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Interactions between nutritional factors and drug biotransformations in man

(carbohydrate/protein/antipyrine/theophylline/diet)

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ABSTRACT **This study was undertaken to examine the influence of nutritional factors on the activity of the mixed function oxidase system in man, which is cytochrome *P*-450 dependent. Three normal volunteers were fed a low carbohydrate–high protein diet for 2 weeks, followed by a high carbohydrate–low protein diet for the following 2 weeks. At the end of each test diet period, the plasma elimination rates of antipyrine and theophylline were determined. The mean plasma half-life for antipyrine was 17.5 hr on the high carbohydrate–low protein diet and 9.2 hr on the low carbohydrate–high protein diet. The mean plasma half-life for theophylline was 8.9 hr on the high carbohydrate–low protein diet and 5.9 hr on the low carbohydrate–high protein diet. These data demonstrate marked influences of dietary carbohydrate and/or protein ingestion on oxidative biotransformation of drugs in man.**

The effects of changes in dietary macronutrient composition on the hepatic microsomal enzymes that metabolize drugs, other foreign chemicals, and endogenous compounds, such as steroid hormones, have been studied extensively in animals (1). These studies show that dietary macronutrient composition, as well as the presence of contaminants and food additives, can influence the activities of these enzymes. Although dietary composition has been shown to be an important environmental determinant in the response of the experimental animal to pharmacological agents, such studies are lacking in man. A significant proportion of normal subjects manipulate their diets in weight-reducing regimens. Similarly, dietary treatments in clinical conditions, including obesity, atherosclerosis, and diabetes, are considered to play a significant role in the management of such disease problems. It is the purpose of these studies to show that nutritional–pharmacological interactions can occur in normal individuals when macronutrient composition of the diet is altered.

In animals, in relation to hepatic microsomal enzyme activities, the dietary constituent most studied is protein. A reduction in dietary protein intake has been shown to decrease microsomal oxidations of various substrates, such as pentobarbital, aminopyrine, and zoxazolamine (2), and to increase the toxicity of foreign compounds, such as drugs (2) and pesticides (3, 4). The decreases in microsomal oxidations are accompanied by decreases in hepatic content of the hemeprotein cytochrome *P*-450, the terminal oxidase of the hepatic mixed function oxidase system. In contrast, the metabolism of the drugs indicated is increased in rats fed a high protein diet (2). A high carbohydrate intake has been shown to increase barbiturate-induced sleeping time in mice (5), to cause cessation of lipid peroxidase activity, and to cause a considerable decrease in liver mixed function oxidase activity in rats (6). A specific lipid role in the mixed function oxidase system was first demonstrated by Strobel *et al.* (7), who established the requirement for phosphatidylcholine in a reconstituted mixed function oxidase system. From a nutritional point of view, lipids are apparently required in the diet only in the case of essential fatty acids (8, 9).

Studies in man of the dependence of hepatic mixed function oxidase system on nutritional status are lacking. It therefore seemed of interest to explore the nutritional effects on drug metabolism rates in normal individuals using two prototype drugs, antipyrine and theophylline; these drugs are substrates for the microsomal oxidative enzyme systems that are cytochrome *P*-450 dependent. Half-life of plasma antipyrine has been used as an index of the mixed function oxidase system, since antipyrine is completely absorbed when given orally, is completely metabolized by the liver (10), and its metabolism is inducible by the barbiturate class of inducing substances (11). Theophylline is rapidly absorbed when administered orally in an aqueous-ethanol solution (12), and is metabolized primarily by the liver microsomal system (13). Unlike antipyrine, however, theophylline metabolism has been shown to be increased *in vitro* by pretreatment of rats with the polycyclic hydrocarbon 3-methylcholanthrene (13), and in man its kinetic disposition is accelerated in chronic smokers (14); however, its disposition is not significantly altered by phenobarbital administration in man (15). These observations indicate that theophylline may be a prototype of a drug metabolized by the cytochrome *P*-448 system, a catalytically distinct hemeprotein induced primarily by polycyclic hydrocarbons and polychlorinated biphenyls (16). The results of this study demonstrate marked influences of dietary carbohydrate and/or protein content on the oxidative biotransformation of drugs in man.

METHODS

Three normal men between 23 and 31 years old and weighing 70–76 kg were selected for the study, which lasted for 8 weeks. Smokers and heavy drinkers of alcohol were excluded. No alcohol or drugs other than the test compounds were permitted during the study, and for 2 weeks prior to its start. During the first 2 weeks of the study, subjects were on their customary home diet. During the second 2 weeks they were maintained on a low carbohydrate–high protein diet. The composition of this diet was protein, 44%, carbohydrate, 35%, and fat, 21%. The high protein content of this diet was achieved by the inclusion primarily of protein-rich foods, such as meats, fish, egg whites, and cottage cheese, as well as a liquid dietary supplement, Sustacal, purchased from Mead Johnson Laboratories. During the third 2-week period, the same subjects were maintained on a high carbohydrate–low protein diet. The composition of this diet was protein, 10%, carbohydrate, 70%, and fat, 20%. For comparative purposes, the macronutrient composition of the average American diet is protein, 15%, carbohydrate, 50%, and fat, 35% (17). The caloric intake during each of the two test diets was 2400–2500 calories per day. Thus, the fat and total caloric intake remained unchanged during the two test diet periods.

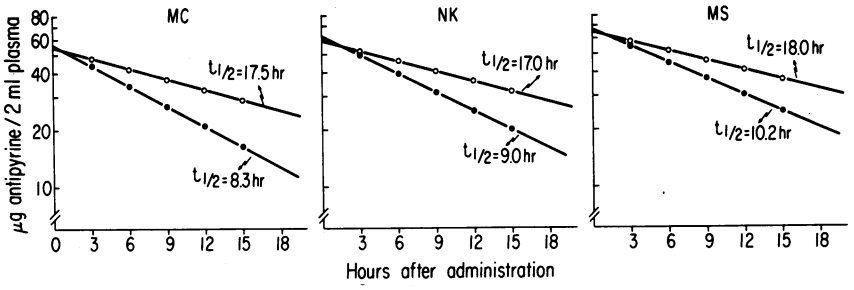

FIG. 1. Decline of antipyrine in the plasma of three normal subjects after low carbohydrate–high protein (●) and high carbohydrate–low protein (○) test diets. The plasma half-life ($t_{1/2}$) was determined from the logarithm of the antipyrine concentration in plasma at various intervals after a single oral dose of 18 mg/kg.

In the final 2 weeks of the study, the subjects returned to their normal home diets. During the two test diet periods, breakfast, lunch, dinner, and evening snacks were prepared at the Rockefeller University Hospital Diet Kitchen. No other food or beverage intake was permitted.

During each of the diet studies, including home diet periods, each subject received antipyrine on day 10 and theophylline on day 14. No coffee, tea, cola drinks, or chocolate were ingested for 24 hr prior to and during the day that theophylline was administered, since these foods have been shown to interfere with the theophylline assay. Antipyrine was dissolved in syrup and administered orally at a dosage of 18 mg/kg; blood was drawn at 3, 6, 9, 12, and 15 hr after its administration. Plasma antipyrine levels were determined by the method of Brodie *et al.* (18). Elixophyllin®, an alcohol–aqueous solution of theophylline containing 80 mg of theophylline per 15 ml, was purchased from Cooper Laboratories. Theophylline, at a dosage of 5 mg/kg, was administered orally, and blood was drawn at 2, 4, 6, 8, and 10 hr after administration. Theophylline concentrations in plasma were determined by the spectrophotometric method of Schack and Waxler (19), as modified by Koysooko *et al.* (20). All samples were analyzed in duplicate, and the half-life of the drug in plasma was determined from the linear portion of the plot of the plasma values on semi-logarithmic paper.

RESULTS

On day 10 of each test diet period, antipyrine was administered to each subject, blood was drawn at 3-hr intervals, and the concentrations of the drug in plasma were plotted as shown in Fig. 1. The plots illustrate the rate of drug elimination from plasma for each subject when maintained on a low carbohydrate–high protein diet or a high carbohydrate–low protein diet. Each of the subjects showed consistently lower plasma concentrations of the drug on the low carbohydrate–high protein diet as compared with concentrations on the high carbohydrate–low protein diet. The mean plasma half-life, for all three subjects, was 17.5 hr on the high carbohydrate–low protein diet and 9.2 hr on the low carbohydrate–high protein diet. Similar results were obtained when the same subjects received theophylline, at a dosage of 5 mg/kg, on day 14 of the test diet period (Fig. 2). The plasma concentrations of the drug were lower on the low carbohydrate–high protein diet than on the high carbohydrate–low protein diet. The mean plasma half-life for theophylline on the high carbohydrate–low protein diet, 8.9 hr, was significantly lower than the mean half-life of 5.9 hr obtained on the low carbohydrate–high protein diet.

A comparison of the drug half-lives obtained on the two test diets with those obtained on the normal diet of the subjects prior to, and 2 weeks after, the test diet study is shown in Table 1. During the 8 weeks of this study, the greatest changes in the plasma elimination rates of the two drugs occurred when each subject's diet changed from the normal home diet to the low carbohydrate–high protein diet and from low carbohydrate–high protein diet to the high carbohydrate–low protein diet. The mean half-lives on the two home diets for antipyrine and for theophylline were similar. The decreases in antipyrine and theophylline half-lives from the high carbohydrate–low protein diet to the second home diet values, home diet-2, were minimal. These decreases were small, probably because each subject's home diet on review appeared to be relatively high in carbohydrate when compared to his protein intake. Analysis of the home diet was possible because a log of the quality and quantity of his food intake during the home diet-2 period was required of each subject. No subject gained or lost more than 1 kg body weight during this study.

DISCUSSION

The hepatic microsomal mixed function oxidase system plays a major role in the biotransformation of various drugs, foreign chemicals, and endogenous substrates, including fatty acids and steroid hormones. This enzyme system can be stimulated or

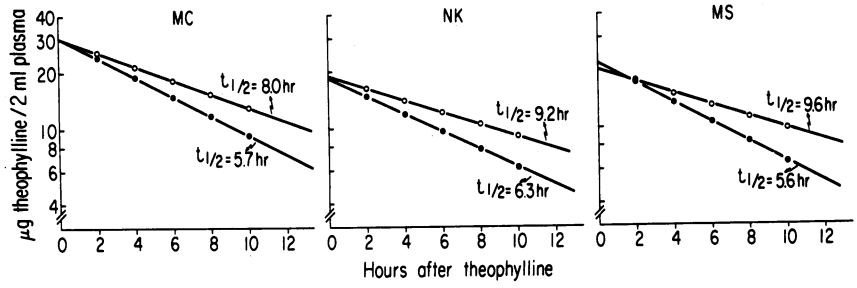

FIG. 2. Decline of theophylline in the plasma of three normal subjects after low carbohydrate–high protein (●) and high carbohydrate–low protein (○) test diets. The plasma half-life ($t_{1/2}$) was determined from the logarithm of the theophylline concentration in plasma at various intervals after a single oral dose of theophylline, 5 mg/kg, administered as Elixophylline®.

Table 1. Antipyrine and theophylline half-lives in subjects maintained on various diets

Subject	Home diet-1 (days 1–14)	Low CHO–high PRO (days 15–28)	High CHO–low PRO (days 29–42)	Home diet-2 (days 43–56)
		Antipyrine, half-life in hr		
MC	12.5	8.3	17.5	13.0
MS	15.0	10.2	18.0	15.8
NK	17.4	9.0	17.0	14.5
		Theophylline, half-life in hr		
MC	8.0	5.7	8.0	6.2
MS	6.8	5.6	9.6	6.5
NK	13.0	6.3	9.2	9.2

Each subject was maintained on each test diet for 14 days. Antipyrine half-lives were determined on day 10 and theophylline half-lives were determined on day 14 of each test diet period. Drug studies were also carried out immediately prior to the start of the test diet study (home diet-1) as well as on the 10th and 14th days (home diet-2) after the test diets. CHO, carbohydrate; PRO, protein.

inhibited by drugs, hormones, and a variety of environmental agents (21). The interaction of environmental chemicals with this system has been extensively investigated, both in man and experimental animals. Studies have also been carried out using prototype drugs, which have demonstrated distinct genetic determinants in the regulation of this microsomal enzyme system in individual subjects (22). The interaction of nutritional status with the hepatic mixed function oxidase system has been well studied in animals. The variables that have been studied include dietary protein, carbohydrate, fat, and starvation, as well as micronutrients, including ascorbic acid, riboflavin, and iron. With the exception of starvation, these nutritional–pharmacologic interactions have not been investigated in man. Recent studies by Reidenberg and Vesell (23) revealed no consistent changes in the metabolic clearance rates of tolbutamide or antipyrine in obese volunteers after at least 7 days of fasting. In animals, however, starvation causes increases or decreases in various drug-metabolizing enzymic activities (24).

The present studies demonstrate that changes in carbohydrate or protein composition of diets can have pronounced effects on the plasma elimination rates of drugs in man. In three normal healthy volunteers, a change of the subjects' food intake from a normal home diet to a low carbohydrate–high protein diet resulted in a mean decrease of plasma half-life for antipyrine from 15.0 hr to 9.2 hr, and a mean decrease in theophylline plasma half-life from 9.3 hr to 5.9 hr. Our data also showed a significant increase in the half-lives for the two drugs, when the subjects diets were changed from a low carbohydrate–high protein diet to a high carbohydrate–low protein diet. With this dietary alteration, the mean antipyrine half-life increased from 9.2 hr to 17.5 hr, and the mean theophylline plasma half-life increased from 5.9 hr to 8.9 hr. Although no effort was made to regulate the caloric intake in the home diets, the differences in drug elimination rates cannot be ascribed to differences in caloric intake, since the caloric intake in the two test diets, namely, the high protein–low carbohydrate and low protein–high carbohydrate diets, was identical. Similarly, the fat intake was maintained at a constant level during the two test periods. From the present data, it is not possible to ascribe the pronounced effects observed on drug metabolism as being due to changes either in carbohydrate content or in protein content alone, since in formulating diets that were made up of natural foods, changes in one macronutrient invariably resulted in changing the relative amount of the other macronutrient in the total diet.

Our results on the nutritional–pharmacological interactions in man are similar to those previously reported with experimental animals in which a high protein diet increased hepatic microsomal enzyme activity and decreased the pharmacological action of drugs (2), whereas a high carbohydrate diet causes a decrease in microsomal mixed function oxidase activities (5, 6). The mechanism of the changes in microsomal enzyme activities due to dietary factors is at present unclear. Animal studies have shown that the feeding of high protein diets results in augmentation of liver weight, which is accompanied by increases in DNA synthesis and mitotic activity (25, 26). Various studies have also shown that feeding a variety of carbohydrates elicits a "glucose effect," which results in decreased activities of many cytoplasmic and mitochondrial enzymes (27, 28), a depression in mRNA synthesis (29), a considerable increase in the concentration of cyclic 3′:5′-GMP, the antagonist of cyclic 3′:5′-AMP (29), and a suppression of chemical inducibility of δ-aminolevulinate synthetase, the mitochondrial enzyme that is rate-limiting for heme synthesis (30, 31).

The nutritional–pharmacological interactions observed in these studies in man have considerable importance in relation to the biological effects of drugs ingested in individuals suffering from protein malnutrition, in debilitated chronically ill patients, in post-operative patients receiving glucose, and especially among that large segment of the normal population among whom dietary manipulations, for example, a decrease in carbohydrate intake, are carried out in weight-reducing regimens. Studies on drug metabolism in normal and diseased states have been extensively carried out in the recent past, and many of the variations observed in rates of drug metabolism have been ascribed to genetic determinants as well as exposure to unidentified environmental factors. It is probable, on the basis of the present studies, that some of the variations observed within population groups may have been due to the dietary habits of the subjects studied or the dietary regimens prescribed in certain diseased states.

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