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Methionine, Cysteine, Cystine, and Taurine Interrelationships in Human Plasma[1,2]

WALTER D. BLOCK, PH.D., MARA E. MARKOVS, B.S., AND BETTY F. STEELE, PH.D.

THE ONLY EXOGENOUS sulfur-containing amino acid necessary for the maintenance of nitrogen equilibrium in adult man is methionine (1). The amino acid may be utilized directly by the body, or undergo a series of metabolic transulfuration reactions involving homocysteine, cystathionine, cysteine, cystine, and taurine.

In the present investigation, the response to test loads of free L-methionine, cysteine, cystine, and taurine by healthy, human adults was studied. The amount and rate of appearance of the administered compound in the plasma and its effects on the presence of the other amino acids were observed. Test loads of leucine served as a control.

MATERIALS AND METHODS

One male and two female healthy adults, ranging in age from 22 to 30 years, served as subjects; their weights remained constant throughout the study. During the investigation, they lived in the Clinical Research Center of the University of Michigan Medical Center.

The subjects were fed a constant diet that contained 35 g of protein daily; 32.5 g from milk and the rest from a special low protein, yeast-leavened bread (2), and lettuce. Foods low in protein content, such as butter, canned fruit, and jelly were included to ensure an adequate calorie intake. The mineral mixture of Leverton et al. (3),[3] 3.6 g, was given daily, along with a multivitamin supplement.[4]

The subjects were allowed a 3-day period to adjust to the diet before the test amino acid was given. A period of at least 3 days, during which only the constant diet was fed, intervened between each of the tests with the different amino acids. On the day of the test, breakfast was withheld, and blood was withdrawn from the cubital vein of the subject. Five grams of free L-methionine, cysteine (as the monohydrochloride), cystine (as the dihydrochloride), taurine, or leucine dissolved in 100 ml of water containing 16 g of a commercial beverage,[5] were given orally. Blood was withdrawn at 1-, 2-, and 4-hr intervals.

The fresh blood from each subject for each hourly period of withdrawal was treated with iodoacetic acid, $NaHCO_3$, and disodium ethylenediaminetetraacetate after the method of Brigham et al. (4), to convert the unstable cysteine to the stable *S*-carboxymethyl derivative. The plasma was separated by centrifugation and prepared for analysis of amino acids and other ninhydrin-reacting substances by the method of Stein and Moore (5), except that the step wherein cysteine is oxidized to cystine was omitted. The extracts were stored at −20 C until analyzed by the method of Spackman et al. (6), modified to use the accelerated system.

RESULTS

The concentrations of free methionine, cystathionine, cysteine, cystine, taurine,

[1] From the Department of Dermatology, Medical School, and Department of Health Development, School of Public Health, University of Michigan, Ann Arbor, Michigan.

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[3] Prepared by Nutritional Biochemicals Corp., Cleveland, Ohio.

[4] Decavitamins, Roerig Division, Chas. Pfizer and Co., N.Y.

[5] Tang, General Foods Corp., White Plains, N.Y.

TABLE I

Concentrations of certain amino acids in human plasma during methionine, cysteine, or cystine-tolerance tests, mg/100 ml

Amino acid	Methionine[a]				Cysteine[a]				Cystine[a]			
	0 hr	1 hr	2 hr	4 hr	0 hr	1 hr	2 hr	4 hr	0 hr	1 hr	2 hr	4 hr
Methionine	0.20 ± 0.06[b]	6.51 ± 1.02	6.18 ± 3.18	4.29 ± 2.32	0.17 ± 0.05	0.16 ± 0.07	0.21 ± 0.18	0.18 ± 0.03	0.24[c]	0.18	0.22	0.22
Cystathionine	>0.00	>0.00	0.25 ± 0.08	0.13 ± 0.03	>0.00	0.05 ± 0.05	0.08[c]	0.03 ± 0.01	0.04	0.03	0.07	0.11
Cysteine	0.15 ± 0.16	1.60 ± 0.97	1.49 ± 0.56	1.33 ± 0.56	0.28 ± 0.08	1.85 ± 0.22	1.96 ± 0.64	1.52 ± 0.59	0.27	0.98	1.47	1.45
Cystine	1.12 ± 0.19	1.26 ± 0.44	1.22 ± 0.51	1.12 ± 0.28	0.89 ± 0.13	2.22 ± 0.20	2.38 ± 0.32	2.16 ± 0.23	1.04	1.77	2.18	2.29
Taurine	1.08 ± 0.19	1.26 ± 0.27	1.42 ± 0.05	1.18 ± 0.30	1.19 ± 0.28	1.44 ± 0.09	1.30 ± 0.23	1.39 ± 0.20	1.40	1.32	1.14	1.20
Methionine sulfoxides	0.53 ± 0.18	0.96 ± 0.42	1.14 ± 0.36	1.17 ± 0.71	0.32 ± 0.01	0.38 ± 0.02	0.32[c]	0.30 ± 0.04	0.29	0.35	0.36	nc[d]
Threonine	1.38 ± 0.39	2.33 ± 1.60	1.82 ± 0.52	1.60 ± 0.38	1.34 ± 0.30	1.92 ± 0.50	1.91 ± 0.60	1.73 ± 0.47	1.38	1.62	1.79	1.74

[a] After the fasting blood was withdrawn, 5 g of free L-methionine, free L-cysteine (as the monohydrochloride) or free L-cystine (as the dihydrochloride) dissolved in 100 ml of a commercial beverage (Tang, General Foods) were given to each subject. [b] Mean ± SD for three subjects. [c] Average value for two subjects. [d] Not calculated for technical reasons.

TABLE II

Concentrations of certain amino acids in human plasma during taurine- and leucine-tolerance tests, mg/100 ml

Amino acid	Taurine[a]				Leucine[a]			
	0 hr	1 hr	2 hr	4 hr	0 hr	1 hr	2 hr	4 hr
Methionine	0.15 ± 0.02[b]	0.14 ± 0.10	0.19 ± 0.06	0.17 ± 0.02	0.23[c]	0.16	0.16	0.14
Cystathionine	0.05 ± 0.00	>0.00	0.10[c]	>0.00	0.08	0.02	0.11	0.10
Cysteine	0.17 ± 0.04	0.28 ± 0.18	0.33[c]	0.20[c]	0.36	0.23	nc[d]	nc[d]
Cystine	1.12 ± 0.39	0.98 ± 0.22	0.92 ± 0.14	0.89 ± 0.17	1.04	0.93	0.93	0.86
Taurine	1.37 ± 0.23	19.54 ± 7.11	14.78 ± 8.03	6.55 ± 3.35	1.66	1.36	1.36	1.21
Methionine sulfoxides	0.42 ± 0.17	0.35 ± 0.02	0.29 ± 0.04	0.38 ± 0.12	0.26	0.28	0.36	0.34
Threonine	1.56 ± 0.21	1.63 ± 0.20	1.49 ± 0.20	1.43 ± 0.15	1.23	1.08	1.00	1.02

[a] After the fasting blood was withdrawn, 5 g of free taurine or free L-leucine dissolved in 100 ml of a commercial beverage (Tang, General Foods) were given to each subject. [b] Mean ± SD for three subjects. [c] Average value for two subjects. [d] Not calculated for technical reasons.

methionine sulfoxides, and threonine in plasma during the methionine-, cysteine-, and cystine-tolerance tests, and during the taurine and leucine tests are given in Tables I and II, respectively.

The salient results from the tolerance tests appeared to be: *1*) the concomitant increase in concentration between methionine and cysteine in the plasma during the methionine test, while cystine concentration remained essentially the same; *2*) the increase in plasma levels of cysteine or cystine regardless of which of these two amino acids was ingested; *3*) the rapid and sustained increase in plasma taurine concentration when taurine was given; and *4*) the lack of effect of leucine ingestion on any of the other free S-containing amino acids and compounds determined in plasma.

Threonine contents of plasma were elevated over the fasting level during the 4 hr of the methionine-, cysteine-, and cystine-tolerance tests. No increase occurred during the taurine and leucine tests.

The other free amino acids and ninhydrin-reacting substances determined (asparagine plus glutamine, glutamic acid, citrulline, glycine, valine, isoleucine, leucine, tyrosine, phenylalanine, lysine, serine, histidine, and arginine) in the plasma occasionally showed a transitory increase, but in general they either were decreased in amount below that of the fasting level or were not affected.

COMMENTS

The results of the present investigation appear to indicate that one of the indices for studying the interrelationships among some of the metabolites of methionine in intact healthy human adults may be the metabolites' levels in plasma derived from blood withdrawn at selected intervals after test doses of methionine, cysteine, cystine, and taurine have been administered. In general, the metabolic pathway outlined by Meister (7).

$$\text{Met} \rightarrow \text{Cystathionine} \leftrightarrow \text{Cyst} \leftrightarrow \text{Cys}$$
$$\text{Ser} \quad \downarrow$$
$$\text{Taurine}$$

appeared operative under the conditions of this study.

The relationship among free methionine, cysteine, and cystine in the plasma was particularly intriguing. When methionine was ingested, cysteine values, although lower in absolute amount, tended to follow the same

general trend as those of methionine throughout the tolerance period, while the amounts of free cystine remained relatively constant. In contrast, when cystine was the test amino acid, a concomitant increase in free cysteine in the plasma occurred; when cysteine was ingested there was a concomitant increase in free cystine.

The reason for this difference in relationship in the plasma among amino acids that supposedly arise from transulfuration of the same amino acid, methionine, is not known, and one may only speculate as to the cause.

That the differences probably are due to excess excretion of one or more of these S-containing amino acids would seem unlikely because 24-hr urine samples contained 21.0 mg of methionine and 11.9 mg of cystine plus cysteine after a test load of 9 g of methionine; 2.4 mg of methionine and 24.2 mg of cystine plus cysteine after a test load of 7.3 g of cystine; and 2.4 mg of methionine and 9.8 mg of cystine plus cysteine after a test load of 7.3 g of cysteine.

Perhaps when adult man is confronted with a large amount of either cysteine or cystine, there is a rapid and almost simultaneous conversion of absorbed cysteine to cystine, or of cystine to cysteine. But when methionine is ingested, the metabolic system is able to cope with the added methionine by transulfuration to form cysteine and this may be rapidly changed to cystine and absorbed by the body tissues or enter into other metabolic functions. The rapidity noted in the elevation of cysteine in plasma after the ingestion of methionine may lend some credence to this theory. On the other hand, the differences in amounts of cysteine and cystine in the plasma after ingestion of methionine, cysteine, or cystine may not be indicative of metabolic conversion, but may reflect interrelationships among S-containing amino acids at the intestinal or renal absorption sites, or be due to alterations between intra- and extracellular amino acids. Whatever the reason, the difference in response by intact healthy human adults to test doses of these S-containing amino acids as measured by their levels in the plasma is striking enough to seem worthy of further investigation.

The increase in free taurine in plasma after cysteine but not after cystine ingestion suggests that taurine arises from the reduced form of the amino acid, as has been previously indicated by Meister (7).

That the apparent increase in threonine concentration of plasma during the methionine-tolerance test was an artifact has been shown in previous studies from this laboratory; in those studies the apparent threonine contents of plasma obtained from bloods treated with iodoacetate was threefold that of the untreated control samples (8).

SUMMARY

Methionine-, cysteine-, cystine-, and taurine-tolerance studies were carried out in healthy human adult subjects to investigate the interrelationships among these S-containing compounds in the plasma. A concomitant increase in methionine and cysteine was found during the methionine test, while cystine concentrations remained constant. In contrast, when cystine was the test amino acid, increased amounts of cysteine appeared in the plasma; and when cysteine was ingested, a concomitant increase in cystine occurred. There was a rapid and sustained increase in plasma taurine concentration during the taurine-tolerance test. Ingestion of test loads of the S-containing amino acids had little or no effect on the amounts of the other amino acids in plasma.

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