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Plasma amino acid levels after single-dose aspartame consumption in phenylketonuria, mild hyperphenylalaninemia, and heterozygous state for phenylketonuria

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Aspartame (*N*-aspartyl-phenylalanine methyl ester), a widely used artificial sweetener, is hydrolyzed in the intestinal lumen to methanol and to its constituent amino acids phenylalanine and aspartic acid. Ingestion of this sweetener causes a sharp increase in plasma phenylalanine levels in normal persons[1] and in patients with phenylketonuria.[2] The label on aspartame-containing products includes a warning to patients with PKU, but no information on the actual sweetener content, and there is concern that aspartame ingestion by those who do not have PKU could produce phenylalanine levels sufficiently high to harm the brain, especially among the estimated 2% of the general population who carry the gene for PKU and thus have a reduced capacity for phenylalanine metabolism. Studies in rats show that elevations of plasma phenylalanine levels, as occur in humans after aspartame ingestion, produce an increase in brain phenylalanine concentration.[3,4] On the other hand, the peak plasma phenylalanine levels after loading doses of aspartame in normal persons and in PKU heterozygotes are still considerably lower than those in mentally retarded patients with PKU.[5]

Most of the studies in humans on the effects of aspartame on plasma amino acids have used high doses of the sweetener,[1,5] and have reported increases in plasma phenylalanine levels up to fourfold in normal and tenfold in PKU heterozygotes. Moreover, no studies in humans have addressed the effects of aspartame on the plasma ratio of phenylalanine to the other large neutral amino acids (valine, leucine, isoleucine, tyrosine, and tryptophan), which is the determinant of phenylalanine availability to the brain.[6]

Phe	Phenylalanine
PKU	Phenylketonuria
LNAA	Large neutral amino acids

We examined the effect of an estimated average single dose of aspartame on plasma phenylalanine levels and the plasma phenylalanine/LNAA ratios in people with PKU,

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Table I. Basal plasma amino acid concentrations

	Normal (n = 10)	PKU (n = 15)	Hyperphenylalanine (n = 10)	PKU carrier (n = 14)
Phenylalanine	44.5 ± 12.9[a]	1369.1 ± 240.1[c]	411.7 ± 207.9[b]	68.8 ± 13.8[a]
Valine	182.0 ± 48.7[ab]	151.1 ± 33.3[b]	201.6 ± 28.6[a]	168.8 ± 43.2[ab]
Isoleucine	49.3 ± 18.9[ab]	40.0 ± 12.1[b]	56.5 ± 8.2[a]	44.1 ± 9.4[b]
Leucine	103.8 ± 32.2[a]	77.2 ± 20.6[b]	112.7 ± 17.8[a]	93.7 ± 22.1[ab]
Tyrosine	57.6 ± 23.0[a]	32.3 ± 6.7[b]	56.9 ± 11.9[a]	47.2 ± 9.7[a]
Tryptophan	57.6 ± 20.4	42.4 ± 9.6[c]	63.0 ± 12.9[a]	56.2 ± 10.8[a]
Phe/LNAA	0.100 ± 0.011[a]	4.212 ± 1.302[c]	0.849 ± 0.414[b]	0.170 ± 0.027[a]

Values represent mean ± SD μmol/L.
Group means with different letters are significantly different by Duncan multiple range test ($P < 0.05$).
Phe/LNAA, Phenylalanine/large neutral amino acids ratio.

Table II. Plasma amino acid concentration 1 hour after aspartame (10 mg/kg) ingestion

	Normal	% Change	PKU	% Change	Hyperphenylalanine	% Change	PKU carrier	% Change
Phenylalanine	58.0 ± 9.5[a]*	+30	1323.3 ± 209.7[c]	−3	412.8 ± 184.1[b]	0	82.3 ± 17.3[a]*	+20
Valine	175.5 ± 27.2[ab]	−4	154.5 ± 26.7[a]	+2	198.6 ± 39.1[b]	−1	159.8 ± 41.2[a]	−5
Isoleucine	44.0 ± 10.2[a]	−11	40.5 ± 9.2[a]	+1	54.7 ± 12.3[b]	−3	41.5 ± 9.2[a]	−6
Leucine	92.9 ± 20.8[a]	−10	78.3 ± 13.4[a]	+2	109.4 ± 17.4[b]	−3	89.3 ± 22.5[a]	−5
Tyrosine	60.7 ± 15.0[a]	+5	34.0 ± 7.5[c]	+5	54.6 ± 11.3[ab]	−4	46.0 ± 9.6[b]	−2
Tryptophan	54.5 ± 12.5[a]	−6	43.5 ± 8.3[b]	+3	58.7 ± 12.4[a]	−7	52.0 ± 14.1[ab]	−7
Phe/LNAA	0.137 ± 0.017[a]*	+37	3.847 ± 0.824[c]	−9	0.892 ± 0.430[b]	+5	0.214 ± 0.028[a]*	+26

Values represent mean ± SD μmol/L. Group means with different letters are significantly different by Duncan multiple range test ($P < 0.05$).
*Significant increase over baseline values, Student t test for paired samples ($P < 0.05$).

those with non-PKU mild hyperphenylalaninemia, those carrying the gene for PKU, and in normal individuals.

METHODS

The subjects studied were from the population of parents and children observed in the IEM-PKU Program of the Children's Hospital, Boston, and all were ingesting a normal diet. The group included patients with classic PKU, with atypical hyperphenylalaninemia, and PKU carriers (heterozygotes). Ten normal young adults were studied as controls.

After an overnight fast, a baseline blood sample was obtained, and each subject ingested, over 10 to 15 minutes, an amount of cherry-flavored Sugar-Free Kool-Aid (General Foods, White Plains, N.Y.) that provided 10 mg aspartame/kg body weight. A second blood sample was obtained 1 hour later. Plasma amino acids were analyzed in duplicate by high-performance liquid chromatography with fluorometric detection, and results were compared by t test or by one-way analysis of variance.

RESULTS

As shown in Table I, pretreatment plasma phenylalanine levels and Phe/LNAA ratios were markedly elevated in subjects with PKU or non-PKU hyperphenylalaninemia but were not significantly elevated in the carrier group. Basal plasma levels of the other LNAAs examined tended to be depressed in patients with PKU; these decreases attained statistical significance for tyrosine, tryptophan, and leucine.

Aspartame administration significantly increased plasma phenylalanine levels and Phe/LNAA ratios in the control and carrier groups but not in non-PKU hyperphenylalaninemic or patients with PKU (Table II). The absolute increases in plasma phenylalanine levels were similar in the control and carrier groups (13.5 μM), producing concentrations that were still within 1 and 2 SD, respectively, of the mean for a general adult population.[7] The percent increases were smaller in the carrier group because basal levels tended to be higher. The artificial sweetener failed to affect the plasma levels of other LNAAs. However, its administration did cause the difference in plasma tyrosine between normal and carrier subjects to become significant (Table II), because absolute plasma tyrosine levels were increased in normal subjects but not in the carrier group.

No serious adverse effects were noted in any of the subjects during the study period. One subject in the control

group complained of severe headache after ingestion of the test dose of aspartame.

DISCUSSION

These observations show that an estimated average dose of aspartame does not accentuate hyperphenylalaninemia in patients with untreated PKU or non-PKU hyperphenylalaninemia, but does produce statistically significant elevations in the plasma phenylalanine level in normal subjects and in PKU carriers. The dose of aspartame used, 10 mg/kg, is one fifth the present ADI (acceptable daily intake) level set by the Food and Drug Administration; it was selected to approximate the expected maximal amount of aspartame that an adult would consume in 10 to 15 minutes. For a 60 kg adult, 10 mg/kg aspartame is present in a little more than one quart of Kool-Aid (34.5 oz) or in three cans of an aspartame-sweetened soft drink.

The plasma Phe/LNAA ratios paralleled the phenylalanine levels, because the other LNAAs were not affected by aspartame. Thus these ratios were also increased by aspartame in both normal and PKU carrier groups but were unchanged in those with PKU and non-PKU hyperphenylalaninemia. Among PKU carriers this ratio was increased by aspartame to values above the normal range reported in persons consuming meals containing varying amounts of protein and carbohydrate.[8] This effect reflects the decreased ability of this group to hydroxylate phenylalanine to tyrosine.

The addition of protein to a meal actually lowers the plasma Phe/LNAA ratio (and presumably, brain phenylalanine concentration in humans), because even though the protein contributes phenylalanine to the bloodstream, it contains and contributes far larger amounts of the other LNAAs. Thus, if an increased Phe/LNAA ratio is undesirable, ingesting aspartame with protein might be preferable to ingesting it only with carbohydrate: the insulin secretion induced by dietary carbohydrates causes major reductions in plasma levels of leucine, isoleucine, and valine, thereby elevating the plasma Phe/LNAA ratio and potentiating the effects of aspartame on brain phenylalanine levels.[4]

The precise levels of plasma phenylalanine required to cause damage to the central nervous system have not been established experimentally, although based on observations of patients, a "safe threshold" of 600 μM has been proposed.[9] Similarly, data are lacking on the plasma or brain phenylalanine levels needed to impair the synthesis of brain neurotransmitters in humans, a possible mechanism for the brain damage in PKU.[10] The plasma phenylalanine levels and Phe/LNAA ratios produced in normal persons and in those who carry the gene for PKU by the amount of aspartame we administered were far below those noted in the basal state among individuals who are brain damaged from PKU, or even those who have a seemingly benign form of non-PKU hyperphenylalaninemia. However, it is possible that an aspartame-induced rise in the plasma Phe/LNAA ratio may have different effects on the brain of a person whose plasma Phe/LNAA ratio and brain phenylalanine levels are usually normal than in someone with a lifetime elevation in plasma phenylalanine. In the latter, adaptive changes could occur at the transport system that carries phenylalanine across the blood-brain barrier. The considerable variability in the extent of functional brain damage observed among people with untreated PKU suggests that additional factors can modulate the neurotoxic effects of high phenylalanine concentration.[11]

Our data indicate that 10 mg/kg doses of aspartame may safely be consumed by persons with hyperhenylalaninemia or PKU who are not on a phenylalanine-restricted diet. This study, however, did not address the question of long-term effects of aspartame use nor the consequences of consuming higher doses of aspartame, alone or with other foods. Moreover, plasma phenylalanine concentrations may increase to unacceptable levels when patients with PKU on phenylalanine-restricted diets consume aspartame-containing soft drinks[12] or after loading doses of the sweetener.[5] The appearance of severe headaches after aspartame intake has also been reported in a non-PKU patient receiving neuroactive drugs.[13]

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