Acute and Chronic Supplementation of Amino Acids

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Introduction

Of the four essential nutrient groups, amino acids may be the most fundamental to brain chemistry. The dietary dependence of the neurotransmitters, dopamine, serotonin and histamine upon their amino acid precursors, is now well established (Wurtman et al., 1980). Many other neurotransmitters, which are either made from amino acid precursors or are amino acids, are likely to be dietary dependent. Plasma amino acid levels have been demonstrated to be directly proportional to brain neurotransmitter levels (Wurtman, R.J., 1980) (De Montis, M. G. et al., 1977). Therefore, neurotransmitters can be influenced to a great degree by the amino acids in the diet or by supplementation (Benedict et al., 1983).

Interest in amino acids in therapeutics is growing. Tryptophan (Trp) has been utilized in insomnia, depression, pain relief and mania. Methionine (M) has been utilized in depression (Muscettola, G. et al., 1984), gall bladder diseases (Frezza, M. et al., 1984) and other medical conditions (Braverman, E. R. and Pfeiffer, C. C, 1984-85). Taurine (T) is a common therapeutic in Japan, where it is used as an inotrope (Azuma, J. et al., 1983) and anticonvulsant (Muscettola, G. et al., 1984). Hence, we studied the effects of acute and chronic supplementation of amino acids on plasma amino acid levels. This is because plasma amino acids are directly correlated to neurotransmitter content in the brain.

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Table 1
Amino Acids as Precursors of Neurotransmitters

Amino Acid	Neurotransmitter(s)
Cysteine	Cysteic Acid
Glutamine	GABA, Glutamic Acid
Histidine	Histamine
Lysine	Pipecolic Acid
Phenylalanine	Phenylethylamine plus same as Tyrosine
Tyrosine	Dopamine, Norepinephrine, Epinephrine, Tyramine
Tryptophan	Serotonin, Melatonin, Tryptamine's

Amino Acids as Neurotransmitters

Amino Acid	Function
Alanine	Inhibitory or calming
GABA	Inhibitory or calming
Glycine	Inhibitory or calming
Taurine	Inhibitory or calming
Glutamic Acid	Excitatory
Aspartic Acid	Excitatory

Methods and Results: Acute Loading of Tryptophan and Other Amino Acids

Five fasted normal subjects were loaded with five grams (per 70 kg) of Trp; plasma amino acids, trace metals, polyamines, growth hormone, and Met-path Lab Flex profile were measured. Trp levels in plasma were 7.8 ± 1.6 uM/DL at 0 hour (before load) 39 ± 10 uM/DL at two hours and 31+8 uM/DL at four hours. Changes in Trp were significant at the less than .001 level (Figure 1). Trp will return to normal in about six to eight hours (Zarcone, V. et al., 1973). A downward trend of valine, leucine, glycine, threonine,

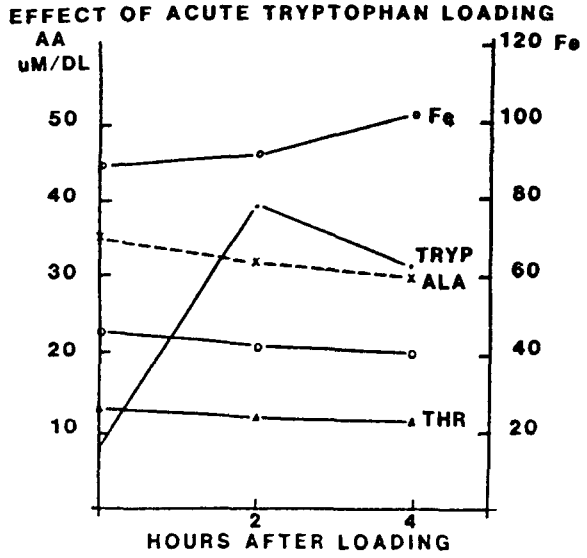


Fig. 1

asparganine, proline, lysine and histidine (Table 1) was noted, but was not significant when compared to a fasted control group that had blood drawn at 0, 2 and 4 hours. Fasting alone decreases plasma amino acids. There were upward trends in serum iron and growth hormone. All differences in biological variables but tryptophan were N.S.

TABLE 2

Absorption of Individual Amino Acids
1Gm/70 Kg – % increase VS controls

A.A.	hr2	hr4
TAUR	663.1	256.9
MET	291.7	172.3
HPRO	155.1	107.8
SER	135.5	62.5
PROL	121.1	54.2
ILE	116.4	121.8
PHE	101.8	52.6
ORN	100.6	42.2
TRP	77.5	57.9
GABA	64.0	.0
THR	62.2	52.3

Similar studies were done for 22 other amino acids (Table 3). Rates of absorption are shown in Table 4. The sulfur amino acids, taurine and methionine, are best absorbed. Munro (1972) and others have suggested that amino acids are better absorbed as peptides.

TABLE 3

Absorption of Individual Amino Acids
1Gm/70 Kg – % increase VS controls

A.A.	hr2	hr4
VAL	60.1	52.6
ASP	40.1	.0
ASN	31.7	14.6
HIS	30.4	12.2
LYS	26.3	8.5
LEU	18.5	5.5
ARG	15.0	18.8
TYR	14.3	21.4
ALA	7.1	1.5
GLN	2.2	.2
CYS	.0	11.7
GLY	-1.4	15.7

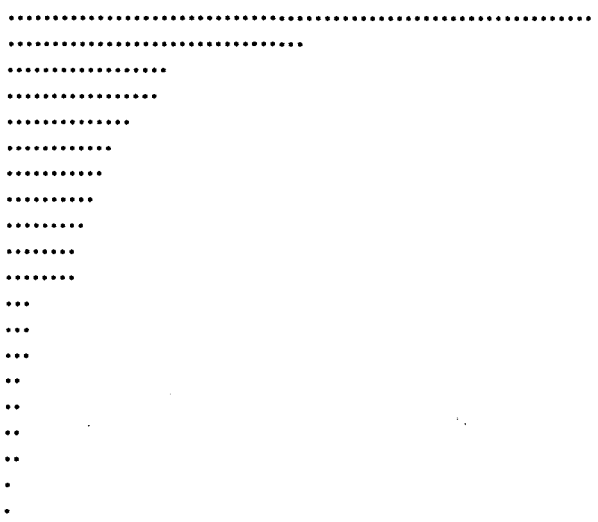
Methods and Results: Chronic Supplementation of Tryptophan and Other Amino Acids

Data on four patients loaded with 2.5 grams (per 70 kg) of tryptophan (Trp) daily for an average of 6 weeks were analyzed retrospectively. The mean Trp level for these patients was 12.8 + 3 uM/DL compared to 7.1 + 2.2 uM/DL for a matched control group of 96 patients (Table 7). The difference was significant at the less than .001 level. There was a significant increase of asparganine, arginine, threonine and alanine (p less than .05) when compared to several matched control groups. Com-

TABLE 4
Absorption of Individual Amino Acids
g/70 Kg - % increase VS controls

AVERAGE % INCREASE FOR HOURS - 2 and 4

Tau	460.0
Met	232.0
hPro	131.4
He	119.1
Ser	99.0
Pro	87.7
Phe	77.2
Om	71.4
Trp	67.7
Thr	57.3
Val	56.3
GABA	24.5
Asn	23.1
His	21.3
Tyr	17.9
Lys	17.4
Arg	16.9
Asp	14.1
Leu	12.0
Gly	7.2
Cys	5.8
Ala	4.3
Gln	1.2



parison of chronic loaded Trp patients showed significant elevations of these amino acids (p less than .02) and T (p less than .05) compared to the acute loaded group at the times determined. These data show that the downward trend in plasma amino acids observed with tryptophan loading is not seen in chronic loading. Furthermore, postulated decreases of amino acids that compete with Trp for absorption do not occur.

TABLE 5
SIGNIFICANT INCREASES IN PLASMA AMINO ACIDS
WITH CHRONIC METHIONINE THERAPY

DOSE 1400mg/70kg FOR 11 WEEKS

N = 3 CTRL = 16 P < .1

METHIONINE ONLY		CONTROL MET	10 ±3.6
3 ± 0.9			
CYS	4 ± 1.0	2.3 ± 1.5	
TAU	7 ± 2.6	5 ± 1.3	
ABU	3.7 ±0.6	2 ± 0.8	
GLY	37 ± 13.9	23 ± 5	
ASN	14 ± 4.0	7.1 ± 1.8	

TABLE 6
SIGNIFICANT INCREASES IN PLASMA AMINO ACIDS
WITH CHRONIC METHIONINE PLUS TAURINE THERAPY

MET (1800mg/70kg-10 WKS) TAU (600mg/70kg-14 WKS)
N = 4 CTRL = 16

MET&	TAU (P< 0.3)		CONTROL 7.5 ± 2.1
MET			3.0 ± 0.9
TAU		15 ±6.1	5 ± 1.3
ABU		3 ± 0.8	2 ± 0.8
GLY	31.8 ± 15	23 ± 5	
ASN		9.5 ± 2.3	7.1 ± 1.7
HPR		4.3 ± 1.3	2.6 ± 1.4
ORN		8.5 ± 3	5.8 ±1.6

TABLE 7
INCREASES IN PLASMA AMINO ACIDS
WITH CHRONIC TRYPTOPHAN THERAPY

DOSE 2.5g/per 70 kg FOR 6 WEEKS
N = 4 CTRL = 1 0 P < 0.5

TRYPTOPHAN ALONE		CONTROL
ASN	9.8 ± 1.9	7.5 ± 1.7
ARG	11.8 ± 0.9	9.1 ± 1.6
THR	15 ± 2.9	11.8 ± 2.2
ALA	46.3 ± 8.9	34 ± 7.6
TRP	12.8 ± 2.9	7.9 ± 1.4

Twelve grams of Trp loaded daily to manic patients increased plasma levels to twice normal at two weeks due to homeostatic compensation (Chouinard and Colleagues, 1978). We have had children with plasma Trp twice normal without decreases in other plasma amino acids.

Chronically loaded tryptophan increases other plasma amino acids. We have observed this with other chronically loaded amino acids, i.e. taurine and methionine.

We retrospectively analyzed plasma amino acids in patients loaded with M alone (N = 3, 1400 mg/70 kg-11 wks.), M ± T (N = 4, M 1800 mg/70 kg-13 wks., T 600 mg/70 kg-11 wks.), Trp alone (N = 4, 2500 mg/70 kg-6 wks.) and M ± Trp (N = 4, M 800 mg/70 kg-9 wks., Trp 900 mg/kg-10 wks.). We compared these groups to two control groups.

M alone (Table 5) increased plasma M and other sulfur amino acids T and Cysteine (Cys), as well as Abu, Glycine (Gly) and Asn (P less than .01).

M + T (Table 6) increased the above amino acids plus Orn and Hpr (p less than .03). M compared to M + T showed only T to be significantly elevated.

Trp alone (Table 7) elevated Trp, Thr and Arg (p less than.03). M ± Trp (Table 8) elevated M, Thr, Arg, and T, Leu, He, Val, Phe, Tyr, Ser, Hpr, and Lys (p less than .03).

The addition of a second amino acid again accentuated the increase in other plasma amino acids. All four groups combined (N = 15) compared to controls (N = 26) showed increases in 10 amino acids (p less than .05) and trends upward in all plasma amino acids. Chronic supplementation of M, T, or Trp leads to an

TABLE 8

SIGNIFICANT INCREASES IN PLASMA AMINO ACIDS WITH CHRONIC METHIONINE PLUS TRYPTOPHAN

	MET (800mg/70kg-9 WKS)	TRP (900mg/70kg-10 WKS)	
	MET ± N = 4	TRP CTRL = 16 CONTROL	
LEU	19.5 ± 4.8	12.3 + 2.7	
ILE	11.0 ± 3.4	6.2 ± 1.4	
VAL	29.2 ± 6.2	21.8 ± 4.4	
MET	7.25 ± 0.9	3.1 ± 0.9	
TAU	14.0 ± 9.0	5 ± 0.94	
PHE	8.25 ± 1.7	5.6 ± 1.2	
TYR	8.8 ± 1.7	6.3 ± 1.0	
SER	13.5 ± 2.4	9.9 ± 2.5	
HPR	9 ± 8	2.6 ± 1.5	
ARG	12.3 ± 1.3	9.1 ± 1.7	
LYS	26 + 4.7	18 ± 2.5	
TRP	8.3 ±0.9	7.9 ±1	N.S.

elevation of many other plasma amino acids.

Discussion

Conditions of stress, pregnancy, zinc deficiency (Mora, R. J. and Lyerly, A., 1985), infection, surgery and cancer consistently lower many plasma amino acids. Hypoaminoacidemia occurs in anorexia, cancer, alcoholism (Ericksson, T. et al, 1983), pregnancy (Gard, P. R. and Handley, S. L.), stress (Milakofsky, L. et al, 1984), chronic hospitalization, hypothermia, fever and infection, (phenylalanine is elevated), and renal failure (except tyrosine). Pellagra is marked by decreases in tryptophan and branched chain amino acids. Rheumatoid arthritis has decreased histidine as do allergy patients who have low plasma histamine. Allergy patients can also have decreases in plasma ornithine (unpublished results). Gout patients are marked by decreased glycine. Scurvy is marked by a decrease in threonine, glycine, lysine, leucine and arginine. Elevated serum copper in females decreases plasma tryptophan and histidine (unpublished results). Decreases in tryptophan, methionine, taurine, tyrosine and/or glycine have been reported in depression (Braverman, E. R. et al, 1984).

Aging is marked by deficiency of glutathione due to failure to meet increased need for sulfur amino acids with age. Hence, aging is marked by a relative deficiency of sulfur amino acids and aromatic amino acids.

For example, elevated plasma amino acids have been found to improve recovery from surgery and therapeutic drug responses to antidepressants and penicillamine have been correlated to elevations in plasma amino acids. Hence, elevation of plasma amino acids may be used in the treatment of a variety of disorders. The most recent example has been the use of intravenous branched chain amino acid solutions (preoperatively) and essential amino acid solutions (Moss, G., 1984) to reduce trauma (Adibi, S. A. et al, 1984) from surgery and sepsis. BC A A (branch-ed chain amino acids) solutions (Mizock, B. A. 1985). Interestingly, the 'Atkins Ketogenic Diet' raises BC A A by 30% (unpublished results).

We studied chronic supplementation of amino acids over several weeks and found that combinations of individual supplementation lead to increases in several plasma amino acids. Elevation of plasma amino acids with dietary supplement of essential amino acid has also been found by Rosell and Zimmerman, 1985. These increases include amino acids other than the supplemented ones. This effect is probably related to nitrogen sparing and has many interesting applications to medical therapeutics. Already mega amino acid therapy is commonly recommended in the scientific literature: tryptophan — 3 g for pain, 6 g for obsessive compulsive, 2-6 for depression and 2 g for migraine, tyrosine 6 g for depression and cocaine abuse, etc. The use of mega amino acids in the doses described is probably not hazardous and may have additional therapeutic benefits not previously suspected.

Acknowledgements

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