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FOOD AND DRUG INTERACTIONS

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This review concerns those physiologic, biochemical, and pharmacologic interactions between food components, additives, chemicals, and therapeutic drugs. That the nutritional status of the person or animal will determine in large measure the degree of undesirable effects of drugs is well known and is not discussed here. The role of nutrition and nutritional status in drug metabolism as distinct from diet effects was the subject of other reviews. In recent years it has become clear that the impact of nutritional and environmental substances on the disposition of drugs is complex and difficult to predict. Several conferences have been devoted to this subject (1–4).

Depending on whether one considers alcohol a drug or a food, the result of administration of ethanol is a modification of the metabolic fate of other substances. Large acute or chronic doses of alcohol inhibit liver enzymes important in the metabolism of drugs. The enormous literature on alcohol-food interactions has not been included in this review.

In a similar vein the complex and controversial literature on food allergies as possibly related to modification of the fate of drugs and their toxicity has been excluded. The subject of food sensitivity and immune complexes, as related to absorption and utilization of therapeutic drugs, is just beginning to be studied by the newer techniques of immunology; thus comprehensive reviews must await the future findings.

Physicians customarily include consideration of the influence of food in the gastrointestinal tract on the absorption and utilization of therapeutic drugs given orally. Pharmacology texts review the issues of gut diffusions, lipid solubility, and absorption of drugs from the alimentary tract, and pharmacokinetic studies include consideration of absorption factors influencing plasma levels of drugs, especially where the plasma concentration

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must be kept within a narrow range. The presence of food in the stomach and the small intestine will prevent the inactivation of some drugs by the low gastric pH or the destruction by digestive enzymes. These are relatively elementary facts related to efficient drug therapy and wisely observed by the careful physician (5). On the other hand, metabolic changes and tissue interactions at target cell sites of drug actions are more arcane and frequently not recognized, indeed, are often not known.

Therapeutic efficacy and drug toxicity may be directly influenced by food-drug interactions. Relatively few investigators, however, pursue studies to develop the necessary knowledge required to understand these relationships. It is unfortunate that a food history is not a part of the information usually obtained by physicians treating patients. If this information were elicited from the patient, superior therapy could be provided in many cases.

Roe (6) has reviewed the issues of diet-drug interactions and pointed out that pharmacokinetics, toxicity, and nutritional physiology interact to yield rational therapeutics. Acute toxic reactions resulting from food-drug incompatibilities should be avoidable. A new note has been added by the developing knowledge of whether non-nutrient food additives may change the pharmacokinetics of therapeutic drugs. With increasing concern about carcinogens in the food supply and with newer sensitive analytical methodology, chemical biotransformation in man is now coming under scrutiny in terms of dietary factors influencing the action of drugs, environmental pollutants, and normal body constituents (7).

Enhancement of the rate and extent of absorption of some drugs is obtained by concurrent administration of food. Thus carbamazine, hydralazine, nitrofurantoin, propranol, and spirolactone have been shown to be more bioavailable when these drugs are taken with food as contrasted with rates and degree of bioavailability on an empty stomach (8–12). However, digoxin, critical for the cardiac patient, is decreased somewhat in rate but not extent of absorption when administered after a food meal (13).

EFFECT OF FOODS ON BIOCHEMICAL TRANSFORMATION OF DRUGS

Living cells have a remarkable capacity to chemically modify drug molecules. This biochemical transformation frequently achieved by the nonspecific enzymes present in the microsomes of liver cells is one of the chief oxidative pathways drug molecules undergo. These are usually hydroxylation reactions leading to detoxification of the drug. More polar metabolites are formed and hence are less capable of penetrating the lipid target cell barrier. The result is subsequent excretion of the less toxic metabolite.

However, not all enzymic reactions of drugs in liver cells produce less toxic metabolites—some are more toxic. Hepatic drug metabolizing enzymes activate some chemically stable drugs to potent alkylating, arylating, or acylating agents. These bind covalently to liver cell macromolecules and frequently cause necrosis (14, 15). Foods yield protective substances such as glutathione that are capable of conjugating with a toxic metabolite. However, when stores of these substances are exhausted the toxicity is increased.

The rates of toxication or detoxication of drugs and xenobiotics are now known to be influenced by age, sex, species, strain, disease, and diet. It appears that for man diet is most varied and therefore most complex as a variable in ascertaining its role in either enhancing toxicity or reducing untoward effects of therapeutic drugs or environmental chemicals.

Following the prolonged administration of numerous drugs or chemicals, hepatic microsomal enzymes may be stimulated and the process of induction takes place (16, 17). The implications of microsomal enzyme induction are just beginning to be appreciated by clinicians. Indeed, this phenomenon explains why repeated drug dosage may lead to decreased therapeutic effectiveness. The detoxification mechanisms of the liver become more efficient in metabolizing the drug and larger doses are required to elicit the desired pharmacologic effects. Microsomal enzymes can also be induced in such tissues as the intestine, lung, adrenals, and kidney, although less is known about these extrahepatic systems. In animals, the increased liver size, total protein content, and weight as a result of enzyme induction are the most prominent signs.

Chhabra & Fouts (18), Tredger et al (19), and James et al (20) have reported the rates of microsomal drug metabolizing enzymes to be from 15 to 50% lower for intestinal cells than hepatic cells for the rabbit when using a variety of chemicals as substrates. Other workers have found similar differences (21). The important point is that diet influences intestinal mixed-function oxidase activities (17). The effects of various diets on intestinal microsomal enzymes have been summarized (22). Apparently, in addition to foods, inhaled particulates into the intestine, environmental contaminants, and food additives are the major causes of intestinal mucosal enzyme changes. However, relatively few of the potentially thousands of these substances have been examined. In reviewing these reports it is noteworthy that these enzymes in liver and intestine require NADPH and O_2 for maximum activity and are inhibited by cytochrome *c*, SKF-525A, and CO (22). These authors note that in vivo studies are necessary to confirm these in vitro findings, and suggest that human intestinal enzymes especially should be evaluated. The finding that tissue samples may be stored under liquid N_2 may encourage more work with human biopsy material (23).

Dietary modification of pulmonary aryl hydrocarbon hydroxylase activity has been found but the reports on pulmonary enzymes are limited (24).

TOXICOLOGICAL SIGNIFICANCE OF ENZYME INDUCTION

Wattenberg, in a long series of experiments, showed that many plant foods serve as inducers of both liver and gastrointestinal hydroxylases (17, 24, 25). These effects will doubtless be added to many other as yet unidentified inducers. For animals, we now know that inducers present in wood shavings, animal bedding, and commercial diets have produced profound changes in the incidence of tumors and presumably other toxic effects in experimental studies. These experimental variables must be carefully evaluated before conclusions can be drawn from animal feeding studies. The term "adapted" animal, meaning one that has undergone metabolic or other physiologic changes in response to exposure to a test substance or dietary ingredient, is becoming common in toxicology. These metabolic changes follow low or moderate repeated doses of a substance and are not the response of the organism to extreme stress levels of the compound.

Enhanced activity of some microsomal enzymes or induction of increased aryl hydrocarbon hydroxylase activity by food additives or naturally-occuring flavones now has been shown to inhibit the action of chemical carcinogens in animals. These inhibitors include both natural food ingredients or synthetic compounds introduced into the environment (25). Wattenberg has reviewed the evidence supporting the possibility that inhibitors play a role in the response of humans to carcinogens (25). He includes three types of evidence: (*a*) chemical diversity of the inhibitors and their occurrence in the environment; (*b*) responsiveness of the detoxification systems; and (*c*) epidemiological studies that suggest individuals consuming large quantities of vegetables, a major source of naturally-occurring inhibitors, are at lower risk from gastrointestinal cancers. Both foods and therapeutic drugs can therefore act as inhibitors. Wattenberg suggests that some of these inhibitors can act by preventing carcinogenic species from reaching or reacting with critical cellular targets and thus exert a barrier function (25).

The inhibitory effects of the phenolic antioxidants, butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT), versus a number of chemical carcinogens have been studied. These comprehensive findings of many investigators were summarized by Wattenberg (25). According to FDA reports 8.86 million pounds of BHT were used in foods to prevent rancidity and other oxidation reactions in 1976 in the United States (26, 27). The health effects of BHA and BHT remain controversial because animal studies have developed a wide variety of adverse effects: liver lesions (27), necrosis of pulmonary cells (28, 29), kidney function (30), and other toxic

effects. Many adverse effects follow the feeding or administration of high doses. Not all the undesirable effects, however, follow doses exceeding reasonable human levels of consumption.

The variety of carcinogens and mutagens inhibited by BHA is remarkable. Most studies suggest BHA causes an enhanced detoxification of a carcinogen. For example, if mice are fed BHA for two weeks and the mixed function oxidase activity of their liver microsomes is measured in vitro with cofactors, DNA and added benzo(*a*)pyrene (BP), the reactive metabolites from the BP are reduced as compared with control mice (31). High pressure liquid chromatography of the metabolites of BP formed upon incubating this carcinogen with microsomes from mice fed BHA as compared with controls demonstrates this change. There is a decrease in epoxidation of BP, an activation process, and an increased formation of the detoxication metabolite 3-hydroxybenzo(*a*)pyrene (32).

Increases in the activities of several conjugating enzymes in animals fed BHA have also been reported, including glutathione-s-transferase (33) and UDP-glucuronyl transferase (34). The diversity of enzyme inductions produced by BHA suggests a similarity to other inducers chemically different, for example, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), polycyclic aromatic hydrocarbons, and *beta*-naphthoflavone [Wattenberg (25)]. The mechanism has been studied by Poland & Kende (35). However, the drug phenobarbital, the anticonvulsive diphenylhydantoin, the antiarthritic phenylbutazone, and the corticosteroid-like pregnenolone-16-carbonitrile all induce hepatic microsomal enzymes by a different route (35).

The significance of these findings lies in the apparent protective effects of these and related substances in inducing increased microsomal monooxygenase activity. Wattenberg stresses the wide range of compounds capable of inducing this protective effect against known potent carcinogens and points out that the substances are present in plants consumed by man as food (25). Thus, the flavones of natural origin, e.g. 5,6-benzoflavone, rutin from the buckwheat family, and similar compounds caused almost total inhibition of pulmonary adenomas in mice when fed these substances and subsequently challenged with BP (36). In a similar finding natural indoles in the edible vegetables Brussels sprouts, cabbage, cauliflower, and broccoli were inhibitory to benzo(*a*)pyrene-induced neoplasia in the forestomach of rodents. Addition of certain of these indoles to the diet also inhibited pulmonary adenoma and mammary tumor formation (37). The mechanism(s) of action of these indoles is not known at present.

These findings suggest numerous possibilities. Wattenberg asks several questions (25). Do these substances play a role in reducing the impact of chemical carcinogens in man? Is there some balance between carcinogens and anticarcinogenic agents that determines whether an individual will develop a neoplasm? That many of the inhibitors are in natural products

consumed as food by man, and some such as BHA are added to foods, suggests a role in the etiology of cancers. Epidemiologic studies of groups of people who follow a vegetarian diet are only partially supportive and their reduced incidence of cancer may simply reflect a different life style (38–41). The intriguing possibility remains that BHT and BHA may act synergistically with natural inducers present in foods. In addition, pesticide residues such as DDT present in low levels in man's foods, while below the level that causes enzyme induction in rats, may also contribute to the total effect.

The influence of diet and socially used drugs on drug oxidation has been studied in vegetarians and non-vegetarians (41). Major differences in diet, cigarette smoking, and use of the steroid oral contraceptives were shown to have significant effects on antipyrine oxidation. If one can generalize from antipyrine to other drugs, these environmental factors could play important roles in drug therapy and prevention of toxicity. Obviously, it is difficult to control for so many different factors in any population group, but the findings emphasize the variables that require study for food-drug interactions.

METABOLITE INDUCTION ENHANCING TOXICITY

Liver drug toxicity may be increased by enzyme inducers and a number of examples are known. Thus, carbon tetrachloride (42), tricholorethylene (43), toluene (44), hycanthone (45), acetaminophen (46), methotrexate (47), and isoniazid (46), among other drugs and chemicals, have been studied in this respect. Typical of these effects, isoniazid is first acetylated and then converted to hydrazine and changed to a potent acylating agent by metabolizing enzymes (46). Liver necrosis follows especially after long-term therapy. Rapid acetylators, e.g. Orientals, are at particular risk. Sherlock (48) noted that the former use of para-amino salicylic acid, an enzyme retarder, in tuberculosis therapy, along with isoniazid, may have accounted for the relative safety of this drug combination. It is conceivable that foods or food ingredients may exert similar enzyme inhibitory actions and thus account for individual differences in the degree of toxicity experienced by patients on isoniazid therapy.

The significance of polycyclic aromatic hydrocarbons (PCH) formed in charcoal-broiled beef has been studied with respect to the ability of these substances to alter the fate of drugs in the body. The bioavailability of phenacetin in human subjects apparently is reduced (49) and the plasma clearance of caffeine is altered (50). Benzanthracene, dibenzanthracene, chrysene, and pyrene, potent inducers of the cytochrome P-448 system in liver microsomes, caused a marked increase in the plasma clearance of caffeine (50). Phenanthracene and anthracene did not change the plasma

clearance of caffeine in the rat. These findings suggest that the metabolism of many drugs may be altered in man exposed to these environmental substances or foods containing PCH.

Long-term anticonvulsive therapy with diphenylhydantoin or phenobarbital is recognized to cause osteomalacia by influencing calcium metabolism (51, 52). Alteration in the metabolism of vitamin D, presumably secondary to induction of hepatic microsomal enzymes, leads to the calcium and bone abnormalities (53). Patients on anticonvulsive therapy with phenytoin exhibit a decrease in serum 25-hydroxyvitamin D (54). The absorption of vitamin D is normal in rats receiving large doses of phenobarbital or diphenylhydantoin, although patients have been found to have a depressed circulating level of 25-hydroxy-vitamin D (55). These studies have been reviewed by Haussler (56). Dietary changes with adequate amounts of vitamin precursors or microsomal enzyme stimulators might prevent these effects of long-term drug therapy.

The ingestion of foods containing tyramine, such as cheese, and the hypertensive crisis produced in patients taking the antidepressive drug tranylcypromine is a classic example of food-drug toxicity. Tyramine-containing foods apparently stimulate the release of norepinephrine, which likely results in the sharp elevation in blood pressure. The norepinephrine release is also accelerated by the drug itself, a monoamine oxidase inhibitor (57). As a result of this well-publicized interaction, patients receiving the monoamine oxidase inhibitors are now cautioned to avoid the foods that have been recognized to contain high amounts of tyramine. The list of foods that contain tyramine or related amines capable of causing these reactions is long and it is difficult for patients on drug therapy with monoamine oxidase inhibitors to follow these dietary restrictions. This unfortunate food-drug toxicity reaction has limited the therapeutic usefulness of these drugs.

HIGH FIBER DIETS

The recent enthusiasm for high fiber foods may carry a special challenge in considering food-drug toxicities. Vegetable fiber diets have been shown to reduce toxicity to some drugs for animals (58, 59). Presumably, phytates hold inorganic ions in a clathrate matrix that prevents absorption of the metal from the gut; other substances, e.g. bile acids, may also be bound (60). The bioavailability of iron as influenced by phytates in cereal foods via the formation of insoluble iron phytates is an example of a well known but little understood problem in gastrointestinal physiology and nutrition (61). Magnesium, zinc, and tin are covalently bound by fiber and it is possible to produce zinc deficiency in animals by feeding high soybean-protein diets (62). Potentially toxic substances in foods such as aflatoxins may become

less toxic in the presence of fiber in the gut. In experimental animals there is evidence that vegetable fiber is protective against estrogen-induced ovarian and uterine tumors (58). Natural ingredient diets protect rats against 2-acetyl-aminofluorene or 7,10-dimethylbenzanthracene induction of mammary tumors (63–65). There is an obvious need to evaluate these potentially useful or harmful effects in man as we come to a better understanding of the effects of changing diets on drug toxicity and therapeutic usefulness

BACTERIAL METABOLISM

A large number of exogenous and endogenous substances are metabolized and changed by the microflora of the intestines, including food ingredients and drugs. The degree and type of degradation depends on the flora and whether the substance consumed is a stimulator or inhibitor or bacterial growth. Obviously, microbial metabolites have the potential for toxic or beneficial effects. The major types of biochemical reactions involved in microbial drug transformations have been reviewed by Prins (66). The significance of these changes has been stressed for animals. Unfortunately, only indirect evidence can be assumed for man. The major microbial gut reactions are hydrolysis, reduction, and degradation to a smaller chemical species. The nutritional and toxic interactions with several classes of chemicals have been studied and the research needs in this field summarized (66).

SUMMARY

A significant contribution could be made to patient care if nutritional biochemists, basic and clinical toxicologists, and pharmacologists in the various fields were to mount the studies needed to understand the nature of food-drug interactions. If only a small fraction of the 120 billion dollars per year spent for food or the 10 billion dollars expended for drugs were allocated for research in this area, advances might be made for the health of the nation.

Changes in man's diet produce marked effects on drug metabolism. We know that changing a customary diet to one high in protein and low in carbohydrate increases the rates of metabolism of antipyrine and theophylline, and shifting to an isocaloric diet of low protein-high carbohydrate slows the rates of metabolism of these drugs. Presumably, high-protein-low carbohydrate diets in man resemble the animal studies with high protein diets that show enhanced hepatic drug metabolism (2). However, numerous studies emphasize the considerable individual variability to changes in human diets; some people have dramatic changes, whereas others exhibit little

or no response. Similar individuality has been found in the response to enzyme induction by smoking (67).

Numerous foods and food ingredients affect drug metabolism in human beings and apparently follow the same patterns as found in experimental animal studies with changes in the levels of cytochrome P-450 dependent monooxygenases in the liver and intestine. These changes presumably exert some protective action against environmental carcinogens, cocarcinogens, or promoters.

Dietary modifications are brought about by use of weight-reducing diets, vegetarian diets, hospitalization, or post-operative regimens. These diets are often continued for long periods of time and it is likely they result in changes in the metabolism by the body of subsequently administered drugs or exposure to environmental chemicals. Methods are needed to measure inter-individual and inter-group differences in metabolism of foreign compounds in order to accurately assess dietary influences on drug metabolism and vice versa. Epidemiologic studies of rigorously selected human populations, coupled with the newer sensitive chemical analytical methods, will provide the necessary data base for these investigations.

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