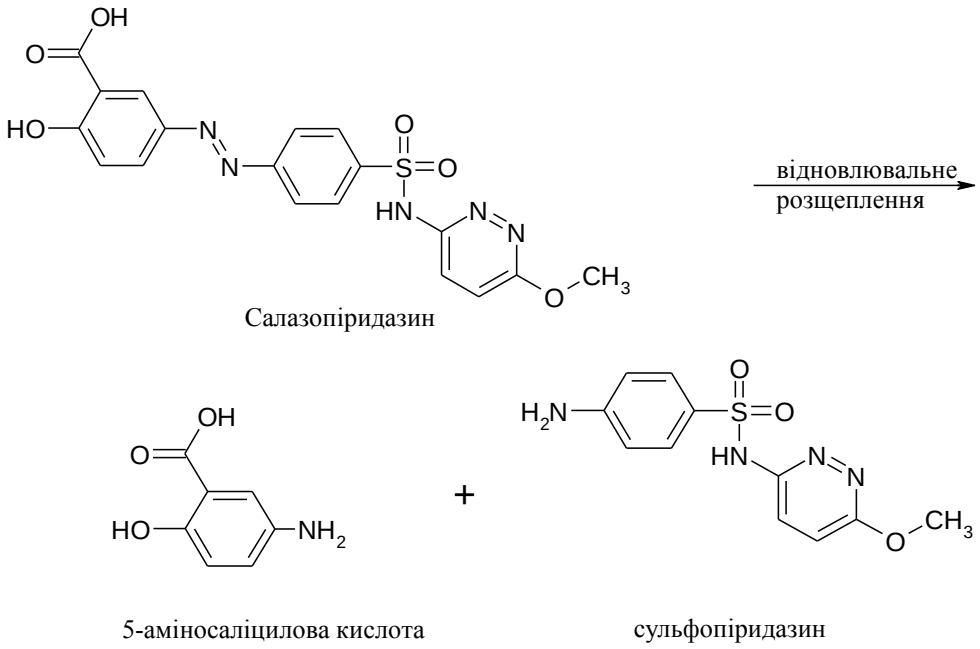


Basic regularity of metabolic reduction

Liver microsomes contain reductase enzymes that catalyse the reduction of nitrogen and nitro compounds to primary amines. The aromatic nitro compounds originally are changed to nitroso compounds, hydroxylamine derivatives, and then to aromatic amines:



Salazopyridazine:



Салазопіридазин

5-аміносаліцилова кислота

сульфопіридазин

Phase II

Glucuronic Acid Conjugation

Glucuronidation is the most common conjugative pathway in drug metabolism for several reasons: (a) a readily available supply of D-glucuronic acid (derived from D-glucose), (b) numerous functional groups that can combine enzymatically with glucuronic acid, and (c) the glucuronyl moiety (with its ionized carboxylate [pK_a 3.2] and polar hydroxyl groups), which, when attached to xenobiotic substrates, greatly increases the water solubility of the conjugated product." [7359_361]

Sulfate Conjugation

Conjugation of xenobiotics with sulfate occurs primarily with phenols and, occasionally, with alcohols, aromatic amines, and A-hydroxy compounds.[389-391] In contrast to glucuronic acid, the amount of available sulfate is rather limited.

The body uses a significant portion of the sulfate pool to conjugate numerous endogenous compounds such as steroids, heparin, chondroitin. catecholamines, and thyroxine. The sulfate conjugation process involves activation of inorganic sulfate to the coenzyme 3'-phosphoadenosine- 5'-phosphosulfate (PAPS). Subsequent transfer of the sulfate group from PAPS to the accepting substrate is catalyzed by various soluble sulfotransferases present in the liver and other tissues (e.g.. kidney, intestine).[392] The sequence of events involved in sulfoconjugation is depicted in Figure 3.13. Sulfate conjugation generally leads to water-soluble and inactive metabolites. It appears, however, that the O-sulfate conjugates of some Af-hydroxy compounds give rise to chemically reactive intermediates that are toxic.[241]

Conjugation with Glycine, Glutamine, and Other Amino Acids

The amino acids glycine and glutamine are used by mammalian systems to conjugate carboxylic acids, particularly aromatic acids and arylalkyl acids.[408 409] Glycine conjugation is common to most mammals, whereas glutamine conjugation appears to be confined mainly to humans and other primates. The quantity of amino acid conjugates fomied from xenobi- otics is minute because of the limited availability of amino acids in the body and competition with glucuronidation for carboxylic acid substrates. In contrast with glucuronic acid and sulfate, glycine and glutamine are not converted to activated coenzymes. Instead, the carboxylic acid substrate is activated with adenosine triphosphate (ATP) and coenzyme A (CoA) to form an acyl-CoA complex. The latter intermediate, in turn, acylates glycine or glutamine under the influence of specific glycine or glutamine N-acyltransferase enzymes. The activation and acylation steps take place in the mitochondria of liver and kidney cells. The sequence of metabolic events

FACTORS AFFECTING DRUG METABOLISM

Drugs and xenobiotics often are metabolized by several different **phase I and phase II pathways** to give several metabolites. The relative amount of any particular metabolite is determined by the concentration and activity of the enzyme(s) responsible for the biotransformation. The rate of metabolism of a drug is particularly important for its pharmacological action as well as its toxicity.

For example. if the rate of metabolism of a drug is decreased, this generally increases the intensity and duration of the drug action. In addition, decreased metabolic elimination may lead to accumulation of toxic levels of the drug.

Conversely, an increased rate of metabolism decreases the intensity and duration of action as well as the drug's efficacy. Many factors may affect drug metabolism, and they are discussed in the following sections. These include age, genetic or hereditary factors, sex, enzyme induction, and enzyme inhibition.

Age Differences

Age-related differences in drug metabolism are generally quite apparent in the newborn. In most fetal and newborn animals, undeveloped or deficient oxidative and conjugative enzymes are chiefly responsible for the reduced metabolic capability seen. In general, the ability to carry out metabolic reactions increases rapidly after birth and approaches adult levels in about 1 to 2 months.

In humans, oxidative and conjugative (e.g., glucuronidation) capabilities of newborns are low compared with those of adults. Infants possess poor glucuronidating ability because of a deficiency in glucuronyltransferase activity. The inability of infants to conjugate chloramphenicol with glucuronic acid appears to be responsible for the accumulation of toxic levels of this antibiotic, resulting in the so-called gray baby syndrome. Similarly, neonatal hyperbilirubinemia results from the inability of newborn babies to glucuronidate bilirubin.[387]

The effect of old age on drug metabolism has not been as well studied. There is some evidence in animals and humans that drug metabolism diminishes with old age. Much of the evidence, however, is based on prolonged plasma half-lives of drugs that are metabolized totally or mainly by hepatic microsomal enzymes (e.g., antipyrine, phénobarbital. acetaminophen). In evaluating the effect of age on drug metabolism, one must differentiate between "normal" loss of enzymatic activity with aging and the effect of a diseased liver from hepatitis, cirrhosis, etc., plus decreased renal function, because much of the water-soluble conjugation products are excreted in the liver.

Hereditary or Genetic Factors

Marked individual differences in the metabolism of several drugs exist in humans. Many of these genetic or hereditary factors are responsible for the large differences seen in the rate of metabolism of these drugs. Genetic factors also appear to influence the rate of oxidation of drugs such as isoniazid, phenytoin,

phenylbutazone, dicumarol, and nortriptyline. The rate of oxidation of these drugs varies widely among different individuals. In general, individuals who tend to oxidize one drug rapidly are also likely to oxidize other drugs rapidly. Numerous studies in twins (identical and fraternal) and in families indicate that oxidation of these drugs is under genetic control.

Many patients state that they do not respond to codeine and codeine analogs. It now is realized that their CYP2D6 isozyme does not readily O-demethylate codeine to form morphine. This genetic polymorphism is seen in about 8% of Caucasians, 4% of African Americans, and less than \% of Asians.[504] Genetic polymorphism with CYP isozymes is well documented as evidenced by the many examples in this chapter. There is limited evidence of polymorphism involving MAO-A and MAO-B. The chemical imbalances seen with some mental diseases may be the cause.

Enzyme Induction

The activity of hepatic microsomal enzymes, such as the CYP mixed-function oxidase system, can be increased markedly by exposure to diverse drugs, pesticides, polycyclic aromatic hydrocarbons, and environmental xenobiotics. The process by which the activity of these drug-metabolizing enzymes is increased is termed enzyme induction. The increased activity is apparently caused by an increased amount of newly synthesized enzyme. Enzyme induction often increases the rate of drug metabolism and decreases the duration of drug action.

Inducing agents may increase the rate of their own metabolism as well as those of other unrelated drugs or foreign compounds. Concomitant administration of two or more drugs often may lead to serious drug interactions as a result of enzyme induction. For instance, a clinically critical drug interaction occurs with phénobarbital and warfarin. Induction of microsomal enzymes by phénobarbital increases the metabolism of warfarin and consequently, markedly decreases the anticoagulant effect. Therefore, if a patient is receiving warfarin anticoagulant therapy and begins taking phénobarbital, careful attention must be paid to readjustment of the warfarin dose. Dosage readjustment is also needed if a patient receiving both warfarin and phénobarbital therapy suddenly stops taking the barbiturate. The ineffectiveness of oral contraceptives in women on concurrent phénobarbital or rifampin therapy has been attributed to the enhanced metabolism of estrogens (e.g., 17a-ethinylestradiol) caused by phénobarbital and rifampin induction.

Inducers of microsomal enzymes also may enhance the metabolism of endogenous compounds, such as steroidal hormones and bilirubin. For instance, phénobarbital can increase the metabolism of cortisol, testosterone, vitamin D, and bilirubin in humans. The enhanced metabolism of vitamin D3 induced by phénobarbital and phenytoin appears to be responsible for the osteomalacia seen in patients on long-term therapy with these two anticonvulsant drugs. Interestingly, phénobarbital induces glucuronyltransferase enzymes, thereby enhancing the conjugation of bilirubin with glucuronic acid. Phénobarbital has been used occasionally to treat hyperbilirubinemia in neonates.

In addition to drugs, other chemicals, such as polycyclic aromatic hydrocarbons (e.g., benzo[a]pyrene, 3-methyl- cholanthrene) and environmental pollutants (e.g., pesticides, PCBs. TCDD), may induce certain oxidative pathways and. thereby, alter drug response. Cigarette smoke contains minute amounts of polycyclic aromatic hydrocarbons, such as benzo[a]pyrene, which are potent inducers of microsomal CYP enzymes. This induction increases the oxidation of some drugs in smokers. For example, theophylline is metabolized more rapidly in smokers than in nonsmokers. This difference is reflected in the marked difference in the plasma half-life of theophylline between smokers (t4.1 hours) and nonsmokers ($f_{1/2}$ 7.2 hours). Other drugs, such as phenacetin. pentazocine, and propoxyphene, also reportedly undergo more rapid metabolism in smokers than in non- smokers.

Occupational and accidental exposure to chlorinated pesticides and insecticides can also stimulate drug metabolism. For instance, the half-life of antipyrine in workers occupationally exposed to the insecticides lindane and dichlorodiphenyltrichloroethane (DDT) is reportedly significantly shorter (7.7 vs. 11.7 hours) than in control subjects. A case was reported in which a worker exposed to chlorinated insecticides failed to respond (i.e., decreased anticoagulant effect) to a therapeutic dose of warfarin.

Enzyme Inhibition

Several drugs, other xenobiotics including grapefruit, and possibly other foods can inhibit drug metabolism. With decreased metabolism, a drug often accumulates, leading to prolonged drug action and serious adverse effects. Enzyme inhibition can occur by diverse mechanisms, including substrate competition, interference with protein synthesis, inactivation of drug-metabolizing enzymes, and hepatotoxicity leading to impairment of enzyme activity. Some drug interactions resulting from enzyme inhibition have been

reported in humans. For example, phenylbutazone stereoselectively inhibits the metabolism of the more potent (S)(—) enantiomer of warfarin. This inhibition may explain the excessive hypoprothrombinemia (increased anticoagulant effect) and many instances of hemorrhaging seen in patients on both warfarin and phenylbutazone therapy. The metabolism of phenytoin is inhibited by drugs such as chloramphenicol, disulfiram, and isoniazid. Interestingly, phenytoin toxicity as a result of enzyme inhibition by isoniazid appears to occur primarily in slow acetylators. Several drugs, such as dicumarol. chloramphenicol, and phenylbutazone inhibit the biotransformation of tolbutamide, which may lead to a hypoglycemic response.

The grapefruit-drug interaction is complex. It may be caused by the bioflavonoids or the furanocoumarins. Grapefruit's main bioflavonoid, naringin, is a weak CYP inhibitor, but the product of the intestinal flora, naringenin. does inhibit CYP3A4. The literature is very confusing because many of the studies were done in vitro, and they cannot always be substantiated under in vivo conditions. In addition, components in grapefruit also activate P-glycoprotein, which would activate the efflux pump in the gastric mucosa and thus interfere with oral absorption of the certain drugs. The combination of CYP enzyme inhibition and P-glycoprotein activation can lead to inconclusive results. The general recommendation when a drug interaction is suspected is that the patient avoid grapefruit and its juice.

TABLE 2. Potential Drug-Grapefruit Interactions Based on Grapefruit Inhibition of CYP 3A4

Drug	Result
Amiodarone	Increased bioavailability
Diazepam	Increased AUC
Carbamazepine	Increased AUC, peak and trough plasma concentrations
Cisapride	Increased AUC
Cyclosporine, tacrolimus	Increased AUC and serum concentrations
Atorvastatin, simvastatin	Increased absorption and plasma concentrations
Saquinavir	Increased absorption and plasma concentrations

Miscellaneous Factors Affecting Drug Metabolism

Other factors also may influence drug metabolism. Dietary factors, such as the protein-to-carbohydrate ratio, affect the metabolism of a few drugs. Indoles present in vegetables such as Brussels sprouts, cabbage, and cauliflower, and polycyclic aromatic hydrocarbons present in charcoal- broiled beef induce enzymes and stimulate the metabolism of some drugs. Vitamins, minerals, starvation, and malnutrition also apparently influence drug metabolism. Finally, physiological factors, such as the pathological state of the liver (e.g.. hepatic cancer, cirrhosis, hepatitis), pregnancy, hormonal disturbances (e.g., thyroxine, steroids), and circadian rhythm, may markedly affect drug metabolism.

Stereochemical Aspects of Drug Metabolism

Many drugs (e.g., warfarin, propranolol, hexobarbital, glutethimide, cyclophosphamide, ketamine, and ibuprofen) often are administered as racemic mixtures in humans. The two enantiomers present in a racemic mixture may differ in pharmacological activity. Usually, one enantiomer tends to be much more active than the other. For example, the (S)(—)enantiomer of warfarin is 5 times more potent as an oral anticoagulant than the (R)(+) enantiomer. In some instances, the two enantiomers may have totally different pharmacological activities. For example, (+)-a-propoxyphene (Darvon) is an analgesic, whereas (-)-a-propoxyphene (Novrad) is an antitussive.[528] Such differences in activity between stereoisomers should not be surprising, because Chapter 2 explains that stereochemical factors generally have a dramatic influence on how the drug molecule interacts with the target receptors to elicit its pharmacological response. By the same token, the preferential interaction of one stereoisomer with drug-metabolizing enzymes may lead one to anticipate differences in metabolism for the two enantiomers of a racemic mixture. Indeed, individual enantiomers of a racemic drug often are metabolized at different rates. For instance, studies in humans indicate that the less active (+) enantiomer of propranolol undergoes more rapid metabolism than the corresponding (—) enantiomer. Allylic hydroxylation of hexobarbital occurs more rapidly with the(—) enantiomer in humans. The term substrate stereoselectivity is used frequently to denote a preference for one stereoisomer as a substrate for a metabolizing enzyme or metabolic process.