Ann. Rev. Nutr. 1984. 4:207-31

EFFECTS OF NUTRITIVE FACTORS ON METABOLIC PROCESSES INVOLVING BIOACTIVATION AND DETOXICATION OF CHEMICALS

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0199-9885/84/0715-0207$02.00

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INTRODUCTION

People are exposed to a wide variety of chemicals foreign to the body, including natural products, food additives, drugs, insecticides, industrial chemicals, and pollutants, which are collectively termed xenobiotics. Metabolism influences the biological effects of these compounds, e.g. detrimental effects of these compounds are often enhanced by bioactivation processes and suppressed by detoxication reactions (68). Although chemicals have been associated with tumors for over 200 years, only very recently have some of the mechanistic details been presented. Many gaps still exist in our knowledge of metabolic processes involving chemicals and their relevance. Metabolism of these chemicals is known to be affected by genetic and environmental factors including nutrition. Many of the techniques needed to carry out careful studies of the effects of nutrients are only now coming into use, and this area is still in its infancy.

ENZYMATIC BASIS OF METABOLISM

The major enzymes involved in the metabolism of xenobiotic compounds are presented below in four categories. Oxygenation is often referred to as a Phase I reaction and the other processes as Phase II reactions because the oxidation products are often substrates for the subsequent transformations. The overall driving force generally appears to be the conversion of hydrophobic xenobiotics to more polar materials that can be readily excreted (68). Many of the enzymes exist in multiple forms, usually as genetically determined isozymes. Further, the levels of many of these individual isozymes in animals can be elevated and depressed by treatment with various xenobiotics, which can often be but are not necessarily substrates (32, 84). Many of the products of these enzymes, particularly the oxygenases, produce electrophiles that, if not further metabolized, can cause damage to cells (94). While these enzymes are often studied in terms of their metabolism of xenobiotics, they also have endogenous substrates, many of which are of nutrients (e.g. vitamins, lipids, and hor-

mones,), and a number of which use cofactors or prosthetic groups derived from nutrients.

Oxygenation

Oxygenation is a special category of oxidation in which oxygen atoms are inserted into organic substrates; dioxygenases incorporate two atoms of oxygen into substrates, and monooxygenases (mixed-function oxidases) incorporate one atom of molecular oxygen into an organic substrate while using reducing equivalents (usually from pyridine nucleotides) to reduce the other atom of molecular oxygen to water concomitantly (78).

Oxygenases can involve heme, nonheme iron, flavins, or copper (Table 1). Often, electron transport chains are operative in transferring reducing equivalents to a terminal oxidase, and the enzymes in these chains also involve flavoproteins, iron proteins, and other structures such as pterins. Perhaps the most widely studied of these enzymes is the cytochrome P-450 system (48). Some of this attention is due to the tremendous variety of substrates that can be

Table 1 Some oxygenases of interest in mammalian systems[a]

Prosthetic group	Enzyme	Source
Copper	Dopamine β-hydroxylase	Adrenal
Nonheme iron	Lipoxygenases	Many tissues
	3-Hydroxyanthranilate 3,4-dioxygenase	Liver, kidney
	β-Carotene 15,15'-dioxygenase	Intestine
	Tryptophan pyrrolase	Brain, liver, spleen
	Cysteamine dioxygenase	Kidney
	Cysteine dioxygenase	Liver
	γ-Butyrobetaine hydroxylase	Liver
	Prolyl hydroxylase	Skin
	p-Hydroxyphenylpyruvate oxidase	Liver, kidney
	Inositol oxidase	Kidney
	Phenylalanine 4-hydroxylase	Liver, kidney
	Fatty acid desaturase	Liver
	1-Alkyl 2-acyl glycerophosphatide desaturase	Sarcomas
Heme	Tryptophan dioxygenase	Liver
	Cytochrome P-450	Liver, most other tissues
	Heme oxygenase[b]	Liver, spleen, kidney
	Prostaglandin cyclooxygenase	Many tissues
Flavin	5-Hydroxytryptophan 2,3-dioxygenase	Brain
	0-Acylthiamine hydroxylase	Liver
	Kynurenine 3-hydroxylase	Liver
	Flavin-containing monooxygenase	Liver, other tissues

[a]Source: Keevil & Mason 1978 (78).
[b]The heme is converted to biliverdin during catalytic turnover.

metabolized (151). This diversity of substrates is due in part to the existence of isozymes (84). The substrates include a great variety of oxidizable chemicals, which generally tend to be hydrophobic. In the liver, these enzymes collectively can account for 5–25% of the protein in the endoplasmic reticulum. They are found at lower levels in most other tissues as well. The number of individual forms of liver microsomal cytochrome P-450 is not known, although at least nine have been purified from rat liver (50). The enzymes found in mitochondria catalyze specific hydroxylations of endogenous steroids. Steroidogenic tissues such as adrenals and testes are rich in these enzymes (140). The microsomal cytochromes P-450 tend to be less specific.

Dioxygenases either incorporate both oxygens into one organic substrate, as in the case of prostaglandin synthase or lipoxygenase, or insert one oxygen into each of two substrates, as in the case of γ-butyrobetaine hydroxylase and lysyl and prolyl oxidases.

The oxidative reactions of cytochrome P-450 can be grouped into six major categories (52): carbon hydroxylation (insertion of an oxygen atom into a C–H bond of an aliphatic compound), heteroatom oxygenation (addition of an oxygen atom to heteroatoms), heteroatom release (oxidative cleavage of a carbon-heteroatom bond), epoxidation (conversion of olefins and aromatic compounds to epoxides), oxidative group transfer (52, 82, 96), and suicide destruction, which occurs with many olefins and alkynes, including a number of drugs (111).

The substrates can be considered to be of three classes: (*a*) endogenous compounds, i.e. those normally found in the body, such as fatty acids, steroids, prostaglandins, and vitamins (29); (*b*) natural products that are found in foodstuffs or are subsequently formed, i.e. vitamins, steroids, fatty acids, mycotoxins, alkaloids, and compounds such as amino acid and carbohydrate derivatives formed during pyrrolysis, nitrosamines formed by reaction of amines with nitrite, and polycyclic hydrocarbons found in charred food (29, 94); and (*c*) synthetic chemicals, i.e. model substrates, industrial chemicals, pesticides, drugs, and pollutants (94, 151). Compounds in the latter two categories often have toxic and carcinogenic potential (Table 2).

Cytochrome P-450 also undergoes oxidative turnover to produce H_2O_2. NADPH-cytochrome P-450 reductase also produces H_2O_2 and superoxide anion (O_2^-). Superoxide anion and H_2O_2 can react in the presence of iron to produce hydroxyl radicals in the Haber-Weiss reaction. Cytochrome P-450 can also transfer electrons directly to substrates instead of oxygen: *N*-oxides are reduced to amines, epoxides to the corresponding unsaturated compounds, azo groups to hydrazines, and tetrahalomethanes to halide ion plus reactive trihalomethyl radicals (151).

Microsomal flavin–containing monooxygenase also carries out heteroatom oxygenations with many synthetic chemicals and cysteamine (157). Prosta-

Table 2 Some carcinogens found in foods and formed during food processing[a]

Source	Compound	Site of tumors	Apparent proximate carcinogen formed by metabolism
Gymnosperms	Cycasin	Several	Diazomethane
Bracken Fern	(Unknown)	Bladder	(Unknown)
Several plants, honeys	Pyrrolizidine Alkaloids	Liver	Pyrroles
Betel nuts	(Unknown)	Oral cavity	(Unknown)
Seaweed	Carrageean	Colon	(Unknown)
Mushrooms	Hydrazines	Several	Esters of hydroxyl-amines(?)
Sassafras, sweet basil, cinnamon	Safrole	Liver	1'-Hydroxysafrole
Tarragon, sweet basil, anise	Estragole	Liver	1'-Hydroxyestragole
Sweet bay, cloves, lemongrass	Methyleugonol	Liver	1'Hydroxymethyl-eugonol
Molds (*Aspergillus*)	Aflatoxins	Liver	Epoxide
Molds (*Aspergillus*)	Sterigmatocystin	Liver	Epoxide
Molds (*Penicillium*)	Luteoskyrin	Liver	(Unknown)
Molds (*Penicillium*)	Cyclochlorotine	Liver	(Unknown)
Molds (*Penicillium*)	Griseofulvin	Liver	(Unknown)
Molds (*Strepto-myces*)	Azaserine	—	(Unknown)
Molds (*Strepto-myces*)	Mitomycin C	—	Pyrrole(?)
Molds	Patulin	(Local)	(Unknown)
Molds	Penicillic Acid	(Local)	(Unknown)
Molds (*Aspergillus, Penicillium*)	Ochratoxin A	Liver, Kidney	(Unknown)
Molds	Trichothecenes	Several	(Unknown)
Several plants	Flavanoids	Several	(Unknown)
Croton oil	Phorbol esters	—	Promoter
Several plants	Teleocidin	—	Promoter
Several plants	Dihydroteleocidin	—	Promoter
Several plants	Lyngbyatoxin A	—	Promoter
Algae	Aplysiatoxin	—	Promoter
Algae	Debromoaplysiatoxin	—	Promoter
Sumac, Dillweed	Quercitin	(Mutagen)[b]	(Unknown)
Dillweed	Isorhamnetin	(Mutagen)[b]	(Unknown)
Secondary Amines and Nitrite	*N*-Nitrosamines	Several	Carbonium ions

Table 2 *(Continued)*

Source	Compound	Site of tumors	Apparent proximate carcinogen formed by metabolism
Charred foods	Polycyclic hydrocarbons	Several	Epoxides, diol-epoxides
Alcoholic beverages	Ethanol	Esophagus	Promoter
Food additives	2-(2-Furyl)-3-(5-nitrofuryl)-acrylamide (AF-2)	Forestomach	(Unknown)
Artificial sweeteners	Saccharin	—	Promoter(?)
	Tryptophan	—	Promoter
	Bile acids	Colon	Promoter
	Estrogenic hormones	Breast	Promoter
Pyrrolysis of tryptophan	3-Amino-1,4-dimethyl-5*H*-pyrrido[4,3-*b*]indole (Trp-P-1)	Liver	Ester of hydroxylamine
Pyrrolysis of tryptophan	3-Amino-1-methyl-5*H*-pyrrido[4,3-*b*]indole (Trp-P-2)	Liver	Ester of hydroxylamine
Pyrrolysis of glutamate	2-Amino-6-methyldipyrrido [1,2-*a*:3',2'-*d*]imidazole (Glu-P-1)	Liver	(Unknown)
Pyrrolysis of glutamate	2-Aminodipyrrido [1,2-*a*:3'2'-*d*]imidazole (Glu-P-2)	Liver	(Unknown)
Pyrrolysis of lysine	3,4-Cyclopentenopyrido [3,2-*a*]carbazole (Lys-P-1)	(Mutagen)[b]	(Unknown)
Soybean globulin pyrrolysate	2-Amino-α-carboline	(Mutagen)[b]	(Unknown)
Soybean globulin pyrrolysate	2-Amino-3-methyl-α-carboline	Liver	(Unknown)
Broiled sardines	2-Amino-3-methyl-imidazo [4,5-*f*]quinoline	(Mutagen)[b]	(Unknown)
Broiled sardines	2-Amino-3,4-dimethylimidazo [4,5-*f*]quinoline	(Mutagen)[b]	(Unknown)
Fried beef	2-Amino-3,8-dimethyl-imidazo [4,5-*f*] quinoxaline	(Mutagen)[b]	(Unknown)

[a]Sources: Hirono (61); Miller et al (95); Sugimura (128). Also see Ames (158) for additional information published after submittal of this review.

[b]In some cases mutagenic activity has been found but cancer bioassays have not been carried out. When indicated, promoters have been found to enhance carcinogenesis initiated by other chemicals.

glandin cyclooxygenase can catalyze certain formal oxygenations during the metabolism of arachidonate (90).

Oxidation and Reduction

In addition to the alcohol dehydrogenase family, a variety of other enzymes catalyze the interconversion of alcohols and carbonyl compounds (13, 37, 137,

142), utilizing pyridine nucleotides. Monoamine oxidases oxidize primary amines to aldehydes. These enzymes are involved in the metabolism of neurotransmitters but can also oxidize xenobiotic chemicals (134).

Reactive oxygen species (e.g. O_2^- and H_2O_2) can be detrimental to cells, and there are enzymes to destroy these species. Superoxide dismutase catalyzes the destruction of O_2^- (56). Two enzymes can remove H_2O_2: catalase decomposes H_2O_2 to H_2O and O_2, and glutathione (GSH) can reduce H_2O_2 and other hydroperoxides in a reaction catalyzed by glutathione peroxidase. One type of GSH peroxidase, found predominantly in erythrocytes, contains selenium. Nonselenium GSH peroxidase reduces organic hydroperoxides but not H_2O_2; this enzyme is also a GSH transferase (147). GSH disulfide (GSSG) is reduced by the action of the enzyme GSH reductase.

Hydrolysis

The body contains a number of hydrolases that break down a variety of esters and amides. These reactions can be important in the degradation of certain drugs and in the processing of GSH conjugates and other materials (59). An enzyme that can be important in the degradation of potentially reactive epoxides (oxiranes) is epoxide hydrolase, found in the liver and other tissues (49). If not destroyed, many epoxides can react with nucleophilic sites of proteins and nucleic acids.

Conjugation

Conjugation of foreign chemicals is an important process in rendering them more polar for excretion. Many of the products of oxidation and reduction reactions are conjugated as well.

Glucuronides are formed by the enzyme UDP-glucuronyl transferase. Functional groups forming glucuronides include alcohols, carboxylic acids, α,β-unsaturated ketones, hydroxylamines, carbamates, amines, sulfonamides, thiols, dithiocarbamates, and activated carbons (e.g. 1,3-dicarbonyl systems) (74).

Conjugation of electrophiles with GSH also occurs (69). In contrast with glucuronidation, where the common electrophile UDP-glucuronic acid reacts with a number of nucleophiles, here a single nucleophile, the thiol group of the ubiquitous tripeptide GSH, reacts with a great variety of electrophiles, such as epoxides, alkyl and aryl halides, sulfates, and 1,4-unsaturated carbonyl compounds. GSH transferase is abundant and can account for $\geq$ 10% of total hepatic protein. It also functions as a binding protein (ligandin) for hydrophobic compounds such a bilirubin. GSH thioethers lose glutamate in a reaction catalyzed by γ-glutamyl transpeptidase and glycine in a reaction that apparently can be catalyzed by a number of dipeptidases. The resulting cysteinyl thioethers are *N*-acetylated to form mercapturic acid derivatives, which are

excreted in urine. Alternatively, the cysteinyl moiety can be cleaved by cysteine conjugate β-lyase, a pyridoxal phosphate–dependent enzyme that catalyzes such a β-elimination (126).

N-, *O*-, and *S*- groups can be methylated by *S*-adenosylmethione-linked enzymes (85) or acetylated by acetyl SCoA–dependent acyl transferases (58). The acyl transferase can also transfer an acetyl group from the nitrogen of a hydroxylamine derivative to the oxygen. Formation of other amide linkages can be involved in the metabolism both of amines and of carboxylic acids. Utilizing the cofactor 3'-phosphoadenosine 5'-phosphosulfate, hydroxyl groups also form sulfates through the action of the sulfotransferases (70).

The enzyme rhodanese converts cyanide to thiocyanate with sulfur from the thiane pool (149).

MOLECULAR BASIS OF FACTORS THAT CAN INFLUENCE METABOLISM

Our understanding of the basis of the effects of nutrients on the metabolism of chemicals via the above pathways comes from studies at varying levels of organization, including model chemical systems, purified enzymes, nucleic acids coding for these enzymes, subcellular organelles, isolated and cultured cells, perfused organs, and in vivo studies with experimental animals and man. All of these methods have advantages and disadvantages, and one must put observations made in any single system into context. In vitro studies will be discussed first. Ultimately all in vivo studies should be understood in terms of basic mechanisms so that situations encountered in humans can be modulated rationally. Some basic factors that are postulated to influence metabolism are discussed below.

Enzyme Localization

The metabolism of chemicals is a function of where enzymes are located and the manner in which the chemicals are delivered to them. Pharmacokinetic considerations such as hepatic first-pass clearance should be considered, as some chemicals are essentially completely metabolized in an organ during the first pass of the blood (44). Other ingested chemicals are not metabolized immediately and are delivered to other tissues. Another factor to consider is transport of metabolites. GSH conjugates formed in the liver are delivered to the kidney and intestine for further processing. Other conjugates may be hydrolyzed in the acidic environment of the stomach to form electrophiles. Reactive metabolites can be formed in the liver (or at another site) and

transported to other targets as an alternative to formation by metabolism in the target cells (15, 17).

Many tissues contain a variety of cell types, and the enzymes under discussion are localized in only one or a few of these. Even in the liver, which contains predominantly parenchymal cells, different enzymes are localized in centrilobular, midzonal, and periportal regions (5, 27, 73). Isozymes of a family are also preferentially localized (5, 115). Further phenotypic variability of hepatocytes may exist, as variation in activities of individual cells is greater than can be attributed to the differences among regions. Intracellular localization of enzymes should also be considered. Localization of enzymes in subcellular compartments may favor their interaction when they catalyze sequential reactions, as metabolites may be sequestered for further biotransformation. Enzyme interaction also must be considered with electron transport chains such as the cytochrome P-450 system, where interaction between cytochrome P-450 and its reductase is needed for efficient electron transport (39,100). Cytochrome P-450 can also interact with epoxide hydrolase to decrease the effective lifetime of epoxides (51, 72).

Enzyme Induction

In general, chemicals are not particularly selective in inducing these enzymes; phenobarbital can induce at least four cytochromes P-450 plus epoxide hydrolase, GSH S-transferase, UDP-glucuronyltransferase, and other enzymes. Many other hydrophobic compounds also induce some of these enzymes (84), and chemicals induce enzymes for which they are not substrates. One chemical can induce several enzymes, and a single enzyme can be induced by a variety of chemicals (32). Enzyme induction is a relatively slow process, i.e. it requires hours. The extent of induction is variable: with cytochrome P-450, induction may involve less than a twofold increase in the level of an enzyme or an increase of two orders of magnitude, and levels of other enzymes may be simultaneously lowered by as much as an order of magnitude (32). The levels of individual isozymes are under hormonal and genetic control, and the inducibility of enzymes also appears to be under genetic control (107).

The mechanism of induction has several potential control points (16). Cytosolic receptors transport chemicals to the nucleus to activate genes. The levels of messenger RNAs have been shown to increase in several cases. The enzymes of interest apparently are not synthesized as larger molecular weight precursors, except in the cases of mitochondrial cytochrome P-450 (140). Post-translational modification involves the addition of heme in the case of cytochrome P-450, and heme synthesis is under complex regulatory control. Phosphorylation (123) and glycosylation (65) have been postulated for some but not all of the cytochromes P-450 (50). The involvement of "second

messengers" such as cyclic AMP has been observed in the case of the mitochondrial cytochromes P-450 (140). Conceivably, cytochrome P-450 metabolites (e.g. steroids) may induce the synthesis of other isozymes (53).

Cytochromes P-450 have half-lives of 10--30 hours (122). In cell culture they are rather unstable, and stability is influenced by media nutrients (12). Various factors that stabilize cytochromes P-450 include δ-aminolevulinic acid, dihydroxyacetone, ascorbate, adenine, nicotinamide, hydroxycortisone, metyrapone, and others. To illustrate the complexity of the system, the addition of metyrapone or the deletion of cysteine can affect both the relative stabilities of different cytochrome P-450 isozymes and the ratio of holo-cytochrome P-450 to apo-cytochrome P-450 (127). Selenium has been shown to be necessary for the induction of some cytochromes P-450 in culture (53, 108).

Phospholipids

Some of these enzymes, e.g. cytochrome P-450 and UDP-glucuronyl transferase, are membrane-bound and have been shown to require phospholipids for maximum expression of activity in vitro. Radicals produced during lipid peroxidation (133) can destroy the heme of cytochrome P-450 as well as inactivate residues of proteins and mark them for proteolytic digestion (40). The hypothesis has been advanced that lipid peroxidation can disturb calcium sequestration and lead to cell toxicity (23). Others have argued that these calcium disturbances probably result from other phenomena such as alkylation of critical amino acid residues related to calcium homeostasis (124).

Availability of Substrates

A number of lines of evidence indicate that hydrophobic compounds are rapidly taken up by hepatocytes and other isolated cells without active transport; Cytochrome P-450 spectra are perturbated in a manner indicative of binding immediately upon addition of substrates to cells (47). Inhibition of ATP production does not block oxidative metabolism in hepatocytes. Conceivably the presence of endogenous substrates could inhibit the metabolism of other chemicals. GSH transferases serve as binding proteins for many hydrophobic materials such as bilirubin, which can inhibit metabolism of other materials (69).

Cofactor Supply

Many of the enzymes under discussion utilize cofactors (cosubstrates) in carrying out reactions. Oxygenases require O_2, of course, and gradients of O_2 tension are known to exist in the liver (2, 71). The K_m for O_2 with most cytochrome P-450-linked oxygenases is less than 1 μM, below the normal

tension, and oxygen is probably not limiting in normal liver; however, oxygen tension can influence the degree to which cytochromes P-450 partition between oxidative and reductive pathways in metabolizing compounds such as polyhalomethanes (151).

NADPH supplies can limit cytochrome P-450–dependent reactions (131). Reducing equivalents are derived from the cytosolic pentose phosphate shunt and from the mitochondria through the isocitrate/α-ketoglutarate shunt and malic enzyme. In a fasted rat in which the cytochrome P-450 level has been elevated and a high dose of a substrate has been presented, the NADPH supply quickly becomes rate-limiting. Several regulatory control mechanisms govern the $NADPH/NADP^+$ ratio; e.g. lowering the ATP/ADP ratio triggers NADPH production. Further, in addition to elevating levels of enzymes that metabolize chemicals, phenobarbital and 3-methylcholanthrene induce enzymes of the pentose shunt (28, 131).

UDP glucuronic acid, a cofactor for UDP-glucuronyl transferase, is synthesized from UTP and glucose-1-phosphate. Since UDP glucose dehydrogenase utilizes NAD^+, the production of UDP glucuronic acid is regulated by the $NADH/NAD^+$ ratio as well as by the carbohydrate supply (101, 117, 132). Sulfation is dependent upon the cofactor phosphoadenosine phosphosulfate, and ATP is needed at two points in the synthesis of this cofactor (131).

GSH is formed from methionine via the cystathionase pathway in hepatocytes and from cysteine in other tissues (116). The addition of sulfur-containing amino acids or analogs can raise the level of GSH and prevent chemical toxicity (93, 116), although cysteine itself is toxic when administered at high levels. The level of thiane sulfur is probably more important in controlling the conversion of cyanide to thiocyanate than is the level of rhodanese (149).

Enzyme Inhibition and Stimulation

While enzyme induction is a relatively slow process, direct inhibition and stimulation of enzymes is rapid, and many chemicals found in foodstuffs can be considered in these roles. Some activities of cytochrome P-450 are stimulated and some are inhibited by the same compounds, such as acetone, metyrapone, and flavones, which are widespread in foods (18, 25, 63, 64). Further, mutagenesis by carcinogens such as aflatoxin B_1 and benzo(a)pyrene can be altered in vitro and in vivo. One hypothesis that has been advanced to explain this phenomenon, which is selective for the isozymes of cytochrome P-450 affected, is enhanced coupling of cytochrome P-450 and NADPH-cytochrome P-450 reductase (63, 64). Many of these compounds can also induce these enzymes.

Certain epoxide hydrolase activities are stimulated by metyrapone and other carbonyl compounds (49). Natural products have not been extensively studied in this regard, and the physiological relevance of this enhancement is unknown.

Cytochromes P-450 are considered in the types of suicidal inactivation that can occur. First, metabolites of some drugs, pesticides, and other chemicals can bind avidly to the heme in a noncovalent manner to block catalytic turnover of the iron (148). Second, heme can be destroyed through covalent interaction with enzyme-substrate intermediates formed with certain olefins and cyclopropyl compounds, including some drugs and industrial chemicals (111). Finally, the metabolites of some chemicals can bind to protein moieties to modify residues and inhibit activity (106). The considerations extend also to other enzymes, e.g. cystathionase (116).

Inactivation of Reactive Metabolites by Small Molecules

Recently two compounds have been found that bind to reactive benzo(a)pyrene diol epoxides through hydrophobic interactions and, by general acid base catalysis, promote the hydrolysis of these epoxides to nontoxic tetrols. The compounds are the vitamin derivative FMN (154) and the natural product ellagic acid (152). These compounds can block bacterial mutagenesis in vitro but their effects have not yet been examined in vivo.

Repair

Little is known about the effects of nutrition-related factors on the repair of damaged DNA, which occurs through several mechanisms, involving excision of large patches, dealkylation of modified purines, etc. (46). Toxic compounds do tend to induce some repair enzymes (114).

Balance of Useful and Detrimental Effects of Enzymes

While the discussion presented thus far may suggest that the enzymes under consideration are beneficial, the same enzymes can also carry out reactions that increase risk. Cytochromes P-450 can generate a variety of electrophiles (94, 151). Epoxide hydrolase can hydrolyze benzo(a)pyrene 7,8-oxide so that a cytochrome P-450 then forms a more dangerous diol-epoxide (153). GSH transferases can activate 1,2-dihaloethanes to form sulfur mustards and episulfonium ions that react with DNA (112). Glucuronides formed by UDP glucuronyl transferase can break down in the acidic environment of the bladder and cause tumors (74). Sulfation and acetylation can place better leaving groups on hydroxylated sites to promote nitrenium ion formation and alkylation (103, 150).

FACTORS THAT INFLUENCE METABOLISM IN VIVO

Many studies have involved the effects of food components and other environmental factors on humans as well as on experimental animals (22). Commonly used endpoints are clearance rates of prototype drugs (e.g. antipyrine, caffeine)

in vivo and measurement of enzyme activities in vitro. Both approaches have deficiencies and the knowledge of basic mechanisms is still meager.

Fasting and Starvation

Decreases in mixed-function oxidase activities in vitro were shown as early as 1960 when rats were starved for 36 hours (33). Decreases were a function of the particular substrate used and the sex and animal species (20, 75, 113). Some activities preferentially expressed by females were actually increased upon starvation (76). UDP-glucuronyl transferase activity fell during starvation (91), as did the level of glutathione (116).

The effects of starvation on drug metabolism in integrated systems are attributable to decreases in cofactors due to carbohydrate depletion (131). The extended chronic effects of starvation on other measurements are complex and may be related to hormonal changes, as evidenced by the sex differences (20, 75). The effects of fasting and starvation on humans are less clear. Anderson et al (1) did not observe changes in clearance of several drugs in obese fasting adults. Another study with adult women showed no changes in drug clearance during anorexia nervosa (4). However, other studies with children in underdeveloped countries suggest that starvation may decrease rates of drug metabolism (1).

Protein

High-protein diets appear to enhance rates of oxidative drug metabolism in humans, as judged by rates of clearance of antipyrine and theophylline from plasma (1). Rats on low-protein diets were at increased risk when exposed to pesticides (14). Children with kwashiorkor disease also had lower rates of metabolism of drugs (1, 113). In rats, protein deficiency decreased the levels of cytochrome P-450 and its reductase by 50–75% after two weeks (20). Decreased synthesis of these particular proteins was postulated to be responsible for the lowered activities, although the effect could involve hormonal or other complex phenomena. Protein quality is another factor to consider (21).

Protein deficiency also lowered glutathione levels, and conjugation via this pathway was impaired (116). Epoxide hydrolase activity fell during protein deficiency, but the activity of UDP-glucuronyl transferase increased during protein deficiency (155). Protein deficiency can lower the carcinogenic and toxic effects of aflatoxin B_1 (88, 121), although the effect may be more complex than simply decreasing oxidative bioactivation.

Carbohydrate

Short-term deprivation of carbohydrates decreases rates of oxidative and conjugative metabolism by depletion of cofactors (131). Chronic high-carbohydrate diets decrease the activity of mixed function oxidases (1, 20,

113). Such inhibition has also been observed in humans through the use of antipyrine and theophylline clearance (1). The explanation for this observation has been hypothesized to be the "glucose effect," in which high glucose levels inhibit the synthesis of δ-aminolevulinic acid synthetase, a key enzyme in the synthesis of heme for cytochrome P-450 (1, 42). Carbohydrate supplies are also necessary for UDP-glucuronyl transferase activity (131).

Lipids

Early studies indicated that rats on diets deficient in essential fatty acids had decreased rates of drug metabolism, as measured in vitro (109). High unsaturated fatty acid levels increased mixed-function oxidase and UDP-glucuronyl transferase activity in some studies (109) and decreased activity in others (60). Unsaturated fatty acids were necessary for the induction of cytochrome P-450 and UDP-glucuronyl transferase by phenobarbital (92, 109). Cholesterol has also been reported to enhance cytochrome P-450– and UDP-glucuronyl transferase–dependent activities (113). Lipotrope (lipid methyl donor) deficiency decreased microsomal mixed-function oxidase activity and its inducibility (20). However, a considerable portion of the lipid in microsomal vesicles can be removed in vitro without affecting activities related to cytochrome P-450 (138). Further, more than 70% of the phospholipid in rat liver microsomes can be replaced with highly saturated egg yolk lecithin without affecting activities linked to cytochrome P-450 (105). Changes in drug metabolism were not observed in humans fed unsaturated and saturated fat diets (1, 104). Gallenkamp (41) concluded that "there is no established correlation of phospholipid content in liver disease to the activity of drug metabolizing enzymes in vivo."

B Vitamins

Some of the enzyme systems under consideration utilize vitamin derivatives as prosthetic groups and cofactors, and they might be expected to be influenced by dietary changes. Most of the attention has been given to the cytochrome P-450–related enzyme activities. Some changes have been observed, but the results are not often easily interpreted. Further, information available on humans is rather sparse.

Although pyridine nucleotides are synthesized from niacin, tryptophan is an alternate source. One early report suggests that niacin deficiency can lower the metabolism of an anaesthetic (80). A high-thiamin diet decreased mixed-function oxidase activity (45), and thiamin-deficient diets resulted in increased in vitro rates of metabolism of some substrates but not of others (20, 139). One study indicated no major effect of altering pyridoxine levels on mixed-function oxidative activity (139). Pyridoxal phosphate is a prosthetic group for cysteine conjugate β-lyase (126), but the effects of nutritional changes have not been reported. Riboflavin is of interest because flavins are prosthetic groups of

NADPH-cytochrome P-450 reductase, DT-diaphorase (36), NADH-cytochrome b_5 reductase, and microsomal flavin–containing monooxygenase. Riboflavin deficiency has been shown to decrease the activity of the former two enzymes, and supplementation with riboflavin results in the restoration of activity in rats (156). The effects of riboflavin deficiency on overall mixed-function oxidase activity are variable (20). DT-diaphorase inactivates some carcinogenic azo dyes, and hepatic *N,N*-dimethyl-4-aminoazobenzene carcinogenesis was decreased by supplementation of diets with riboflavin (156). A number of drugs produce folate deficiency, which has been reported to block the induction of cytochrome P-450 by barbituates (113). Administration of folates to deficient patients has been reported to enhance rates of drug metabolism (113).

Other Vitamins

Retinol deficiency can lower cytochrome P-450–linked activities (6, 20, 113). Responses depend upon the species and tissue under consideration, and in some cases activities have been elevated (97). Retinoid inhibition of tumor formation is probably not related to changes in bioactivation of chemical carcinogens, as it appears to be at a promotional level and is related to hormonal stimulation of proliferation (54).

Early in vitro and in vivo studies indicated that animals deficient in vitamin C showed decreased rates of drug metabolism (20). The effects of vitamin C on metabolism in humans are rather minimal (1). Large doses can be dangerous because ascorbate can inhibit sulfation by competing for sulfate pools (62). However, ascorbate can block nonenzymatic formation of nitrosamines to inhibit chemical carcinogenesis (98). Vitamin D_3 is a cytochrome P-450 substrate, and some conditions that affect cytochrome P-450 may influence the metabolism of vitamin D. Vitamin D_3 binds tightly to some cytochromes P-450 and could block the metabolism of other substrates (113). Dietary vitamin E deficiency reduces mixed-function oxidase activities in rats, although the reasons for this remain unclear (20). As an antioxidant, vitamin E appears to be able to block lipid peroxidation, which is postulated to be important in toxic properties of foreign compounds (23). Vitamin E can also block formation of *N*-nitrosamines and can inhibit tumor formation (156). Menadione (vitamin K) is reduced by NADPH-cytochrome P-450 reductase and reoxidizes to produce potentially dangerous species of reduced oxygen (7). The effects of low levels of such quinones are unknown.

Minerals

Iron levels in the liver are rather stable; dietary iron deprivation had no effect on some cytochrome P-450–related activities and increased others (20). High levels of iron may contribute to hepatic lipid peroxidation (3). Extrahepatic

cells such as intestinal mucosal villae can lose cytochrome P-450 during iron deficiency (113). Selenium is related to the enzyme glutathione peroxidase and antioxidant activity (147) but is toxic at high concentrations (83). Iodide deficiency resulted in increased mixed-function oxidase activity in mice (24), and thyroid hormone affected flavin levels (120) and some cytochrome P-450–related activities (129). High concentrations of cobalt, cadmium, and other heavy metals can block the synthesis of heme and lower cytochrome P-450 levels in rats (34). The influence of copper, zinc, magnesium, calcium, and other metals upon the metabolism of xenobiotics is not well established (20).

Food Additives

The antioxidants butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA) scavenge radicals and inhibit lipid peroxidation (146). They can also inhibit cytochrome P-450 in a competitive manner (130). Cummings & Prough (31) found that BHA is demethylated by cytochrome P-450 to form a dihydroquinone that oxidizes and interacts with NADPH-cytochrome P-450 reductase to uncouple normal electron transfer. BHA and BHT also induce glutathione *S*-transferase, UDP-glucuronyl transferase, DT-diaphorase, and epoxide hydrolase (8–10, 125, 141). These observations may explain why these compounds can inhibit tumorigenesis (141).

Natural Products in Foods

Phenols such as *o*-hydroxycinnamic acid, 3,4-dihydroxycinnamic acid, and 4-hydroxy-3-methoxycinnamic acid (ferulic acid) are found in foods and can act as antioxidants. They also inhibit chemical carcinogenesis (141). Methyl xanthines such as caffeine, theophylline, and theobromine are found in beverages and can inhibit oxidative drug metabolism (26). The mechanism may involve binding to cytochrome P-450. Coumarin derivatives, found in vegetables and fruits, are capable of inducing glutathione *S*-transferase and inhibiting chemical carcinogenesis (141). Cruciferous vegetables such as cabbage, broccoli, brussels sprouts, and cauliflower contain a number of indole derivatives such as indole-3-carbinol, 3,3'-diindolylmethane, and indole-3-acetonitrile. These compounds and the vegetables themselves have been shown to inhibit tumor formation and also to induce cytochrome P-450-related activities and glutathione *S*-transferase (1, 25, 141). Aryl isothiocyanates in cruciferous vegetables induce glutathione *S*-transferase activity and inhibit tumorigenesis (141, 156). Flavanoids are found in a variety of plants and exert a host of biological effects (57). While some can act as mutagens and carcinogens (Table 2), others inhibit chemical carcinogenesis (141). Flavones can induce cytochrome P-450 and glutathione *S*-transferase (141). Different flavones also act directly on cytochrome P-450 in vivo to stimulate or inhibit activity, as discussed above. Except in the case of a few studies with cruciferous vegetables

(1), studies with these natural products have been carried out only with experimental animals, and not with humans.

Bulk

Bulk in the diet has been related to the incidence of colorectal cancers, but studies with experimental animals suggest that this effect cannot be rationalized in terms of effects on the mixed-function oxidative enzymes (1).

Ethanol

The complexity of ethanol effects results from the need to change other dietary constituents to balance high-ethanol diets as well as from the myriad changes which are produced by ethanol. Acute ethanol administration lowers mixed-function oxidase activity by interrupting the flow of reducing equivalents of mitochondrial origin into the cytosol (118, 131). Ethanol also acts as a competitive inhibitor of some cytochrome P-450–mediated reactions (156). Chronic ethanol administration appears to increase some mixed-function oxidative activities. In rats, increases in *N*-nitrosamine dealkylation in vitro were seen after three days (156). The metabolism and toxicity of perhalomethanes are enhanced in rats and mice after several days of treatment with a variety of alcohols or ketones (55), while up to three weeks are needed for enhancement of other activities (99).

Microsomal preparations oxidize ethanol to acetaldehyde (81, 110); it has been postulated that cytochrome P-450 is a specific catalyst (81, 102) or a nonspecific generator of hydroxyl radicals (67). Others (11, 131) have concluded that microsomal ethanol oxidation does not operate in intact cells and that no relationship exists between levels of microsomal mixed-function oxidase components and rates of ethanol elimination in whole cells. Epidemiological studies show nondrinkers to be at decreased risk from several tumors (128). The shift of tumors produced by *N*-nitrosodiethylamine from the liver to the esophagus by ethanol may be due to induction of hepatic cytochrome P-450 (156).

Smoking and Charred Foods

Smoking enhanced the rates of drug metabolism in humans in vivo (25). Hepatic cytochrome P-450–linked activities were not readily affected by smoking to the same degree as these enzymes in tissues such as placenta, peripheral blood cells, and other extrahepatic sites were (145). The effect is thought to be due to enzyme induction by polycyclic hydrocarbons and other materials in smoke.

Ingestion of charred meat enhanced oxidative metabolism of several drugs in rodents and humans (1, 25), but rates of glucuronidation of phenacetin were not increased (1). The effect was abolished by wrapping meat in aluminum foil

during the cooking process. Thus, the effect appears due to polycyclic hydrocarbons or related pyrrolysis products produced during charring. Pyrrolysis of foods also produces a variety of *N*-nitrosamines (35) and complex mutagens derived from amino acids (128). These compounds can become potent carcinogens after activation (Table 2) but their own effects on metabolism are not known.

Genetics

The response of enzyme systems to induction has been shown to be heritable (107, 135, 136). Perhaps the most thoroughly studied example of genetic polymorphism in drug metabolism is the 4-hydroxylation of debrisoquine (66, 119), a cytochrome P-450–mediated activity that is absent in about 10% of several populations.

Age and Sex

The significance of these considerations depends upon the enzyme and species in question. In general, fetal levels are low and tend to rise rapidly after birth before decreasing slowly later in life (86, 87). Some individual activities are sex-dependent and some are not (77). Induction of different cytochromes P-450 by xenobiotics can affect the metabolism of endogenous steroids, some of which have hormonal roles (25). In humans, the effect of aging on drug metabolism is complex and may also involve pharmacokinetic phenomena not directly related to metabolism (43).

Disease

Disease itself can be related to changes in the metabolism of chemicals. For instance, disease states can involve changes in nutritional status. The drugs that are administered often induce enzymes that metabolize these and other drugs and can put some strains on the drug-metabolizing machinery. The enzymes that are induced conceivably may metabolize steroids and other endogenous materials to influence other physiological processes. Some drugs may also lower enzyme levels, as discussed above. Stimulation of interferon production depressed cytochrome P-450 (89). Finally, tumors generally have decreased levels of mixed-function oxidase activity but often have extremely elevated levels of enzymes such as epoxide hydrolase, glutathione-S-transferase, and γ-glutamyl transpeptidase (79).

Hypoxia

Oxygen does not appear to be limiting for mixed-function oxidation under normal physiological conditions (131). In hypoxia, the availability of high-energy cofactors is decreased due to effects on cytochrome oxidase (2). Patients exposed to hyperoxia can experience oxygen toxicity when partially

reduced species of oxygen are produced, as occurs in poisoning with paraquat or quinones (38).

CONCLUSIONS

This review briefly describes some of the relevant enzyme systems, the molecular basis by which factors related to nutrition can influence these enzymes, and some of the observations that have been made. Overall, this is a complex area about which we know little. However, epidemiological studies strongly suggest that nutrition is important in affecting chemical carcinogenesis (19, 30, 143, 144), and further studies in this area should be encouraged.

The relationships are complex. In summary, there are enzymes that metabolize nutritive factors as well as typical xenobiotics. Both xenobiotics and nutritive factors can influence the levels of these enzymes, and can directly stimulate or inhibit them. Supplies of nutrients can also influence the levels of cofactors and prosthetic groups for these enzymes. Chemicals in foods or produced during processing of foods can be activated by these enzymes to toxic materials. We deal here not with only a few compounds, but with most classes of chemicals, and perhaps with many which are not yet even known.

ACKNOWLEDGMENTS

The author's research has been supported by NIH grants ES 00267, ES 01590, ES 02205, and CA 30907; an NIH Research Career Development Award (ES 00041); and a Burroughs Wellcome Scholar in Toxicology Award. Dr. M. J. Meredith and particularly Dr. R. G. Thurman are thanked for their criticism of the manuscript, as are the many individuals who shared reprints of published and unpublished work.

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