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Fasting Plasma Amino Acids in Relation to Serum Lipids in Human Male Subjects

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ABSTRACT

FASTING PLASMA AMINO ACIDS IN RELATION TO SERUM LIPIDS IN HUMAN MALE SUBJECTS

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The association of fasting plasma amino acids with serum lipids was studied in 23 healthy human male subjects with ages ranging from 31 to 62 years (45±9, mean± SD). There were 12 normocholesterolemic (serum cholesterol = 183±17 mg/dL) and 11 hypercholesterolemic (271±27 mg/dL) subjects. Venous blood samples were drawn three times at weekly intervals. Plasma amino acids were determined by ion-exchange chromatography, and serum cholesterol and triglycerides by enzymatic methods. Hypercholesterolemic subjects had significantly higher lysine and lower serine levels than normocholesterolemic subjects ($p < .05$). Serum cholesterol levels were positively correlated with plasma levels of lysine, ornithine and the lysine/arginine ratio ($p < .04$); and negatively correlated with phenylalanine and urea ($p < .05$). Serum triglyceride levels were positively correlated with plasma levels of lysine, glutamic acid, and valine ($p < .02$); and negatively correlated with serine, glutamine, and asparagine ($p < .04$). These results add support to the hypothesis that specific plasma amino acids are associated with the metabolism of serum lipids.

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Each person whose signature appears below certifies that this manuscript in his opinion is adequate, in scope and quality, in lieu of a thesis for the degree Master of Science.

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INTRODUCTION

The role of dietary cholesterol, fat, and carbohydrate in the etiology of hypercholesterolemia and atherosclerosis has been well established (1,2). Recently, the possible association of dietary protein with serum cholesterol and cardiovascular disease has been the subject of intensive investigation (3).

Reviews of epidemiological data derived from human populations show a positive correlation between animal protein in the diet and mortality from coronary heart disease (4-7). Nonvegetarians have higher plasma cholesterol levels than vegetarians (8-10). Serum cholesterol levels are increased in animals when the level of animal protein (casein) in the diet is increased (11). Experimental studies show that substituting plant protein for animal protein in the diet decreases serum cholesterol levels in humans (12-15) and animals (16-19), and also decreases atherosclerosis in animals (20).

Kritchevsky (21,22) and Carroll (23) have postulated that the role of dietary protein in modulating the level of serum cholesterol is due to the amino acid composition of the proteins. Particularly, the lysine to arginine (lys/arg) ratio is directly associated with hypercholesterolemia and atherogenesis. Casein has a relatively high lys/arg ratio (2.0) and is hypercholesterolemic and atherogenic in animals while the reverse is observed with

soy protein which has a relatively low lys/arg ratio (0.9). However, whole egg protein, with lys/arg ratio of only 1.0 has a hypercholesterolemic effect in rabbits (23), suggesting that amino acids other than lysine and arginine may be involved in the regulation of serum cholesterol.

Studies by Sanchez et al. (24) show that the lys/arg ratio in the plasma of human subjects drops significantly when subjects change from a meat-based diet to a vegetarian diet. Fasting plasma levels of arginine, glycine, serine, and threonine are elevated while levels of leucine, valine, tyrosine, and histidine are decreased. The changes in plasma amino acids are statistically associated with the changes in the levels of serum cholesterol (25). Descovich et al. (26) also found an elevated arginine level in blood as serum cholesterol decreases in humans fed plant proteins. The purpose of this study is to determine first, the association between plasma amino acid concentrations and levels of serum cholesterol and triglycerides in healthy human subjects having relatively low or high levels of serum cholesterol; and second, the weekly variability of fasting plasma free amino acid concentrations.

METHODS

Subjects

Twenty-three healthy, non-smoking male adults, with ages ranging from 31 to 62 years, and with no personal history of diabetes or cardiovascular disease were selected for the study. Subjects were not using any prescription or over-the-counter drugs or alcohol for a period of one week prior to the study. Except for five referred subjects (friends and relatives of participants or staff), all were selected from the clients of the Health and Risk Evaluation Program of the Loma Linda Center for Health Promotion. Eleven had high ($\geq$ 240 mg/dL) and 12 had low ($\leq$200 mg/dL) levels of serum cholesterol. The study was approved by the Loma Linda University Institutional Review Board for human research studies. All subjects signed an informed consent prior to the initiation of the study.

The study was conducted for four consecutive Sundays from 6:30 A.M. to 9:00 A.M. After an overnight fast, blood was drawn from the antecubital vein during three of the four days for each subject. Anxiety, depression, and hostility levels, as indicators of stress for the day, were measured each test week using the Multiple Affect Adjective Check List (27). Subjects marked those words describing their feelings at the time of the test. Each word description is given a value of 0 to $\pm$1 corresponding to anxiety, depression, and hostility; and stress levels were computed

by adding up all the scores for words marked by each subject. Weights were taken every morning of the test, and the body mass index was calculated based on heights and weights taken at the beginning of the study (28).

Analyses

Blood samples for cholesterol and triglyceride measurements were collected in 10 mL clot tubes. These were immediately placed on ice, allowed to coagulate for 10 to 15 minutes, and centrifuged. Samples were analyzed on the same day of blood drawing by the enzymatic methods for cholesterol (29) or triglycerides (30) using the Technicon SMAC II system. Standards were run with every 10 samples to assure quality control.

Blood samples for amino acid analysis were collected in 7 mL EDTA tubes, centrifuged, then deproteinized with 150 mg of sulfosalicylic acid/mL of plasma, and kept frozen at -20^{o} C until analyzed. Samples were analyzed in either a Beckman Model 121 or Model 7300 Amino Acid Analyzer (Beckman Instruments Inc., Palo Alto, CA). Both systems employ the cation exchange method of chromatography (31). All samples were compared to standards of known concentrations, and agreement between the two systems was established by comparison of standards and plasma amino acid values from 4 subjects. The method of operation for the 7300 system has been reported (32). The typical procedure of operation for the Model 121 was modified to include a column, 29.8 $\pm$0.2 cm

in length and 0.9 cm in diameter, packed with Beckman W-1 spherical resin. The buffer flow rate and the ninhydrin flow rate were 70 and 35 mL/hr., respectively. Buffers were composed of lithium citrate solutions. Buffer 1 (pH 2.83, 0.2N) flowed for 145 minutes, Buffer 2 (pH 3.70, 0.2N) continued for 205 minutes, Buffer 3 (pH 3.75, 1.0N, later adjusted to pH 3.56, 1.1N) ran an additional 80 minutes, completing the analysis. Temperature 1 (36^{o}C) was raised to temperature 2 (62^{o}C) 65 minutes after beginning the run. The total run time was 430 minutes.

Statistical analysis

The student's t-test and analysis of variance were used to measure the differences between groups. Simple correlation, stepwise multiple regression and partial correlation analyses were used to test for associations between plasma amino acid and serum lipid levels using the Statistical Package for the Social Sciences (SPSS) (33). The plasma amino acids most closely related to serum lipids as determined by stepwise multiple regression analysis were the variables used to determine their strength of correlation with serum lipids by partial correlation analysis.

RESULTS

Mean fasting plasma amino acid concentrations, and mean levels of serum cholesterol and triglycerides were not significantly different from week to week when data were statistically evaluated by analysis of variance.

Table 1 shows the personal characteristics and mean stress levels of subjects with high or normal levels of serum cholesterol. Mean age for both groups was in the fourth decade of life. Mean body mass index and mean serum cholesterol and triglyceride levels were significantly greater for the hypercholesterolemic group. Body weights of the subjects did not significantly change during the 4-week study period. Both groups had the same levels of stress measured as anxiety, depression, and hostility.

Table 2 shows the mean fasting concentrations of plasma amino acids in normocholesterolemic and hypercholesterolemic subjects. The levels of lysine were significantly higher and serine lower in hypercholesterolemic compared to normocholesterolemic subjects.

Table 3 shows the plasma amino acids associated with serum lipids by simple correlation analysis. Serum cholesterol levels were positively correlated with the levels of plasma lysine and the lys/arg ratio. Serum triglyceride levels were positively correlated with the levels of plasma lysine, glutamic acid, and valine; and negatively correlated with asparagine, glutamine, and

serine.

Table 4 shows the partial correlation between plasma amino acids and serum lipids. The variables chosen for this analysis were selected from a stepwise multiple regression analysis. Serum levels of cholesterol were positively correlated with the levels of plasma lysine and ornithine, and negatively correlated with phenylalanine and urea. Serum triglyceride levels were positively correlated with the levels of plasma lysine, and negatively correlated with serine and glutamine. Age was also positively correlated ($r = 0.63$, $p < .002$) with the levels of serum cholesterol but not with triglycerides.

DISCUSSION

There were no significant differences in mean concentrations of fasting plasma amino acids, cholesterol, and triglycerides from week to week. This suggests that the differences observed in this study were not due to temporal variations. The weekly constancy of plasma amino acid concentrations indicates that the variations in fasting plasma amino acid levels may be metabolically meaningful in relation to serum cholesterol and triglyceride levels. Furthermore, the stress levels of normocholesterolemic and hypercholesterolemic subjects were similar; thus, ruling out stress as a factor in the differences observed in serum lipid levels between the two groups.

There were significant correlations of amino acid concentrations with serum cholesterol and triglyceride levels (tables 3 and 4) even when most of the mean concentrations of plasma amino acids were similar between hypercholesterolemic and normocholesterolemic subjects (table 2).

It is significant to note that the mean plasma concentration of lysine was significantly higher and serine lower in hypercholesterolemic compared to normocholesterolemic subjects (table 2). The dietary lysine content of proteins has been consistently associated with hypercholesterolemia (20,21). Sanchez et al. (24,25) have also found lower concentrations of serine, glycine,

threonine and arginine, and an association of plasma lysine with elevated serum cholesterol levels in human subjects.

Serum cholesterol levels were positively correlated with fasting levels of plasma lysine, ornithine, and the plasma lys/arg ratio; and negatively correlated with phenylalanine and urea when the data were evaluated by either the simple (table 3) or partial (table 4) correlation analysis. Fasting levels of plasma lysine, ornithine (25) and the plasma lys/arg ratio (24) are associated with serum cholesterol levels in humans. This correlates well with the levels of lysine and the lys/arg ratio in the diet which have been associated with the levels of serum cholesterol and atherogenesis (20,21). There is evidence that the levels of plasma amino acids may depend on the amino acid composition of the protein ingested (34,35). Changes in levels of serum cholesterol are correlated to changes in concentrations of plasma amino acids (25).

Serum triglyceride levels were positively associated with fasting levels of plasma lysine, glutamic acid, and valine; and negatively associated with asparagine, glutamine, and serine when data were evaluated by either the simple or partial correlation analysis (tables 3 and 4). Aside from lysine, other amino acids related to serum triglycerides were not related to serum cholesterol. In contrast, an earlier study (25) shows that many of the amino acids correlated with serum cholesterol are also correlated

with triglyceride levels. This may be due to differences in experimental design: all subjects in the previous study were fed the same controlled plant protein diet while subjects in the present study ate their varied habitual diet.

The association of plasma amino acids with serum lipids is not simple. The association does not conform to whether the amino acid is essential or nonessential (e.g. lysine and ornithine), or whether it is basic, neutral or acidic (e.g. lysine, phenylalanine, or glutamic acid). Plasma lysine, ornithine, and ammonia ($p < .001$, data not shown) were positively associated with the levels of serum cholesterol. In contrast, the levels of urea and phenylalanine which is gluconeogenic (36) were negatively associated with serum cholesterol levels. In view of this, it is important to note that hypercholesterolemic compared to normocholesterolemic subjects had significantly higher levels of lysine which is ketogenic, and lower levels of serine which is glucogenic (36) (table 2). These results are consistent with the hypercholesterolemic effect of lysine supplementation in animals (37) and with an inverse association between serum cholesterol levels and the concentrations of serine and glycine in humans fed a plant protein diet (24,25). Gibney has suggested that the glucogenic amino acids glycine and alanine may have a more significant effect on serum cholesterol than lysine or arginine (38).

Obese subjects in a previous study (24) have decreased levels of serum cholesterol with increased concentrations of fasting plasma glycine and serine. Fisler et al. (39) found a consistent increase in plasma glycine concentrations in severely obese persons fed calorie-restricted soy protein or collagen, which are rich sources of glycine. Apparently conflicting data of Marliss et al. (40) show a decrease in plasma levels of glycine and serine among calorie-restricted obese subjects, but these were fed tuna, chicken, egg white, cottage cheese, milk, and casein as their protein sources. Protein from egg white and dairy sources are relatively low in glycine (41). Thus a decrease in serum cholesterol may be consistent with elevated plasma glycine in obese or normal weight individuals (24,39) but the increase in glycine and serine may be modified by the dietary protein (39,40). These data are of particular interest since obesity is a risk factor in cardiovascular disease (42) and is associated with elevated blood insulin (43) and serum cholesterol levels (44). Unpublished data from our laboratory also show that hypercholesteromic subjects have increased levels of blood insulin.

In this study we found that certain fasting plasma amino acids are associated with serum cholesterol and triglyceride levels in men. The weekly stability of concentrations of fasting plasma amino acids in humans warrant further studies on the metabolic association between

plasma amino acids and serum lipid levels.

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Table 1. Characteristics of Subjects (Mean ±SD)

	Normal	Hyper-
N	12	11
Cholesterol (mg/100 mL)	183 ±17	271 ±27[1]
Triglycerides (mg/100 mL)	95 ±46	180 ±90[1]
Age (years)	42 ±9	49 ±10
Body Mass Index[2] (kg/m^2)	23.8±2.1	26.7±2.2[1]
Anxiety[3]	4.3±2.9	4.1±3.1
Depression[3]	9.3±4.9	9.4±5.8
Hostility[3]	5.0±2.9	5.5±3.0

[1]significant difference between groups (student's t-test), $p < .01$.
[2]weight in kg divided by the square of the height in meters.
[3]according to the Multiple Affect Adjective Check List (27).

Table 2. Fasting Concentrations (Mean ±SD) of Plasma Amino Acids (nM/mL) in Normocholesterolemic and Hypercholesterolemic Subjects

Amino Acids	Normal N=12	Hyper- N=11	p value[1]
Threonine	71 ±10	68 ±10	
Valine	110 ±16	118 ±18	
Tryptophan	18 ± 6	21 ± 8	
Phenylalanine	28 ± 3	28 ± 3	
Methionine	11 ± 3	10 ± 2	
Isoleucine	31 ± 9	33 ± 6	
Leucine	66 ± 8	66 ± 9	
Lysine	80 ± 8	91 ±13	<.05
Histidine	41 ± 4	43 ±10	
Taurine	33 ±17	33 ±18	
Serine	52 ± 8	45 ± 8	<.05
Asparagine	20 ± 5	17 ± 5	
Glutamic	96 ±14	97 ± 12	
Glutamine	206 ±42	189 ± 42	
Proline	106 ±23	101 ± 29	
Glycine	127 ±27	115 ± 17	
Alanine	205 ±56	196 ± 37	
Cystine	24 ± 4	25 ± 5	
Tyrosine	29 ± 4	33 ± 4	
Ornithine	38 ± 8	41 ± 7	
Arginine	39 ± 9	34 ± 7	
Phosphoethanolamine	16 ± 8	12 ± 6	
Sarcosine	6 ± 2	6 ± 2	
Alpha-amino adipic	3 ± 1	3 ± 1	
Citrulline	20 ± 3	19 ± 4	
Alpha-aminobutyric	11 ± 3	10 ± 3	
Ammonia	1041 ± 67	1078 ± 50	
Urea	3128 ±798	2601 ±457	

[1]Student's t-test

Table 3. Simple Correlation of Fasting Plasma Amino Acid Concentrations with Serum Cholesterol and Triglyceride Levels (N=23)

Amino Acids	Cholesterol		Triglycerides	
	r	p[1]	r	p[1]
Lysine	.49	<.02	.59	<.002
Lys/arg	.40	<.04		
Glutamic			.46	<.02
Valine			.45	<.02
Asparagine			-.67	<.002
Glutamine			-.58	<.002
Serine			-.56	<.002

[1]Two-tailed significance levels

Table 4. Partial Correlation Analysis of Fasting Levels of Plasma Amino Acids and Urea with Serum Levels of Cholesterol and Triglycerides (N=23)

Amino Acids	Cholesterol		Triglycerides	
	r^1	p^2	r^1	p^2
Lysine	.66	<.002	.55	<.01
Ornithine	.67	<.002		
Phenylalanine	-.52	<.01		
Urea	-.40	<.05		
Serine			-.57	<.004
Glutamine			-.42	<.04

[1]Each partial correlation controlled for the other 4 variables (including age, data not shown) for cholesterol, [2]and the other 2 for triglycerides.
[2]Two-tailed significance levels