Metabolism of toxicants pdf

The excretion of most toxic substances and their metabolites is by the kidneys. Some excretion occurs in the digestive tract and some through milk. Many polar and high molecular compounds are excreted in the bile. An enterohepato cycle occurs when these compounds are excreted from the liver by bile, reabsorbed from the intestine and returned to the liver. Milk is also an excretion route for some toxic substances. The degree of excretion may be of paramount importance as certain toxic substances may cause live residues in food-producing animals. The method of administration, the dose and condition of the animal – to name a few factors – can have a profound effect on the rate of excretion. Toxic agents are removed in the kidneys by glomerular filtration, tubular excretion by passive diffusion and active tubular secretion. Kidney damage from the excretion of xenobiotics is specific to the anatomical place where excretion occurs. The excretion of the objects are proximal tubules, glomeruli, medulla, papilla and henle contour. Proximal complex tubule is the most common place of toxic-induced injury. Important phase I enzymes present in the kidneys are cytochrome P450, prostaglandin synthase, and prostaglandin reductase. Phase I enzyme cytochrome P450 is present in the kidneys at 10% of the liver level. Important phase II enzymes in the kidneys are UDP-glucuronosyltransferases (UGT), sulfotransferases and glutathione-S-transferase. Medulla and papilla are the target sites for phenylbutazone, tubules are targets for many plant toxins, henle's contour is the target site for fluoride and glomeruli for immune complexes. The elimination or disappearance (by metabolic changes) of a chemical by an organ or body is expressed as a half-life (t1/2) defined as the time required for the disappearance of half of the compound. The elimination rate usually depends on the concentration of the compound. The constant (e.g. 1/2) eliminated per unit of time is called first-line kinetics. Metabolic reaction may dictate the rate of elimination. The constant amount eliminated per unit of time is called zero-value kinetics. In different compartments of the body there are probably different elimination rates. A two-compartment system describes elimination, which is initially rapid (eg, from the central or plasma component) and subsequently slower than the peripheral component (eg, liver, kidney, or fat). Daily roots The amount of free plasma toxic is a function of absorption, distribution and elimination of toxic (Figure 9.1). In Chapter 8, various factors were discussed that govern the absorption of toxic substances into the gastrointestinal tract (GI) tract. This chapter focuses on factors that affect the spread and elimination of toxic substances. metabolism of toxic agents conversion with intent to excrete toxicants and other compounds (xenobbiotics) undergo metabolic transformation in the body. In many of the the rate of metabolism is the main determinant of the substance for both duration and intensity of action. Compounds that are disabled by metabolism tend to be more active and stopping in the body when the metabolic rate is slow compared to compounds that are quickly metabolized. Any substance, if not eliminated, may eventually reach a toxic level. A characteristic feature of most toxic substances is that subsequent metabolic products are more polar than the original compound. Thus, the metabolism of toxic substances reduces biological activity and increases polarity or reduces lipid solubility. The importance of increased toxic polarity is that such compounds are more likely to be excreted by renal or biliary processes. On the other hand, compounds with high coefficients of lipid water distribution pass effortlessly through the membranes and diffusely back free from tubular urine through the renal tubular cells in plasma, and such compounds tend to have low renal clearance and long endurance in the body. But if the toxic substance is metabolized to a more water-soluble compound or one with a lower partition coefficient, the tubular reabsorption of the compound is significantly reduced. The terms metabolism and biotransformation are often used synonymously, especially when applied to xenobbiotic compounds such as drugs. Sometimes the conlotation associated with metabolism is to describe the general fate of the compound, including absorption, distribution, biotransformation, and elimination. But more often, metabolism is used to demark biotransformation, because metabolites are products of xenobbiotic biotransformation. Metabolism has an evolutionary significance, because if humans have not developed with such abilities, compounds such as pentobarbital would be pharmacologically active for hundreds of years. Toxication-metabolizing systems have evolved as adaptations to earthlife. It is likely ingestion of toxicating DISTRIBUTION tissue storage ABSORPTION Plasma protein related toxicity Free plasma toxic site of action Metabolism Elimination Excretion FI 9.1 In vivo distribution of toxic substances. that toxic substances are metabolized by living systems, since the first cells were formed in the primary mucus. Marine organisms often do not have the main toxic metabolising systems found in mammals; However, they secrete lpid soluble compounds directly into the surrounding water through the gill membranes. Turning a methyl group into a carboxylic group can reduce the biological half-life of a compound from many hours to several minutes. Enzymatic biotransformation of xenobiots facilitates the elimination of such compounds from the body. Without such enzymes, lipophilic xenobbiotics will remain in the body for a prolonged duration after exposure. These compounds will accumulate in the body exposures reaching toxic levels. Animals, especially herbivores, which consume a wide variety and amount of plant material laden with unusual secondary secondary biotransfer xenobbiotics. Some compounds that are metabolic become more toxic, e.g. tetrachlorometrochloride or benzo(a)pyrene. Reduced solubility of toxic lipids does not necessarily mean increased solubility in water, for example, acetylsulfentazole transformed by sulfaziol. The reduced solubility in water of acetylsulphtazole leads to a compound with serious toxicity, which is obtained by precipitation of renal tubules. In general, two scenarios can be mediated by biotransformation reactions: (1) xenobiotics (toxic), converted into intermediates (toxic or non-toxic), converted into products (non-toxic), or (2) xenobiotics (not toxic) converted into intermediate (toxic) converted into products (non-toxic). The main site of toxic metabolism is the liver, but other tissues can also play an active role. Table 9.1 summarizes the relative tissue distribution of toxic metabolism. Hepatopancreas and fatty organs are the main organs involved in biotransformation in lobsters and insects, respectively. Thus, the liver is the richest source of enzymes for metabolizing toxic substances, but there is sufficient evidence that enzyme systems are ubiquitous, which can be streamlined based on the importance of such enzymes for detoxifying various compounds. Intestinal microflora plays an important role in the biotransformation of TABLE 9.1 Organs, tissues and cells involved in toxic metabolism and their organ/tissue/cell percentage distribution of liver kidney intestines (intestinal flora) Adrenal glands Lung xenogenetics skin due to the impact of evolution on the survival of the species. Ruminants can cope with the relatively high intake of fungal toxins, for example, aflatoxin, due to their decay by the bacteria in the ruminant. Within the liver and other organs, microsomes or endoplasmic reticulum and cytosol or soluble fractions of the cytoplasm are the main sites of xenobiotic metabolism. Lipid-rich endoplasmic reticulum is a strong attraction for lipophilic xenobbiotics. To a lesser extent, metabolism occurs in mitochondria, nuclei and other subcellular organelles. Although some extrahepatic sites contain relatively high levels of enzyme systems for xenobbiotic metabolism, their size reduces their overall contribution to the metabolism of such compounds. Differences in tissue in their ability to metabolise toxic substances can have important toxicological consequences, such as in tissue-specific chemical injuries. Biotransformation Enzymology One of the unique aspects of toxicological metabolism is that although the structures of these potentially toxic products, be they natural or synthetic, are so extremely diverse, the body seems to have evolved detoxifying processes that can cope with almost any of the many different compounds. Animals possess enzymes, may metabolise medicines, pesticides, secondary plant metabolites and synthetic compounds as protective mechanisms that are likely due to evolution in protection against many natural toxic products. There are two categories of animal enzyme systems: (1) those for the transformation of normal endogenous chemicals into tissues, such as nutrients and metabolic by-products of nutrients; and (2) those that change the structure of many foreign compounds and essentially do not have established normal endogenous substrates. The first category of enzymatic systems is thoroughly studied for their general biochemistry. These are enzymes of intermediate metabolism and are characterized by a large number of revolutions and huge improvements in speed over non-returning reactions. Also, these reactions require a precise chemical fit between substrate and enzyme (lock and key model), TABLE 9.2 Catalytic Specificity and Enzyme Efficiency Intermediary Metabolism Xenobiotic Metabolism High Efficiency (High Turnover) Broad Substrate Specificity High Catalytic Efficiency and Fit Dictates Strict Substrate Specificity. Typically, enzyme systems involved in intermediate metabolism have low KM values or are closely related and high Kcal values or high efficiency and rapid turnover. Examples include cholinestherase and hydrolysis of acetylcholine, and monoamine oxidase, acting on epinephrine, tyramine, and short-chain amines. Genetic capacity and thus the metabolic ability of the body limits its ability to produce many different enzymes to detoxify all foreign compounds with which it can come into contact. Thus, enzyme systems involved in xenobiotic metabolism exhibit a wide specificity of the substrate and low catalytic efficiency. These enzyme systems represent compromises with metabolism. To compensate for the specificity or cost of reduced accuracy of the substrate binding enzymes, these enzymes can metabolize various substrates. Table 9.2 lists the differences in these enzymatic systems. The ultimate goal of xenobbiotic metabolism is to increase hydrophilic properties of the compound. This metabolism is outlined in Figure 9.2 showing the integration of phase I and phase II biotransformation reactions. When an organism is dealing with a toxic substance or an inactive compound that can be converted into toxic, biotransformation usually proceeds through a two-phase process. The purpose of enzymatic reactions responsible for biotransformation is to form hydrophilic products that are less toxic and can be released from the body. Phase I or type I reactions These biotransformation reactions include oxidation, reduction, and hydrolysis of foreign compounds. Table 9.3 to Table 9.5 gives a detailed description of phase I reactions. Therefore, the essence of the reactions is to introduce or expose a functional group that is solubility of the lipids of the compound. They encourage the insertion, addition or exposure of functional groups on the structure of the lipophilic compound to the formation of electrophilic compounds (Figure 9.1). Such action gives the compound a polar group, making it a suitable substrate for phase II reactions. Phase II reactions alter compounds by combining them with endogenous substrates to produce water-soluble conjugated products that can be easily excreted. The predominant biotransformation enzyme systems in Phase I reactions are cytochrome P450 and mixed function amine oxidase. Other phase I enzymes Ingestion of toxic foreign compound phase I reactions oxidation hydrolysis phase II reactions conjugation Glucuronidation Sulfanation Acetylene Glycine glutathione Elimination FIGURE 9.2 Metabolism of toxic. TABLE 9.3 Oxidative reactions Reaction Oxidative effect Oxidation oxidation oxidation N-oxidation of aliphatic alcohols Direct insertion of hydroxyl functional group Cellation of alkyl groups and aromatic groups of amines or ethers Loss of amino groups Nitrogen oxidation TABLE 9.4 Reductive reactions Reducing nitrogen reduction in keto reduction ANI 9.5 Characteristics of hydrolytic reactions Compounds , possessing ester bonds (amides and esters) The formation of alcohol and acids includes flavin-containing monooxygenase (FMO) , prostaglandin synthetase (PGS; performs cooxidation), molybdenum hydroxylases, alcohol dehydrogenase, aldehyde dehydrogenase, esterases and amidases, epoxy hydrolase, DDT-dehydroamino-rinase and glutathione reductase. Cytochrome P450 and flavin-containing monooxygenase are found in the microsome. Microsomal enzymes Cytochrome P450 (CYP) Enzymes Cytochrome P450 enzymes of microsomal enzyme systems are embedded in phospholipid, which is important because phospholipid facilitates the interaction between NADPH-cytochrome P450 reductase and cytochrome P450 enzymes (Figure 9.3). Cytochrome P450 is derived from the fact that reduces cytochrome P450 (Fe2+) forms a carbon monoxide (CO) ligand that can be observed with spectral absorption of 450 nm. Cytochrome P450 has been found to be more than one enzyme and the location of the gene on a particular chromosome has been determined for isoenzymes cytochrome P450. Since 1987, a system of nomenclature based on such findings has been used. Since the latest update, P450 human genes have been defined as CYP. Each designation shall be followed by an Arabic numeral marking denoting the individual gene followed by a letter denoting a subfamily and finally by Arabic numerals denoting the individual gene. Cytochrome P450 microsomal monooxygenase reactions are similar, but enzyme classes differ in substrates and products. Therefore, these activities are classified on the basis of chemical reactions. Classes may overlap and the same substrate may be subjected to more than one oxidative reaction. • Aliphatic hydroxylations (Figure 9.4). Alkyl side chains of aromatic compounds are easily oxidized to alcohol. Epoxy of aromatic rings are intermediate products in aromatic hydroxylations. It is known that oxides of polycyclic hydrocarbons (areoxides) are involved in carcinogenesis. Proximal carcinogens derived from the metabolic activation of benzo(a)pyrene are isomers of benzo(s) 7,8-diol-9,10-epoxide. Fe3+ ROH NADPH-cytochrome P450 reductase Fe2+ OOH RH Fe2+ O2 RH Cytochrome b5 FIGURE 9.3 Enzyme system cytochrome P450. • Shaking. The reaction could include the O-, N-and-S-deal. An example of O-dealcylation is the demethylation of p-nitroanisol. Many drugs and insecticides pass through N-dealkylation (Figure 9.5). • N-oxidation. These reactions may lead to hydroxylanin formation, oxime formation and N-oxide formation (Figure 9.6). Several amines can undergo N-oxidation to form hydroxylamine. The classic example is aniline. Iminins and primary amines may be subjected to N-hydroxylation. The formation of noxide is a function mainly of flavin-containing monooxygenase. • Oxidation (S and P). Both microsomal monooxygenases and flavin-containing monooxygenase act on thioesters to oxidize them to sulfoxide-edi and trisublist phosphines of phosphine oxides (Figure 9.7). Sulfoxides are further metabolized to sulphons, a common reaction for insecticides and drugs, chlorinated hydrocarbons and chlorpromazine, respectively. • Desulphurisation and cleavage of esters. These reactions may turn the P-S dual connection into a P-O dual connection. When cholinestherases are converted, potent cholinestherase inhibitors are produced, for example, paraocone of par-aton (Figure 9.7). Flavin-containing monooxygenase These microsomal enzymes are involved in the oxidation of several inorganic compounds and organic compounds containing nitrogen, sulfur, phosphorus or phosphorus. The catalytic cycle of PMO is shown in Figure 9.8 and requires NADPH and oxygen figure 9.4 Aliphatic and aromatic hydrosoxylations. cytochrome P450. Many of the reactions catalyzed by the CMO can be catalyzed by cytochrome P450 too. Several techniques can determine whether compounds are metabolized by FMOs or by cytochrome P450. FMO is inactivateed in the absence of NADPH by subjecting microsomes to 50°C for 1 min, with no effect on cytochrome P450. Cytochrome P450 can be inactivate with non-ion preparations that have no effect on FMO. Antibodies to cytochrome P450 can identify the specific enzyme P450 that catalyzes the reaction. Substrates oxidized by FMO include inorganic compounds (HS-, I-, IO-, I2, and CNS-); organic nitrogen compounds (acyclic and cyclic amines, N-alkyl and N, N-dialkylaniamines, hydrazine, primary amines); organic sulfuric compounds (thiols and disulphides, cyclic and acyclic sulphides, mercaptopururines, pyrimidines, imidazoles, dithioacids and dithiocarbamide-eds, thiocarbamides and thio amymids); organic phosphorus compounds (phosphins, phosphonates); and seleenids and Non-microsome enzymes These oxidorductas are found either in mitochondrial fraction or cyto-soz fraction (soluble supernatant) of tissue homogenate. och3 och3 p-Nitroanisol p-Nitrophenol OCN(CH3)2 ocnhch3 HCHO sch3 Sh Was this article useful? Studying 10 ways to fight cancer can have amazing life benefits the best tips on how to keep this killer in Bay Discovering that you or a loved one has cancer can be completely terrifying. 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