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DIETARY REGULATION OF CYTOCHROME P450

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INTRODUCTION

Cytochrome P450 Enzymes and the Mixed Function Oxidase System

Many drugs and other chemicals are metabolized in the liver mainly by the hepatic mixed function oxidase (or monooxygenase) system before excretion from the body (36). The mixed function oxidase system receives electrons from NADPH or NADH. Reducing equivalents are then passed via NADPH-cytochrome P450 reductase (a flavoprotein containing both FAD and FMN) to cytochrome P450 (P450) hemoproteins. Cytochrome b_5 is an important component of the system for metabolism of some substrates. Formation of a complex of P450, molecular oxygen, and a chemical substrate precedes the transfer of one atom of oxygen to the substrate to form the product and the other atom to form water. Many P450 proteins, cDNAs, and genes have been isolated and sequenced. The term P450 refers collectively to a superfamily of individual P450 enzymes. Forms of P450 found primarily in liver have been classified into four gene families, designated I through IV, based primarily on their amino acid sequences. Subfamilies are designated by sequential capital letters and genes within a subfamily by Arabic numbers (59, 120). Hepatic P450 enzymes have preferential as well as overlapping specificities for chemical substrates. Some chemicals, including many products of P450 enzymes, are conjugated by other enzymes in the cytosol and endoplasmic reticulum, which form glucuronide, sulfate, glutathione, and other conjugates.

P450 enzymes found in the liver and in some other tissues such as the intestine and lung may have evolved to enable the organism to inactivate diverse chemicals from the environment. The diet is probably the most substantial route of exposure to environmental chemicals, including those naturally synthesized by plants or formed during food storage and preparation. Both P450 and conjugating enzymes are inducible by many chemicals and drugs, some of which are also substrates for these enzymes. Well-known inducing influences on the mixed function oxidase system include barbiturates and the polycyclic aromatic hydrocarbons found in cigarette smoke and some foods. In general, P450 enzymes are more likely to be induced by environmental factors than are conjugating enzymes.

Some products of P450 metabolism are biologically active and may have actions that differ from the parent drug or chemical. For example, many carcinogens and toxins require activation by P450 for their harmful effects to occur. P450 and conjugating enzymes also are important for the metabolism of many endogenous chemicals, such as steroid hormones (36, 92).

Species Differences and Effects of Diet on P450 Enzymes

Most studies of effects of dietary composition and nutritional deficiencies on the metabolism of drugs and other chemicals in animals were carried out before various P450 isoforms had been identified and characterized [see (31) for review]. Interpretation of some studies may have been complicated by extreme dietary variations leading to other pathologic processes (53). Procedures such as overnight fasting before killing, or pair-feeding that may involve lengthy periods of fasting for control animals, may also complicate interpretation (172).

It is difficult to extrapolate results of studies of the mixed function oxidase system in animals to humans. Differences between species in P450 enzymes, in drug metabolism rates, and in toxicity or resistance to various chemicals can be substantial (59, 120, 164). There may even be substantial differences among strains of the same species. The laboratory rat is unusual in showing large sex differences in a number of P450-dependent enzyme activities in liver. Greater enzyme activities in the male rat are determined in large part by endogenous androgens. There appears to be little or no such sex difference in humans. Species may also differ in the responsiveness of P450 enzymes to exogenous chemicals or endogenous hormones.

Studies to identify dietary components that can influence drug metabolism in humans have been conducted mostly in healthy subjects consuming nutritionally adequate diets under controlled conditions. This approach is more likely to provide consistent and clear information on the effects of specific dietary changes than are studies in patients, in whom underlying disease, concurrent drug therapy, and many other factors are likely to influence the results. However, a few studies have been carried out in patient populations and have suggested that changes in diet and nutritional status may have clinically important influences on drug metabolism.

Other Effects of Foods on Drug Metabolism

This review concerns primarily the effects of diet and nutritional status on the postabsorptive metabolism of drugs and other chemicals by hepatic P450 enzymes. Foods can also influence the gastrointestinal absorption and bioavailability of chemicals (110, 142, 167). Bioavailability may be altered by direct binding of a drug by substances in food or by altering luminal pH, gastric emptying, intestinal transit, and mucosal absorption and splanchnic-hepatic blood flow. Food may induce changes in bioavailability of some drugs in part by altering hepatic clearance mechanisms or by competing with drugs for first-pass metabolism in the intestine (2, 102, 109). Drugs may undergo metabolic transformation by microorganisms in the intestine. Therefore, di-

etary influences on the gastrointestinal flora may alter metabolism of some drugs (146).

EFFECTS OF DIETARY MACRONUTRIENTS, FASTING, AND ENERGY RESTRICTION

Studies in Laboratory Animals

DIETARY PROTEIN Considerable evidence indicates that dietary protein can influence P450 enzymes. For example, in male and female rats that for two weeks were fed diets in which the protein (casein) content varied from 5 to 50%, toxicities of pentobarbital and strychnine were increased and the in vivo metabolism of the barbiturate was reduced by lower protein intakes (84). Metabolism of pentobarbital, strychnine, aminopyrine, zoxazolamine, and aniline by liver microsomes was decreased by protein restriction; the effects were more marked for the first three substrates. Most of these effects of dietary protein restriction were more marked in males. The flavoprotein reductase and cytochrome b_5 were somewhat decreased by protein restriction; no clear sex differences were noted. In this study, glucose was substituted isocalorically for casein. Rats on high protein intakes gained weight, whereas those on low protein intakes lost weight, indicating that the animals on the lower protein intakes consumed less energy. Nevertheless, this study demonstrated a clear dose-response relationship between dietary protein and hepatic mixed function oxidase activities. The inducibility of P450 by phenobarbital in rats is also decreased by a reduced protein intake (105). The effects of diets containing primarily poor-quality protein (e.g. gluten) on P450 enzymes are similar to the effects of protein restriction (31). Protein deficiency in female monkeys can reduce hepatic P450 levels, but other components of the mixed function oxidase system and some associated enzyme activities are less affected in this species than in rats (144).

Toxic effects of a number of chemicals that are inactivated by the mixed function oxidase system in the liver are increased by protein restriction. These include pesticides such as endosulfan, captan, lindane, and diazinon when given to weanling rats with a kwashiorkor-like condition (25–27, 31). Experiments using microsomes to activate precarcinogens to ultimate carcinogens in vitro in the presence of a bacterial mutagenicity test system indicate that low protein diets decrease the activation of precarcinogens such as *N*-methyl-*N*'-nitrosoguanine (39) and 1,2-dimethylhydrazine (81). The level of dietary protein intake and the development of 7,12-dimethylbenz-(*a*)anthracene (DMBA)-induced breast cancer in the rat are inversely related, suggesting that a high protein diet enhances the oxidative degradation of the

precarcinogen to inactive metabolites so that the more active metabolites do not reach the target tissue (35). Lower activities of conjugating enzymes during protein restriction may also increase the harmful effects of reactive metabolites formed by P450 enzymes.

Protein restriction can decrease the toxic or carcinogenic effects of chemicals that are transformed to more potent metabolites during oxidation by P450 enzymes. For example, the hepatotoxicity of carbon tetrachloride is increased by pretreatment with a barbiturate or other P450 inducers but is reduced by protein restriction (30, 107). Protective effects of protein restriction have been found for dimethyl nitrosamine (39, 108) and heptachlor (165, 166). A low protein intake decreases the formation of aflatoxin B_1-DNA adducts as well as tumor formation in rats, whereas protein deficiency increases acute toxicity, which may be due to the parent compound (1).

The mechanisms of the effects of dietary protein on the mixed function oxidase system are not known. Although decreased food intake can contribute, it does not account fully for decreases in P450 enzymes observed in animals on a low protein diet (111). In animals with severe protein restriction and a kwashiorkor-like state, nutritional factors other than protein intake per se may have been a factor. Changes in phosphatidylcholine in membranes of the endoplasmic reticulum, or effects on the interaction between P450 enzymes and the flavoprotein reductase may be involved (31, 121). High protein intakes, on the other hand, augment hepatic microsomal P450 content, liver weight, and mitotic indices (18, 31); these effects are similar in many respects to the inducing effects of phenobarbital. Certain amino acids such as tryptophan and oxidized sulfur amino acids may increase liver protein synthesis and induce the mixed function oxidase system in laboratory animals and in liver cell cultures (17, 47, 125, 148, 168). Dietary protein-associated variations in microsomal drug oxidations are additive to the inducing effects of ethanol feeding (114). A low protein diet can potentiate an endotoxin-induced depression of drug oxidation rate in the rat (150).

DIETARY CARBOHYDRATE A high carbohydrate intake can reduce oxidative drug metabolism in laboratory animals. For example, Strother et al (152) found that high intakes of glucose, fructose, or sucrose increased barbiturate-induced sleeping times and decreased in vitro metabolism of barbiturates and *p*-nitrosoanisole in male mice. Ring hydroxylation of aniline was not affected. In most of these studies, carbohydrate was dissolved in drinking water (e.g. 35% glucose solution), and the solution was provided ad libitum with laboratory animal food for 24–48 h before the mice were killed. Mice on high carbohydrate intakes consumed less feed and lost weight. Semi-starved controls also lost weight but, compared with carbohydrate-fed animals, had much less change in drug oxidation rates. The findings suggested that the carbo-

hydrate effect was not mediated by decreased intake of other nutrients (152). Similar findings in rats have been reported (29).

A primary role for carbohydrate was suggested by studies in which glucose or fructose was given by intraperitoneal injection to male rats and other nutrients were administered by gavage so that all groups gained weight, and microsomal protein and mixed function oxidase activities (ethylmorphine *N*-demethylase and aniline hydroxylase) were decreased by carbohydrate administration (62). However, the interpretation was complicated by greater increases in liver weight, hyperglycemia, hepatic fat deposition, and glycogen depletion in the carbohydrate-treated animals. In some studies in mice and rats the effects of glucose were more pronounced than the effects of fructose (44, 152). However, others noted that in rats the effects of glucose and fructose were similar (62). A low carbohydrate diet and an associated lower energy intake enhanced the P450-inducing effects of phenobarbital, 3-methylcholanthrene, and polychlorinated biphenyls in male rats (119).

Carbohydrate feeding can influence the oxidative metabolism of carcinogens. For example, studies of liver microsomes from male rats treated with glucose suggest that glucose treatment inhibits the microsomal metabolism of benzo(*a*)pyrene and benzo(*a*)pyrene 7,8-dihydrodiol. Microsomal-mediated mutagenesis of these compounds in *Salmonella typhimurium*, TA100, as well as DNA binding and adduct formation, is also reduced (158). Similar effects of glucose feeding on metabolism and mutagenic effects and DNA binding of benzo(*a*)pyrene and aflatoxin B_1 have been reported in the hamster (143).

A number of mechanisms for the carbohydrate-induced changes in P450 enzymes have been suggested. In some studies, carbohydrate reduced metabolism of drug substrates in vivo and in vitro without changing microsomal protein and total P450 content (137, 151). However, changes in specific isoforms of P450 may have occurred. Liver cytosol from glucose-treated animals does not alter the metabolism of *p*-nitroanisole when added to liver microsomes from control animals. The level of blood glucose or insulin did not increase, and cyclic AMP did not increase substantially in most studies (62). Changes in hepatic glycogen content were not well correlated with hepatic microsomal drug-oxidizing activities (29). The ratio of dietary protein to carbohydrate may be important (44). Glucose administration increases hepatic microsomal phospholipids and fatty acids. These fatty acids might compete with drug substrates for P450 binding sites. Carbohydrate-induced changes in membrane phospholipid composition may alter binding of substrates such as hexobarbital and methadone to microsomal P450 after glucose administration (29). High carbohydrate intakes can lead to decreases in hepatic P450 content; in some of these studies, decreased levels of fat in the diet may have played a role (150). Rates of microsomal drug oxidations in normal male rats, and in rats after carbohydrate feeding, starvation, or

phenobarbital administration, are determined primarily at the level of P450 and seem to be limited by the rate of transfer of electrons to P450. Drug- and nutrition-induced changes in components other than P450, such as NADPH-cytochrome P450 reductase or cytochrome b_5, are small and seem less important (72).

Glucose administration also reduces δ-aminolevulinic acid synthase, the rate-limiting enzyme for the heme biosynthetic pathway in liver (157). Most of the heme formed in the liver is used for the synthesis of P450 enzymes, which are present in large amounts and turn over relatively rapidly in this tissue. Because hepatic δ-aminolevulinic acid synthase activity and P450 content are closely related under a number of conditions (10), the "carbohydrate effects" on hepatic δ-aminolevulinic acid synthase and P450 enzymes are probably determined by closely related mechanisms.

DIETARY FAT Phospholipid, and particularly phosphatidylcholine, is an essential component of the mixed function oxidase system, and the nature of its fatty acid constituents can influence P450-dependent enzyme activities. There is a close relationship between dietary fatty acids and the composition of lipids in many tissues, including the phospholipids of liver microsomes (162).

Effects on P450 enzyme activities of a number of experimental alterations in dietary lipids have been studied. Essential fatty acid (EFA) deficiency can develop in rats within seven weeks after beginning an EFA-deficient diet and is associated with fatty liver, scaling of the skin, weight loss, and marked changes in fatty acid composition of cellular lipids. Rats fed a linoleic acid-deficient diet manifested decreased in vitro hydroxylation of substrates such as aniline, hexobarbital, and benzo(*a*)pyrene as well as a decrease in hepatic P450 content, although inducibility of benzo(*a*)pyrene hydroxylase was preserved (33, 82, 163).

Rats fed a fat-free diet for three weeks have no obvious signs of EFA deficiency. However, they exhibit decreased hepatic metabolism of aniline, hexobarbital, ethylmorphine, and benzo(*a*)pyrene and decreased content of P450 when compared to controls fed diets containing 3 or 10% corn oil (96, 122). A number of studies indicate that the maintenance and the induction of P450 enzymes are optimized by a dietary source of polyunsaturated fatty acids such as corn oil (85, 106, 162) or fish oil (43, 95, 172). In rats on a 20% corn oil diet, induction of P450IIB1 and IIB2 is greater than on a fat-free diet, whereas induction of P450IIE1 is unaffected (85, 172). A high fat intake can enhance the stimulation of the mixed function oxidase enzymes by ethanol (73) and can accelerate microsomal ethanol oxidation (75). Increased polyunsaturated fatty acids in the diet might increase fluidity of cellular membranes, which might facilitate activation of carcinogens by P450 enzymes. How-

ever, the interrelationships of diet and chemical carcinogens are complex and may be modified by other factors such as membrane cholesterol content and levels of micronutrients such as vitamin E, dietary antioxidants, and selenium (60).

FASTING AND ENERGY RESTRICTION The effects of fasting vary considerably with the species and sex of laboratory animals (55). In male mice, fasting leads to decreased in vivo and in vitro rates of metabolism of a number of P450 substrates (45). Inclusion of an NADPH-generating system in vitro does not correct the defect. Mixing microsomes from starved and normal animals did not suggest the presence of an inhibitor of P450 in the starved animals. In rats there are marked sex differences in the effects of starvation on monooxygenases (83). In males, fasting for 48 h impairs the metabolism of substrates such as aminopyrine, pentobarbital, and morphine. In females, however, fasting either has no effect or enhances in vitro drug metabolism. Aniline hydroxylation was enhanced in both sexes. The net effect of fasting in rats was to reduce sex differences in drug metabolism because the activities that were increased in females and decreased in males by fasting were those that displayed the greatest sex differences in fed animals (83). Starved rats are responsive to phenobarbital induction. Starvation-induced changes in the Km and Vmax for P450-dependent enzyme activities differ with various substrates (61). Hepatotoxicity of chloroform, some other chlorinated or brominated hydrocarbons, and acetaminophen is enhanced by fasting in rats (40, 136). This effect may be due to increased metabolism of these compounds to toxic metabolites in the fasting state and to depletion of hepatic glutathione, which has an important role in inactivating reactive intermediates (118).

A number of mechanisms may contribute to reduced drug metabolism rates in starved animals. Starvation has much more profound effects on the hepatic endoplasmic reticulum than on nuclei and mitochondria in animals, and the effects are reversed quite promptly by refeeding (31). Starvation can lead to disaggregation of polyribosomes and reduction of hepatic protein synthesis. Amino acids in portal blood and liver cytosol are not substantially reduced during fasting. Altered protein synthesis during fasting can be corrected not only by feeding protein or a complete amino acid mixture but also by glucose. The effect of glucose is posttranscriptional (173). During fasting, reducing equivalents for mixed function oxidations are derived primarily from mitochondria, and fatty acid oxidation is important for the generation of mitochondrial NADPH. Studies in the isolated perfused liver suggest that, particularly in the fasted state, NADPH supply can influence the rate of oxidation of foreign chemicals (23).

Although mixed function oxidase activities are generally reduced by fasting in male rats, it is interesting that P450IIE1 (P450j, P450ac) and its mRNA are

increased by fasting in both male and female rats (67). Aniline hydroxylase and *N*-nitrosodimethylamine demethylase activities, which are attributable to this isoform, are also increased by fasting. This enzyme is also induced by acetone and by experimentally induced diabetes. However, acetone treatment does not lead to increased mRNA for this P450 enzyme. This finding suggests that under different conditions this P450 is induced by different mechanisms (67, 172). Fasting and streptozotocin-induced diabetes had different effects on several other P450 isoforms. P450 UT-A (a male-specific form, probably P450IIC11) was more markedly reduced in diabetic rats than in fasting rats; P450 PCN-E (P450IIA1) was decreased in diabetic rats but was increased by fasting; slight changes in other forms of P450 were also observed (104).

Dietary restriction increases longevity and reduces the risk of spontaneous or chemically induced neoplasms in animals. In contrast to the effects of fasting, a number of hepatic monooxygenase activities and P450 levels are increased by caloric restriction in male rats and decreased in female rats (63, 145). Caloric restriction in male rats increases hepatic microsomal monooxygenase activities considered to be reasonably specific for several isoforms of P450, namely IIC11, IIE1, IIIA, and IVA1 (98). In diet-restricted male rats, hepatic nuclear binding of aflatoxin B_1 is decreased and its clearance increased compared with ad libitum-fed animals (135).

PARENTERAL NUTRITION The route of administration of nutrients can influence their effects on P450 enzymes in the rat. Pentobarbital hepatic clearance and the content of P450 and associated enzyme activities in liver were lower in healthy rats receiving total parenteral feeding when compared with animals receiving either an intragastric infusion of the same solution of nutrients or standard laboratory feed ad libitum (87, 88).

Studies in Humans

DIETARY PROTEIN, CARBOHYDRATE, AND FATS Protein intakes vary widely between and within human populations. Variations in dietary protein in humans might alter rates of metabolism of drugs and other substrates of P450 enzymes. Therefore, it is important to determine if drug oxidation rates are influenced by dietary protein in humans.

Effects of carbohydrate, fat, and protein are difficult to identify in individuals who self-select their own diets because foods are complex mixtures of macronutrients, and dietary variations are unpredictable. Studies of healthy subjects under controlled conditions have circumvented some of these difficulties. In these investigations, one macronutrient (e.g. protein) was increased isocalorically at the expense of another (e.g. carbohydrate) while keeping the third macronutrient (e.g. fat) as well as total energy intake

constant. Particular drugs were chosen for study because their clearances depend on metabolic transformations by P450 enzymes and in the liver.

Dietary protein when substituted for carbohydrate can accelerate the oxidative metabolism of a number of substrates of the mixed function oxidase system in humans. In an initial study (3, 77), the isocaloric change from a high protein diet to a high carbohydrate diet in six healthy men resulted in a decrease in dietary protein from 44 to 10% of total calories; carbohydrate content increased from 35 to 70%; dietary fat remained constant at 20 to 21% of total calories. Average plasma half-lives for antipyrine and theophylline were substantially shorter and metabolic clearance rates were greater during the high protein diet. Furthermore, the addition of a pure protein supplement (100 grams of sodium caseinate each day for two weeks) to a calculated well-balanced diet in two subjects increased the rates of metabolism of both drugs, whereas in two other subjects a supplement of carbohydrate (200 grams of sucrose daily for two weeks) had the opposite effect (77). Others have shown that increasing the protein content of the diet can accelerate the metabolism of propranolol (48) and perhaps aminopyrine and caffeine (74). Dietary protein also affects theophylline and propranolol clearance in women (48).

Effects on drug metabolism of high carbohydrate, high fat, and high protein diets were also compared in six men (9). Composition of the three diets permitted observations on the effects of the isocaloric substitution of fat for carbohydrate while keeping protein constant at 10% of total calories, and the substitution of dietary protein for fat while keeping carbohydrate constant at 20% of total calories. The metabolic clearances for antipyrine and theophylline were greater during the high protein dietary period than during the other two diets. There were no differences in the drug clearances between the high fat and high carbohydrate dietary periods. Thus, substitution of protein for either fat or carbohydrate can increase drug oxidation rates (9).

Effects of large isocaloric exchanges of carbohydrate for either unsaturated fat (corn oil) or saturated fat (butter) were examined in nine normal men (9). Dietary protein was maintained at a constant level of 15% of total calories. No significant changes in the metabolism of antipyrine and theophylline were observed (9). Mucklow et al (116) confirmed that substituting saturated and unsaturated fat in the diet of normal subjects has no effect on the metabolism of antipyrine. Thus, although changes in dietary fat can influence hepatic drug oxidations in animals, isocaloric exchanges of saturated fat, unsaturated fat, and carbohydrate do not appear to influence the metabolism of at least a few substrates for P450 enzymes in humans.

As described above, the mechanisms of protein and other macronutrient effects on P450 enzymes in laboratory animals are not established. In humans, dietary protein can substantially alter drug metabolism during test diets

that are adequate in protein and other essential nutrients. Therefore, under these conditions such effects are clearly not due to deficiencies in protein or other nutrients. As reviewed elsewhere, impaired gastrointestinal absorption or altered distribution after absorption of the test drugs has also not been a factor (5). Dietary protein can alter the disposition of other drugs that are cleared primarily by the kidneys by influencing renal plasma flow, creatinine clearance, and renal tubular transport, (86, 134).

Dietary protein intake may be an important influence on drug metabolism in patients with various diseases. For example, in 14 hospitalized asthmatic children during long-term treatment with theophylline, clearance of the drug was greater during a high protein diet than during two diets lower in protein content. Steady state plasma concentrations of theophylline were higher and wheezing episodes and requirements for additional medications less frequent during consumption of a low protein diet (52). In eight adult patients with airways obstruction, theophylline concentrations were lower during a high protein diet than during a high carbohydrate diet (153). Inadequate protein intakes may influence drug metabolism in patients with cirrhosis (49).

ENERGY RESTRICTION Krishnaswamy et al (91) studied antipyrine and aminopyrine metabolism in seven men after 18–22 days on a series of diets differing in total calories (1500, 1800, or 3000 kcal daily) and protein (5, 10, or 15% of total calories). Body weight decreased during diets containing 1500 and 1800 kcal and increased during consumption of 3000 kcal diets. Reducing the energy intake while keeping protein constant (as a percentage of total calories) was associated with increased half-life and reduced clearance for antipyrine, and increased half-life and decreased metabolite formation for aminopyrine. Decreased intake of protein, which occurred when intakes of energy were decreased, could have contributed to the effects of total dietary restriction. A higher level of protein intake at given levels of energy intake in this study tended to accelerate the metabolism of the test drugs (91). Therefore, dietary protein can influence drug oxidation rates at levels of energy intake other than those needed to maintain body weight.

FASTING Effects on drug metabolism of elective fasting for weight reduction have been studied in subjects who were healthy except for obesity. Subjects were studied before and during hospitalization for two-week fasts (139–141). The metabolism of antipyrine and tolbutamide, which are substrates for the mixed function oxidase system; sulfisoxazole and isoniazid, which undergo acetylation in the liver; and procaine, which is metabolized by the pseudocholinesterase pathway, was not significantly changed by fasting. Volumes of distribution of the drugs were reduced in proportion to reductions in total body water and body weight. It is not known whether sex and genetic

factors control such responses to fasting in humans or whether the various isoforms of P450 in humans are regulated differentially by fasting.

PARENTERAL NUTRITION Pantuck et al (131) studied antipyrine kinetics in six healthy men on the fifth day of an intravenous 5% dextrose infusion (440 kcal/day) and on the second day after the dextrose infusion was replaced by a 3.5% crystalline amino acid solution (480 kcal/day). Drug clearance was greater during the amino acid regimen than during the dextrose infusion. This suggests that amino acids given intravenously, like high protein diets or casein supplements (3, 77), can accelerate drug oxidations in humans. In another study, antipyrine metabolism was not significantly different in eight subjects during 3-day regimens of intravenously administered glucose at levels of 8.1 or 30.7 kcal/kg per day (133). This finding suggests that carbohydrate by itself does not affect antipyrine metabolism. However, carbohydrate might have some effect on drug metabolism in subjects receiving both carbohydrate and protein, or in the ill or malnourished (133).

Six chronically ill adults requiring parenteral nutrition for protein-calorie malnutrition were studied while receiving intravenous infusions of 5% dextrose (400–500 kcal/day) and again during two 8-day periods of repletion when they were given an amino acid infusion providing 20 gm nitrogen per kilocalorie basal energy expenditure and, in addition, dextrose to provide a total caloric intake of either 0.95 or 1.75 times baseline energy expenditure (132). Antipyrine metabolism was accelerated by nutritional repletion. The amount of dextrose during the repletion period did not significantly influence antipyrine metabolism. The nitrogen contents of the regimens were substantially greater than is usual for parenteral alimentation. Whether more typical amounts of amino acids produce changes in drug metabolism or whether varying amounts of intravenous dextrose have effects on drug metabolism when amino acids are infused at more usual levels is not known (132).

MICRONUTRIENTS

Substances Found in Vegetables

CRUCIFEROUS VEGETABLES AND INDOLES Cruciferous vegetables added to the diet of laboratory animals, or alfalfa meal found in commercial laboratory diets, can markedly induce chemical oxidations (103, 128, 130). The inducing effects of cruciferous vegetables are accounted for primarily by indoles, including indole-3-carbinol and indole-3-acetonitrile. These compounds can induce a number of monooxygenase activities, including benzo-(*a*)pyrene hydroxylase and *N*-nitrosodimethylamine demethylase (34). Certain strains of cabbage and brussels sprouts are particularly rich in these

inducing substances. Broccoli fed to male rats lowers binding of aflatoxin B_1 metabolites to DNA (138). Indole-3-carbinol enhances metabolism and elimination of aflatoxin B_1 and reduces binding of this carcinogen to DNA in vivo in the trout (58).

Effects on drug oxidations and conjugations of feeding cabbage and brussels sprouts have been studied in normal subjects. Dietary periods consisted of a 10-day control diet period, the same control diet for three more days followed by a diet containing the cruciferous vegetables for seven days, and a return to the control diet for ten days. During the test diet period, brussels sprouts and cabbage were substituted for other vegetables shown not to enhance mixed function oxidations in animals. The cruciferous vegetables significantly enhanced the metabolism of antipyrine and phenacetin (130). In a similar study, glucuronidation and metabolic clearance of acetaminophen were increased during the consumption of cabbage and brussels sprouts (129). A diet rich in brussels sprouts was shown to significantly enhance the elimination rate of warfarin; this effect and the high content of vitamin K in these vegetables can antagonize the anticoagulant effects of this drug (124).

FLAVONOIDS Flavonoids such as tangeretin and nobiletin are found in edible plants and can have a variety of effects on chemical metabolism, including the induction, activation, and inhibition of P450 enzymes. When administered orally, natural flavonoids, including tangeretin and nobiletin, and the synthetic flavonoid 5,6-benzoflavone can induce benzo(*a*)pyrene hydroxylase activity in the rat tissues. These effects are similar to those of 3-methylcholanthrene. Flavone, 7,8-benzoflavone, tangeretin, and nobiletin can activate rat and human benzo(*a*)pyrene hydroxylase and some other monooxygenase activities in rodent and human liver (37). The activating effects of flavonoids are dependent on species of animal and the particular P450 enzyme studied. In some instances, activation by a flavonoid results from enhancement of the interaction between the P450 enzyme and the flavoprotein reductase (171). A number of natural and synthetic flavonoids can also inhibit P450-dependent reactions. This inhibitory effect is sometimes attributable to competitive or noncompetitive inhibition or to inhibition of NADPH-cytochrome P450 reductase. A number of flavonoids inhibit microsome-catalyzed activation of aflatoxin B_1, which leads to less covalent DNA adduct formation (24). Certain flavonoids also antagonize the mutagenic or tumorigenic effects of the ultimate carcinogenic metabolites of polycyclic aromatic hydrocarbons (171).

PLANT COUMARINS Plants contain numerous other chemicals that influence P450 enzymes. For example, some naturally occurring plant coumarins can

decrease P450-dependent enzyme activities in animals and irreversibly inactivate human cytochrome P-450. Coumarin increases hexobarbital sleeping time in rats and protects mice from carbon tetrachloride hepatotoxicity (93, 170). Coumarin is both an inhibitor and an inducer of P450 enzymes and can induce δ-aminolevulinic acid synthase in the chick embryo liver (57).

METHYLXANTHINES Theophylline, caffeine, and related compounds are common nonnutritive components of foods and are extensively metabolized by P450 enzymes. Methylxanthines can accumulate when ingested regularly and can influence drug metabolism. For example, Monks et al (115) studied theophylline disposition in healthy subjects who were consuming their usual diets, after seven days of abstention from methylxanthine-containing foods and beverages, and while taking caffeine and theophylline tablets and still abstaining from dietary methylxanthines. Radiolabeled theophylline was administered intravenously or by mouth, and major urinary metabolites (3-methylxanthine, 1,3-dimethyluric acid, and 1-methyluric acid) were identified. Removal of methylxanthines from the diet increased urinary elimination of two metabolites (3-methylxanthine, 1,3-dimethyluric acid) and parent drug. Adding methylxanthines to the diet in tablet form produced results similar to those during consumption by the subjects of their usual caffeine-containing diets. Thus, a pool of methylxanthines derived from the diet may compete with theophylline for common saturable metabolic pathways.

Theobromine (3,7-dimethylxanthine), the major methylxanthine found in chocolate, appears to induce its own metabolism in rats (147). In healthy human subjects, abstinence from dietary methylxanthines for two weeks was reported to increase clearance of theobromine (46). Daily ingestion of theobromine led to a decrease in theobromine clearance. However, four days after discontinuing theobromine supplementation, clearance was increased. The data suggest that repeated doses of theobromine lower its own metabolism by saturating or inhibiting hepatic enzymes; but several days after the last repeated dose, induction of theobromine hepatic metabolism can be demonstrated (46). Theophylline also can induce its own metabolism in humans (41).

A cross-sectional study employing multiple regression analysis in Gambian villagers suggested that antipyrine half-life was prolonged by cola nut chewing (54). Cola nuts are reported to contain 2.3% caffeine and are commonly chewed in Africa and elsewhere for stimulant effects. However, a controlled study in normal male volunteers in the United States did not demonstrate an effect of chewing cola nuts on antipyrine metabolism (159). It is possible that other less apparent nutritional factors influenced antipyrine metabolism in the West African study.

Food Preparation

Polycyclic aromatic hydrocarbons formed during charcoal broiling are similar to those found in cigarette smoke. These chemicals are produced by incomplete combustion when drippings contact hot coals and are then volatilized and redeposited on the meat (94). Polycyclic aromatic hydrocarbons in cigarette smoke probably account for enhanced drug oxidation rates in smokers. Oral administration of such compounds to rats increases benzo(*a*)pyrene hydroxylase activity in the intestine and liver of animals. Moreover, feeding charcoal-broiled beef induces intestinal metabolism of phenacetin in the rat (127).

Substantial effects of charcoal-broiled beef on drug metabolism have been demonstrated in healthy subjects (38, 76, 126). Standard portions of hamburger (8 oz) and steak (6 oz) were broiled over charcoal and fed twice daily as part of a calculated test diet for 4–5 days before administration of a single dose of a test drug. During control diet periods, aluminum foil was placed under the meat and drippings aspirated by hand to prevent their falling onto the burning charcoal. This aspect of food preparation was the only difference between the charcoal-broiled beef diet and the control dietary periods. Average peak concentration of phenacetin in plasma and the area under the plasma concentration versus time curve in nine subjects were markedly reduced during consumption of charcoal-broiled beef, and the ratio of the major metabolite of phenacetin, *N*-acetyl-*p*-aminophenol (acetaminophen), to phenacetin was increased (38). Thus, both charcoal-broiled beef and cigarette smoking can enhance phenacetin *O*-dealkylation in humans. In a similar study, clearance of antipyrine and theophylline was increased by a diet containing charcoal-broiled beef (76). Metabolism of acetaminophen, which occurs primarily by conjugation, was not influenced by consumption of charcoal-broiled beef in humans (16).

Vitamins

Deficiencies of a number of vitamins can alter hepatic mixed function oxidations in laboratory animals (31) but have been little studied in humans. Selected aspects of these studies are reviewed here.

B VITAMINS Riboflavin deficiency leads to lower levels of FAD and FMN, which are coenzymes for NADPH cytochrome P450 reductase. Decreased activity of this enzyme in the liver of riboflavin-deficient animals contributes to lower activities of a number of P450-dependent enzyme activities. Levels of P450 and of some associated enzyme activities, such as aminopyrine demethylase, aniline hydroxylase, and *N*-nitrosodimethylamine demethylase, are increased during early riboflavin deficiency. These increases might be a compensatory response to lowered activity of the reductase. More severe and

prolonged riboflavin deficiency leads to a general decrease in total P450 and in associated monooxygenase activities (172).

Thiamin deficiency in rats leads to increases in hepatic P450 and cytochrome b_5 and in microsomal monooxygenase activities for substrates such as ethylmorphine, aniline, and benzo(*a*)pyrene (163, 174). Increased hepatic P450IIE1, but not IIC11, was recently demonstrated in liver of thiamin-deficient male rats (174). The mechanism by which this vitamin deficiency increases certain P450 enzymes remains to be clarified.

VITAMIN C The guinea pig, like humans and other primates, cannot synthesize ascorbic acid. Depletion of this vitamin impairs oxidative drug metabolism and reduces P450 and most associated enzyme activities in the guinea pig (66) and in a rat strain unable to synthesize ascorbic acid (68). Ascorbic acid requirements for optimal induction of P450 by exogenous chemicals such as polychlorinated biphenyls appear to be greater than the requirement for maintenance of induced levels of mixed function oxidase activities (68).

Evidence that vitamin C deficiency impairs drug metabolism in humans is inconclusive. Antipyrine half-lives were longer in patients with liver disease and low leukocyte ascorbate levels than in patients with higher ascorbate levels (21). Ascorbic acid supplementation of elderly patients (149) and diabetics (56) with low initial leukocyte or serum ascorbate levels shortened antipyrine half-lives. However, subclinical vitamin C deficiency of short duration in five male volunteers had no significant effect on antipyrine metabolism (65). In ten elderly subjects who underwent ascorbate depletion for four weeks, no significant change occurred in caffeine metabolism (155).

Large doses of vitamin C are reported to decrease monooxygenase activities in animals (172). In humans, large doses of this vitamin reduce sulfate conjugation of drugs such as salicylamide and acetaminophen by competing for available sulfate (70, 71). Large doses of vitamin C increased antipyrine clearance in one study (69), but not in another (169), and influenced warfarin disposition to a degree that was regarded as not clinically significant (51).

FAT-SOLUBLE VITAMINS Vitamin A deficiency modestly decreased hepatic P450 content and associated monooxygenase activities in some studies but not in others (19, 113). Protective effects of vitamin A against chemical carcinogens may, therefore, not involve regulation of enzymes that metabolize these compounds (19). A diet high in vitamin A content increases microsomal metabolism of aniline and 7-ethoxycoumarin (112, 172). Retinol and retinoic acid are substrates for P450 enzymes and can inhibit the metabolism of other substrates such as *N*-nitrosodimethylamine (172). Ethanol ingestion increases retinol dehydrogenase and enhances depletion of vitamin A (99). Ethanol also induces hepatic P450IIE1, leading to enhanced metabolism of a number of

drugs (101). Recent evidence indicates that retinol and retinoic acid are substrates for P450IIC8 and not P450IIE1 (100).

Vitamin E deficiency decreases microsomal metabolism of substrates such as ethylmorphine, codeine, and benzo(*a*)pyrene. These effects are not accompanied by significant decreases in P450 or NADPH-cytochrome P450 reductase (32, 172). The protective effects of α-tocopherol on monooxygenase activities may result from its antioxidant properties, which may prevent oxidative damage to membrane lipids. The effects of α-tocopherol deficiency relate to the nature of fatty acids in the diet (60).

Minerals, Trace Metals, Iron, and Heme

Iron deficiency, unlike most other mineral deficiencies, can increase P450 and associated enzyme activities in animals (22). Marked iron deficiency had no effect on antipyrine metabolism in one study of seven patients (123). However, in another study six patients with iron deficiency metabolized antipyrine more rapidly than did nondeficient subjects (97). Correction of iron deficiency in patients with hookworm infestation was reported to prolong antipyrine clearance (42).

Acute porphyrias are due to inherited deficiencies of enzymes in the heme biosynthetic pathway (7, 80). Clinical expression of these disorders is influenced by certain drugs, nutritional factors, and steroid hormones and their metabolites that increase liver heme and P450 synthesis and the production of heme pathway intermediates. Heme infused intravenously to such patients is taken up by the liver, where it represses δ-aminolevulinate synthase and the overproduction of heme pathway intermediates. Oxidative metabolism of drugs such as antipyrine may be reduced in patients with acute porphyrias (8) and is improved by heme infusions (64, 154). Heme infusions in animals with porphyria induced by chemicals that destroy P450 heme increase hepatic holo-cytochrome P450 and normalize drug metabolism rates (50).

A number of other deficiencies including zinc, copper, selenium, and magnesium may influence the mixed function oxidase system in laboratory animals (22). Studies in humans are lacking.

OTHER IMPLICATIONS

Malnutrition

Drug metabolism in malnourished adults and children, which has been studied most extensively in India and Africa, has been reviewed by others (89, 90). Changes in drug metabolism in malnourished states are complex; they may be due to such factors as altered rates of oxidation by hepatic P450 enzymes and altered binding to plasma proteins and distribution within the body. Malnutrition may also be associated with liver damage and other pathological

processes. Thus, it is difficult to determine the effects of specific nutrient deficiencies on drug metabolism in malnourished humans. Drug oxidation rates are often normal or increased in mild to moderate malnutrition but are generally impaired when edema or other indications of severe malnutrition are present (89). Antipyrine metabolism was not significantly altered in Norwegian women with anorexia nervosa (20). Undernourished patients with deficits in both protein and energy are more likely to have impaired antipyrine oxidation, and their impaired drug metabolism is more likely to be corrected by parenteral feeding than is drug metabolism in patients with energy deficits alone (156).

Variability in Drug Metabolism

The contribution of dietary variations to inter- and intra-individual variability in rates of hepatic drug metabolism by P450 enzymes is not known. Genetic factors are a major determinant of interindividual variation in drug oxidation rates in humans, whereas intraindividual variation is determined primarily by the environment. Even in normal subjects appreciable intraindividual variations in drug metabolism rates occur with time, as was shown by Alvares et al (4) for antipyrine, phenacetin, and phenylbutazone. Recent data indicate that intraindividual variability in disposition of antipyrine and acetaminophen can be reduced by feeding normal subjects a constant diet (14). A comparison of the effects of diet and cimetidine (a P450 inhibitor) on theophylline metabolism showed that the magnitude of a drug-nutrient interaction can be comparable in degree to that of a drug-drug interaction, and that such effects can be additive (13). As noted above, diet-induced changes in drug metabolism can develop and regress over periods of 10–14 days or less. Therefore, it seems likely that environmental factors, including diet, may account at least in part for intraindividual variability in drug metabolism rates.

Vegetarian diets are commonly consumed for cultural and religious reasons or for perceived health benefits. Low protein intakes probably explain lower antipyrine clearances in Asian lactovegetarians living in Britain as compared with Asian nonvegetarians (117). Protein intakes of Caucasian vegetarians and nonvegetarians in Britain are said not to differ, and the metabolism rates of antipyrine, acetaminophen, or phenacetin in subjects selected from these two populations were not significantly different (28).

Diet and Drug Metabolism in the Elderly

Environmental factors, including diet, are likely to contribute to altering drug metabolism in elderly subjects (6). Drug oxidation rates generally decline with age, although there is considerable variability in this response. Drug conjugations appear to be less subject to the influences of age than are drug oxidations. Changes in body composition and in drug distribution, protein

binding, and renal clearance also occur with aging. Cigarette smoking is an environmental factor that may partially explain age-related differences in oxidation rates of drugs such as antipyrine and propranolol (160, 161). Studies are needed to determine the importance of drug-nutrient interactions and associated variations in drug metabolism rates in the elderly.

Dietary Influences on the Metabolism of P450 Substrates Other Than Drugs

Nutrition-induced changes in the mixed function oxidase system will reduce the biological effects of some substances, increase the effects of others, and alter risks for diseases associated with such chemicals. This review has mentioned a number of toxins and carcinogens that are substrates for P450 enzymes in liver and other tissues, and whose adverse effects can be influenced by diet.

The metabolism of steroid hormones occurs primarily in the liver (11). Certain products of steroid hormone metabolism such as the products of Δ^4-5α- and 5β-steroid reductases and P450-mediated estrogen oxidations have substantial biological effects that are different from those of the parent hormones. An increase in the protein-to-carbohydrate ratio in the diet of normal subjects can increase estrogen 2-hydroxylation (12), decrease androgen 5α-reduction (78), alter the plasma concentrations of testosterone and cortisol in a reciprocal fashion, and produce parallel changes in the binding globulins for these steroids (15). These effects mimic those induced by phenobarbital in humans (79) and by a number of environmental chemicals in animals (78). Such diet-induced changes in hormone metabolism may have wide-ranging implications for the development of a number of hormone-related diseases.

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