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Intestinal Absorption and Metabolism of Xenobiotics

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There are five possible processes of intestinal absorption of xenobiotics. These are active transport, passive diffusions, pinocytosis, filtration through "pores," and lymphatic absorption. The passive diffusion is major process for transport of foreign chemicals across the intestine. Though the lymphatic absorption of drugs is not of any major therapeutic significance, the uptake of toxic chemicals such as 3-MC, benzpyrene, and DDT through lymphatics may enhance their toxicity, since they are distributed to other organ systems in the body without being metabolized by liver. A number of factors such as diet, motility of intestine, interference with gastrointestinal flora, changes in the rate of gastric emptying, age of the animal, and dissolution rate of xenobiotic can alter the rate of absorption of chemicals.

Liver is the major site of metabolism of xenobiotics, but the contribution of intestinal metabolism of xenobiotic can influence the overall bioavailability of chemicals. The xenobiotic metabolizing enzymes located in endoplasmic reticulum of intestine possess biochemical characteristics similar to that of liver. In general, the rate of metabolism of xenobiotics by intestinal microsomal preparation is lower than that observed with similar hepatic microsomal preparations. The *in vitro* intestinal metabolism of xenobiotics is affected by several factors including age, sex, diurnal variations, species, and nutritional status of the animal. The intestinal xenobiotic metabolizing enzymes are stimulated by the pretreatment of animals with foreign chemicals, but this depends on the route of administration of chemicals, drug substrate and the animal species used. Rabbit intestinal drug metabolizing enzymes seem to be resistant to induction by foreign chemicals.

Introduction

The chemicals foreign to the biologic system are referred to as xenobiotics. Xenobiotics can be classified in four broad categories (*1*): (1) natural chemicals in excess of the normal dietary level such as nitrates; nitrites, the metabolites of nitrates can react *in vitro* and *in vivo* with secondary amines and form carcinogenic products — nitrosamines; (2) the aflatoxins and cycasins are examples of natural fungal or plant toxins; (3) air and water pollutants consisting of complex inorganic and organic chemical mixtures; and (4) the largest category: drugs, agricultural chemicals such as pesticides and fertilizers, food additives, heavy metals, plasticizers, and industrial and household chemicals including solvents. The number of chemicals in everyday use ranges from 50,000 to 63,000 (*2*). There are over 500 chemicals added intentionally to food in addition to unintentional contamination of food by a variety of other chemicals (*3*). The human population is exposed to xenobiotics through inhalation, ingestion, or dermal absorption. The major route of exposure is the oral route, through which intestinal ingestion of therapeutic agents and unintentional exposure of environmental pollutants present in food and water as well as the swallowing of part of inhaled pollutants occurs. After absorption, the xenobiotics may be distributed in the blood stream as well as in interstitial cellular and transcellular fluids. The physiochemical characteristics of xenobiotics, cardiac output, and regional blood circulation are the major determining factors which influence the rate, extent and pattern of initial distribution. The lipid-soluble chemicals are readily distributed in all fluid compartments and in highly perfused tissues but move less rapidly into muscles and more slowly to fats. The xenobiotics, after absorption can accumulate in tissues which may serve as reservoir and prolong the toxicity of chemicals or the therapeutic effect of

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chemicals when taken as medication. A large number of xenobiotics are lipid-soluble, weak organic acids or bases that are not readily eliminated from the body. They must be transformed into more polar metabolites before they are excreted from the body. After biotransformation, usually the end products of xenobiotics are less lipid-soluble, more ionized at physiological pH, less bound to plasma and tissue protein, and less stored in fat.

This paper presents an overview of xenobiotic absorption and metabolism by intestine; for in-depth information on this subject, reader is referred to reviews on absorption (*4-9*) and intestinal metabolism of chemicals (*10-12*).

Intestinal Absorption of Xenobiotics

Xenobiotics must cross the intestinal epithelium, basement membrane and capillary endothelium before they reach the blood stream. Mammals do not absorb the xenobiotics through any special transport process but share the same processes which are used for absorption of nutrients. There are five possible processes of xenobiotic transport across intestines. These are: active transport, passive diffusion, pinocytosis, filtration through "pores," and lymphatic absorption.

Active Transport

Active transport processes require cellular energy for transfer of substrates across intestine against higher concentration or electrochemical gradients. This system exists mainly for transfer of natural substances, e.g., amino acids, sugars, or bile acids.

Most of the foreign chemicals utilize passive diffusion process of transport, but there are examples of active transport for xenobiotics which are structurally similar to natural substrates. The antitumor agents 5-fluorouracil and 5-bromouracil are actively transported across the rat intestinal epithelium by the process through which natural pyrimidines, uracil and thymine are absorbed (*6*). It seems that lead, an inorganic environmental contaminant, may utilize the active transport process of calcium for its transport (*9*).

Pinocytosis

In pinocytosis the cell membrane forms invaginations which finally close to form vesicles containing fluid from outside the cell. Inside the cell, the contents of these vesicles are delivered to cytoplasm. In suckling animals this process of transport is used for macromolecules, e.g., antigenic peptides and immunoactive protein.

Filtration through "Pores"

Both lipophilic and hydrophilic compounds may pass through "pores" in the cell membrane. Xenobiotics with molecular weight around 100 may be absorbed through this process.

Absorption via the Lymphatics

It is well known that dietary short-chained fatty acids are predominantly absorbed via the lymphatic system in minute droplets known as chylomicrons. These enter the thoracic duct and empty into the systemic venous blood, completely bypassing the liver. A very few systematic studies on xenobiotic absorption through intestinal lymphatics are known. DeMarco and Levine (*13*) have studied the absorption of some drugs through this process and have shown that compounds such as *p*-aminosalicylic acid and tetracycline are absorbed to some extent through the lymphatic system, but the proportion of absorption is too low to be of any therapeutic significance. However, the absorption of environmental toxic chemicals through intestinal lymphatics is important since these chemicals can be distributed throughout the body without being transformed by the liver. Some of the environmental toxic chemicals such as DDT, benzpyrene, and 3-methyl-cholanthrene(3-MC) are partly absorbed through lymphatics. Sieber (*14, 15*) studied the absorption of ^{14}C-labeled compounds structurally related to *p, p'*-DDT in thoracic cannulated rats and identified the parent DDT compounds and their metabolites in the lymph collected during the experiment. The DDT compounds varied in their lipid solubility and extent of their lymphatic absorption, but a strict correlation between lipid solubility and lymphatic absorption was not established, possibly due to other factors such as differences in rate and routes of excretion of each compound. The carcinogens, benzpyrene, 3-MC, and *cis*-dimethylaminostilbene are also absorbed through intestinal lymphatics (*16, 17*).

The absorption of xenobiotics through intestinal lymphatics is influenced by the lymph flow rate. For example, the absorption of *p*-aminosalicylic acid and tetracycline was doubled when intestinal lymph flow was increased by the administration of tripalmitine (*18*).

Passive Diffusion

Passive diffusion is the major process for absorption of xenobiotics. This process is not saturable and

the transfer is directly proportional to the concentration gradient and to the lipid-water partition coefficient of xenobiotics. The higher these are, the faster the rate of diffusion, and when the concentrations are the same on both sides of the membrane, movement of xenobiotics across the membrane stops. Absorption of structurally related chemicals occurs independently; coabsorption does not alter absorption rate of either chemical. The extent of lipid solubility and ionization of xenobiotics influences the rate of absorption of chemicals (*6*). Many weak acids and bases are readily absorbed while stronger, more highly ionized acids and bases are less readily transported. Completely ionized compounds are very slowly absorbed. The role of ionization on absorption of chemicals is further supported by the change in the rate of absorption that resulted from a change in pH of the rat intestinal contents. For instance, raising the pH increased the absorption of bases such as quinine and aminopyrine and decreased the absorption of acids, such as benzoate and salicylates (6).

Factors Affecting Intestinal Absorption of Xenobiotics

A number of factors can influence the intestinal absorption of xenobiotics. For example, serum levels of phenobarbital, when administered orally, were higher in fasted animals than in the animals which were fed ad libitum (*19*). Recently Engström and Nordburg looked at the effect of milk diet on gastrointestinal absorption of cadmium in adult mice. A markedly higher body retention of $^{109}CdCl_2$ was observed in animals given a milk diet compared to other groups on laboratory chow (*20*).

Bile may play some role in absorption of xenobiotics. In a recent study (*21*) on absorption of radioactive lead, it was found that absorption of ^{203}Pb administered into the duodenum was decreased in rats with cannulated bile ducts. Mice showed no difference between absorption of biliary excreted ^{203}Pb and of ^{203}Pb administered into duodenum in rats without cannulation of the bile duct. Presence of bile seemed to enhance the intestinal transport of lead.

The absorption and retention of xenobiotics may be affected by the age of the animal. Cadmium in newborn rats is absorbed greater than in adults and is retained in the intestine for a longer time (*22*).

A number of other factors influence the intestinal absorption of xenobiotics which include the changes in motility of intestinal tract; interference with gastrointestinal contents of microorganisms; changes in the rate of gastric emptying in either direction; dissolution rate of xenobiotics. Further details on this topic are available in the literature (*8, 18, 23*).

Metabolism of Xenobiotics

The chemical reactions involved in metabolism of xenobiotics are classified as phase I and phase II reactions. The phase I or nonsynthetic reactions are oxidation, reduction, or hydrolysis. The phase I reactions of xenobiotic metabolism may result in activation, change in activity or inactivation of parent chemical. The phase II or synthetic reactions are concerned with formation of complex with the parent chemical or its metabolite with an endogenous substrate which usually results in rendering of parent compound to an inactive form. Liver is the major organ where these phase I and phase II reactions or biotransformation or toxication-detoxication reactions of xenobiotics take place. The hepatic endoplasmic reticulum contains a group of nonspecific enzymes which catalyze the metabolic reactions of a variety of xenobiotics as well as that of natural substrates such as fatty acids and steroids. These enzyme systems require NADPH, molecular oxygen, and an electron transport system consisting of NADPH cytochrome c reductase, lipid, and a carbon monoxide binding pigment generally known as cytochrome P-450. The reaction products of xenobiotics by these enzyme systems are usually less lipid soluble and are excreted as such or after conjugation. The hepatic metabolism of foreign chemicals has been extensively studied and reviewed (*24, 25*).

For the last several years our laboratory has been studying the comparative aspects of biochemical properties of intestinal and hepatic xenobiotic metabolizing enzymes (*12*). All these studies were conducted *in vitro* by using microsomal fractions prepared from intestinal and hepatic homogenates. The *in vitro* metabolism of model drug substrates was studied by standard analytical methods. The details of methodology for preparation of microsomal fractions and estimation of drug metabolizing enzymss are well documented in the literature (*26*). Following are the major characteristics of intestinal xenobiotic metabolizing enzymes studied in our laboratory.

Localization, Distribution, and Some Biochemical Properties of Intestinal Xenobiotic Metabolizing Enzymes

The intestinal xenobiotic metabolizing enzymes are localized in endoplasmic reticulum of epithelial cells. The distribution studies of these enzymes along the entire length of small intestine show that the activity of these enzymes is highest in proximal part of intestine and progressively declines towards the caudal end. Figure 1 shows the distribution of

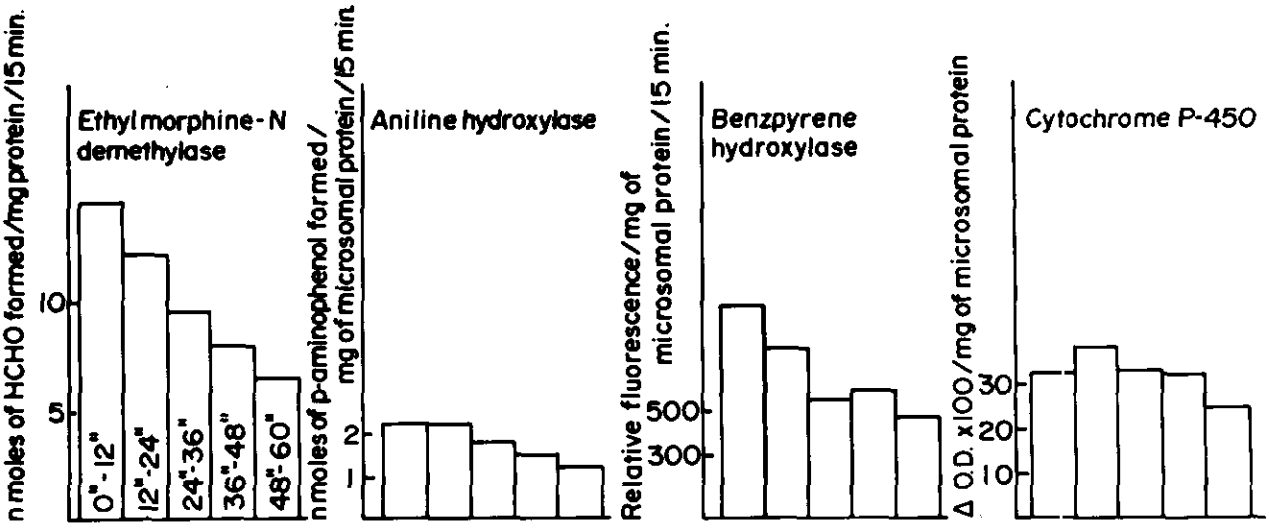

FIGURE 1. Distribution of microsomal drug metabolizing enzymes and cytochrome P-450 content along the proximal 60 in. of rabbit small intestine.

ethylmorphine-*N*-demethylase, aniline hydroxylase, and benzpyrene hydroxylase activities (AHH) and cytochrome P-450 content along the proximal 60 in. of rabbit intestine. The activities of all xenobiotic metabolizing enzymes were highest in the first 30 in. of the intestines. However, the cytochrome P-450 contents were similar in entire length of intestine used in this study. The rat and mice xenobiotic metabolizing enzymes also have similar patterns of distribution in intestines (*27, 28*) as seen in rabbits. A recent study on distribution of xenobiotic metabolizing enzymes among mucosal cell population showed that mature tip cells contained 6-10 times more cytochrome P-450 and xenobiotic metabolizing enzyme activity per mg of microsomal protein than the crypt epithelial cells (*29, 30*). A recent study shows (*31*) that crypt and tip cells differ in their response to inductive actions of 2, 3, 7, 8-tetrachlorodibenzo-*p*-dioxin (TCDD).

The comparison of rabbit intestinal and hepatic metabolism of a number of drug substrates showed that the activities were generally lower in intestine. The activities of intestinal drug metabolizing enzymes were 15-50% of those observed in hepatic microsomes. The study on biochemical properties of both hepatic and intestinal enzyme systems showed that both systems require NADPH and O_2 for maximum activity and are inhibited by cytochrome c, SKF-525A, and CO. The *in vitro* addition of drug substrates to microsomal fractions of both tissues produced typical type 1 and type II binding spectra (*32*), again suggesting similarities in the enzyme systems from liver and intestine.

Perinatal Development of Intestinal Xenobiotic Metabolizing Enzymes

The postnatal development of aminopyrine *N*-demethylase, benzpyrene hydroxylase, biphenyl 4-hydroxylase, 7-ethoxycoumarin *O*-deethylase, NADPH-cyctochrome c reductase activities, and cytochrome P-450 content were compared in microsomes from the liver and small intestines of the rabbit (*33*). The common developmental pattern observed was characterized by enzyme activities which were low or undetectable in the first week after birth and increased slowly during the first 25 days of life. Subsequently, the enzyme activities underwent a rapid 2 to 5-fold increase in magnitude. By 30-40 days of age, values reached or exceeded adult level. At 50 days there was a transient fall in enzyme activities below adult level, but activities returned to adult levels by 75 days postpartum. The same pattern of hepatic enzyme development was noticed except that maximum activities were usually observed later than in the small intestine. Also, no subsequent decline below adult values was observed for any of the hepatic enzyme activities studied during later development. The typical pattern of development of enzymes is represented by the postnatal maturation of AHH shown in Figure 2.

Recently Lucier et al. (*34*) studied the developmental patterns of UDP-glucuronyl transferase (UDPGT) activities in guinea pig and rabbit intestine during perinatal period. The guinea pig intestinal UDPGT activities were not detectable until birth and developed to adult levels by 3 weeks after birth. However, the rabbit intestinal UDPGT activities

were detectable 10 days before birth, declined during the first week after birth, and attained adult levels by 4 weeks of age.

Rhythmic Variations in Intestinal Xenobiotic Metabolizing Enzymes

Changes in the susceptibility of biologic system to therapeutic or toxic effect of chemicals may be influenced by the time of day at which they are exposed. The role of circadian rhythms in rates of extrahepatic drug metabolizing enzymes was recently reported from our laboratory (*35*). The circadian variations in various microsomal drug metabolizing enzymes from rabbit intestine are shown in Table 1. All enzyme activities showed a peak in activity around 0600 hr with a trough around 1200-1500 hr. For biphenyl hydroxylase, aryl hydrocarbon hydroxylase and NADPH cytochrome c reductase activities, the values of these enzymes were significantly different. The microsomal cytochromic P-450 content appeared less rhythmic than the enzymic activities measured.

Nutrition as a Modifier of Intestinal Xenobiotic Metabolizing Enzymes

The importance of dietary components as potential effectors of intestinal drug metabolizing enzymes has been extensively studied by Wattenberg and his colleagues (*27, 36, 37*). Most of their studies were concentrated on the AHH enzyme system in rat. In their studies on the effect of various diets on AHH activities in rat intestine and lung, it was shown that rats on semipurified diet lost all AHH activities in

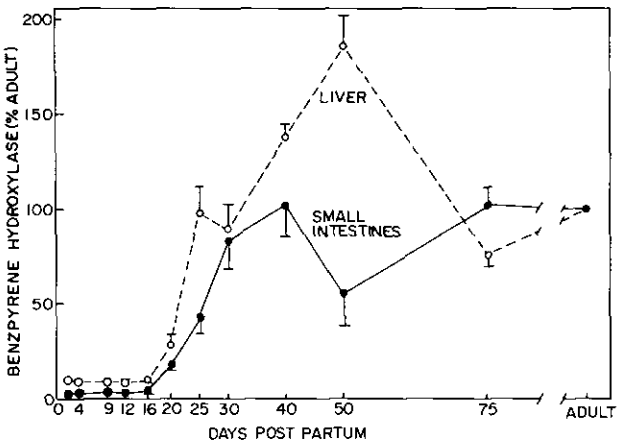

FIGURE 2. Development with age of the activity of benzpyrene hydroxylase in hepatic and small intestinal rabbit microsomes. Figure from Tredger et al. (*33*) reproduced with permission of the American Society for Pharmacology and Experimental Therapeutics.

these tissues. From these experiments, it was suggested that intestinal enzyme activities observed in rats on normal laboratory chow are due to the exogenous factors present in the diet which induce the enzyme activities present at very low levels. This hypothesis was confirmed by their findings that addition of various vegetables to a semipurified diet caused increases in intestinal AHH activity in rat (*38*). Table 2 shows our current studies where the rabbit was used as an experimental animal and the effect of semipurified diet on some of the drug metabolizing enzymes was compared with the enzymes in animals on regular laboratory rabbit chow. Unlike the rat (*37*), the intestinal enzymic activities

Table 1. Circadian variations in rabbit intestinal microsomal enzyme activities.[a]

	Time (hr)							
Enzyme activity	0000	0300	0600	0900	1200	1500	1800	2100
Aryl hydrocarbon hydroxylase, pmole 3-hydroxybenzpyrene produced/mg microsomal protein/min	54 ± 8	58 ± 7	67 ± 6	61 ± 6	51 ± 2	61 ± 10	58 ± 11	53 ± 4
Benzphetamine N-demethylase, nmole formaldehyde produced/mg microsomal protein/min	0.51 ± 0.08	0.57 ± 0.06	0.64 ± 0.08	0.54 ± 0.04	0.48 ± 0.06	0.47 ± 0.10	0.59 ± 0.11	0.60 ± 0.04
NADPH-Cytochrome *c* reductase, nmole cytochrome *c* reduced/mg microsomal protein/min	86 ± 13	97 ± 7	104 ± 12	84 ± 8	81 ± 7	89 ± 16	89 ± 10	94 ± 11
Cytochrome P-450, nmole/mg microsomal protein	0.43 ± 0.03	0.44 ± 0.04	0.50 ± 0.05	0.45 ± 0.02	0.51 ± 0.02	0.49 ± 0.03	0.49 ± 0.06	0.48 ± 0.01

[a]Data from Tredger and Chhabra (*35*). Animals were killed at the times shown and microsomal fractions were immediately prepared and stored. Enzyme activities were determined within 1 week of sacrifice. Each value is the mean ± S.E.M. of four separate determinations.

Table 2. Effect of purified diet on intestinal drug-metabolizing enzymes in rabbit.

Treatment	Enzyme activity, % of controls[a]			
	Ethylmorphine demethylase	Aniline hydroxylase	Arylhydrocarbon hydroxylase (AHH)	7-Ethoxycoumarin deethylase
Purified diet vs. pair-fed controls	82	95	77	110
Purified diet vs. ad lib controls	99	104	87	125

[a]Controls were fed a natural ingredient rabbit diet, either pair-fed to the purified diet group or fed ad lib.

Table 3. Species differences in intestinal microsomal drug-metabolizing enzymes and cytochrome P-450 content.[a]

Species	Enzyme activity in intestine as percent of that in liver					
	Ethyl morphine *N*-demethylase	Biphenyl hydroxylase	Aniline hydroxylase	Benzpyrene hydroxylase	Cytochrome c reductase	Cytochrome P-450
Rabbit	18.6	14.1	20.4	30.0	75.7	34.6
Guinea pig	23.3	16.4	19.8	37.4	78.7	12.4
Rat	ND[a]	9.3	ND	4.6	42.0	ND
Mice	ND	9.0	ND	6.0	79.6	4.0
Hamster	ND	6.8	ND	5.7	60.7	13.0

[a]Data compiled from Chhabra et al. (*39*).
[b]Not detected.

Table 4. Effect of phenobarbital on intestinal microsomal drug-metabolizing enzymes.

Species	Route of administration	Enzyme activity, % of control			
		Ethylmorphine demethylase	Aniline hydroxylase	Arylhydrocarbon hydroxylase (AHH)	7-Ethoxycoumarin deethylase
Mouse	Oral	ND[a]	ND	356[b]	550[b]
	IP	ND	ND	478[b]	406[b]
Rat	Oral	ND	ND	178	109
	IP	ND	ND	27	251[b]
Guinea pig	Oral	137[b]	120	93	248[b]
	IP	113	66	85	163
Rabbit	Oral	93	86	62	139
	IP	112	82	90	69

[a]Not detected.
[b]Significantly different from control, $p < 0.05$.

in rabbit fed semipurified diets were not altered. The reason for this apparent species difference are not immediately obvious but may be of considerable importance should a regulatory role be envisioned for diet in the control of enzyme activities in the small intestine of all mammals including man.

Differences in Intestinal Xenobiotic Metabolizing Enzymes and Their Induction by Foreign Chemicals in Various Species

Table 3 shows the activities of various drug metabolizing enzymes as percent of liver activity in various animal species. In the intestines from mice, rat, guinea pigs, and hamsters, some of the enzymic activities were either absent or require very sensitive methods of detection. The rabbit emerged as the species with highest activities of drug metabolizing enzymes. The interspecies difference noticed in intestinal drug metabolizing enzymes could be due to the genetic factors or due to the induction of these enzymes by environmental chemicals present in the diet of these animals (*39*).

A number of foreign chemicals have been shown to increase the hepatic drug metabolizing enzyme activities. These chemicals are classified into two major categories (*40*). The chemicals in Class I are those which increase the metabolism of a large number of drug substrates accompanied by the increase in cytochrome P-450, while the chemicals in Class II are more specific and induce the enzymic metabolism of a few drug substrates accompanied by

Table 5. Effect of 3-methylcholanthrene on intestinal drug-metabolizing enzymes.

Species	Route of administration	Enzyme activity, % of control		
		AN hydroxylase	AHH	7-EC deethylase
Mouse	Oral	ND[a]	516[b]	135
	IP	ND	96	25[b]
Rat	Oral	ND	879[b]	738[b]
	IP	ND	1615[b]	1231[b]
Guinea pig	Oral	91	103	67
	IP	96	240[b]	58[b]
Rabbit	Oral	97	117	94
	IP	68	83	96

[a]Not detected.
[b]Significantly different from controls, $p < 0.05$.

the increase and shift of reduced cytochrome P450-CO absorption spectra from 450 nm to 448 nm. The Class I is exemplified by phenobarbital, a commonly used inducer of drug metabolizing enzymes. The Class II of these chemicals is exemplified by 3-MC, one of the carcinogenic polycyclic hydrocarbons. There is also another class of chemicals which induces both cytochrome P-450 and P-448-mediated reactions of drug substrates and is represented by Arochlor 1254 and TCDD.

The effect of phenobarbital (Table 4) and 3-MC (Table 5) on some of the xenobiotic metabolizing enzymes in intestine of various species was studied in our laboratory. The effect of these inducers on cytochrome P-450 content is given in Table 6. The results from this study showed that rabbit intestinal xenobiotic metabolizing enzymes and cytochrome P-450 are not induced by either of the inducers used, while the induction of xenobiotic metabolizing enzymes in other species depended on the type of drug substrate and route of administration selected. The lack of induction of xenobiotic metabolizing enzymes in rabbit small intestine could be due to the maximum induced status of these enzymes in intestine caused by the chemical contaminant in the rabbit feed. To test this hypothesis, rabbits were fed semipurified diet for 6-7 weeks and then treated with phenobarbital or 3-MC for 3 days. Table 7 shows the results of that study. The 3-MC or phenobarbital did not induce any of the enzymes studied indicating the inability of rabbit enzyme system to respond to chemical treatment. The resistance to induction of rabbit intestinal enzymes by foreign chemicals seems to be due to genetic factors rather than dietary.

Table 6. Effect of phenobarbital and 3-methylcholanthrene on intestinal cytochrome P-450.

Species	Route of administration	Cytochrome P-450 content, % of control	
		Pb	3-MC
Mouse	Oral	221[a]	60
	IP	139	41[a]
Rat	Oral	73	104
	IP	78	213[a]
Guinea pig	Oral	107	109[a]
	IP	104	100
Rabbit	Oral	91	110
	IP	98	63

[a]Significantly different from controls, $p < 0.05$.

Conclusions

Passive diffusion is the major process through which intestinal transport of xenobiotic takes place.

Table 7. Effect of purified diet and inducers on intestinal drug-metabolizing enzymes in rabbit.

Treatment	Enzyme activity, % of controls[a]			
	Ethylmorphine demethylase	Aniline hydroxylase	Arylhydrocarbon hydroxylase	7-Ethoxycoumarin deethylase
Purified diet plus PB (IP)	101	82	107	145
Purified diet plus 3-MC (IP)	—	59	101	68

[a]Controls were fed purified diet and injected with physiological saline (for Pb) or corn oil alone (for 3-MC).

The overall absorption of environmental chemicals is of lesser magnitude through the lymphatic system but is of greater toxicologic significance since the chemicals are distributed throughout the body without biotransformation by liver. The rate of absorption of xenobiotics is determined by a number of factors.

The intestinal xenobiotic metabolizing enzymes in their biochemical characteristics are similar to that of liver. Though the rate of intestinal xenobiotic metabolizing enzymes is 15 to 50% of those observed in liver, the surface area of the small intestine and the duration of a foreign chemical's residence in the small intestine may be the determining factors in the contribution of the small intestine to the overall metabolism of xenobiotics in animals. A number of factors, such as age, sex, hormones, nutrition, diurnal variation, the content of intestinal microflora can influence the rate of intestinal metabolism of xenobiotics. The administration of foreign chemical can stimulate the *in vitro* metabolism of some drug substrates in various species studied in our laboratory. The exception was rabbit intestinal xenobiotic metabolizing enzymes which were not induced by phenobarbital or 3-MC pretreatment.

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