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Absence of an effect of aspartame on seizures induced by electroshock in epileptic and non-epileptic rats* **

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Summary. Seizure facilitation has been proposed as a possible adverse effect of dietary consumption of aspartame. The conversion of this sweetener to phenylalanine and aspartate in the gastrointestinal tract, and subsequent absorption, elevates plasma levels of these two amino acids. Absorbed phenylalanine competes with other large neutral amino acids, including tyrosine and tryptophan, for transport into brain. Theoretically, this competition might reduce brain tyrosine and tryptophan which could decrease synthesis of norepinephrine, dopamine and serotonin. Diminished synaptic release of these monoaminergic neurotransmitters facilitates seizures in many seizure models. Our present study evaluates effects of oral aspartame on amino acids and electroshock seizures in normal and seizure predisposed rats. Heroic doses of aspartame produced predictable changes in plasma amino acids. However, none of the aspartame doses altered seizure indices. We conclude that aspartame does not alter maximal electroshock seizures in normal rats or in rats predisposed to seizures.

Keywords: Amino acids – Genetically Epilepsy-prone rat: GEPR – Aspartame – Phenylalanine – Tyrosine – Tryptophan – Electroshock seizures

Introduction

Seizure facilitation has been proposed as a possible adverse effect of the dietary consumption of aspartame (L-aspartyl-L-phenylalanine methyl ester). The appearance of seizures in certain humans was attributed to ingestion of aspartame by Wurtman (1985). Kim et al. (1988) have reported that lidocaine-induced

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convulsions are facilitated by aspartame given to mice. A reduction in the threshold for pentylenetetrazol-induced convulsions in CD-1 mice was ascribed as an effect of large bolus doses of aspartame in a paper by Pinto and Maher (1988). Finally, Guiso et al. (1988) have claimed that aspartame increased the fraction of normal, non-epileptic rats exhibiting severe convulsions in response to pentylenetetrazol.

These seizure facilitating effects have been attributed to presumed reductions in brain noradrenergic and/or serotonergic transmission that might be caused by aspartame (Pinto and Maher, 1988; Wurtman, 1985). Such speculations have some intuitive appeal because both types of monoaminergic neurons have been shown to regulate seizure predisposition and threshold in epileptic and non-epileptic animals (Browning, 1987; Burley and Ferrendelli, 1984; Chapman and Meldrum, 1987; Jobe and Laird, 1987). Also, pharmacologically-induced decrements in either or both systems are associated with seizure facilitation (Jobe and Laird, 1987). Supposedly, phenylalanine formed from aspartame accumulates in the plasma and interferes sufficiently with the transport into the brain of precursors to norepinephrine and serotonin so that functional monoaminergic deficits result (Pinto and Maher, 1988; Wurtman, 1985). This idea is based on documentation showing that large neutral amino acids – including tyrosine and tryptophan, the precursors to norepinephrine and serotonin — enter the brain via the same transport system responsible for the uptake of phenylalanine (Oldendorf, 1971; Pardridge, 1977; Pinto and Maher, 1988; Wurtman et al., 1981). In addition to interfering with brain monoamine synthesis by reducing tyrosine and tryptophan transport across the blood brain barrier, aspartame also may influence norepinephrine formation by an effect on tyrosine hydroxylase. According to this idea, the relative excess of phenylalanine entering the brain inhibits hydroxylation of tyrosine competitively so that formation of L-dihydroxyphenylalanine (L-DOPA) and consequently norepinephrine is reduced. Early work by Ikeda et al. (1967) showed that high concentrations of phenylalanine will decrease the conversion of tyrosine to L-DOPA *in vitro*. Using these concepts, Pinto and Maher (1988) and Wurtman (1985) have further hypothesized that an aspartame-induced deficiency in the functional status of the anticonvulsant monoaminergic systems will increase the responsiveness of the brain to seizure evoking stimuli.

The goal of the present investigation was to determine whether large bolus doses of aspartame facilitate seizures in normal rats or in genetically epileptic rats. Neurologically normal rats were included in the investigations because the vast majority of humans ingesting aspartame are not suffering from epilepsy. Genetically epilepsy-prone rats (GEPRs) were chosen as experimental subjects because they are characterized by a marked degree of seizure predisposition (Dailey et al., 1989a). Accordingly, GEPRs exhibit three types of seizure predisposition: (1) they convulse in response to stimuli (sound and hyperthermia) that fail to cause seizures in adult non-epileptic rats; (2) they occasionally exhibit spontaneous seizures, whereas normal rats do not; and (3) they have lower thresholds and/or exaggerated responses to many convulsant modalities that also cause seizures in non-epileptic animals.

Because of these evidences of enhanced seizure responsiveness, we anticipated that the GEPR might be especially useful as a model to detect any possible

proconvulsant effects of aspartame. The use of GEPRs to determine whether aspartame exerts proconvulsant effects also seemed appropriate because innate noradrenergic and serotonergic deficits appear to be partially responsible for seizure predisposition in these animals (Dailey et al., 1989a) and because aspartame has been suggested to produce alterations in monoaminergic neurochemistry which are sufficient to result in seizure facilitation (Pinto and Maher, 1988; Wurtman, 1985). Our previous findings with GEPRs have demonstrated that drugs which reverse the innate monoaminergic deficits cause anticonvulsant effects (Dailey et al., 1989a). Moreover, drugs which exacerbate monoaminergic deficits in GEPRs accentuate their seizure predisposition.

Material and methods

Animals

Our present study was designed to determine the responses of both epileptic and non-epileptic rats to large bolus doses of aspartame. Two types of epileptic subjects were examined: the moderate seizure genetically epilepsy-prone rat (GEPR-3) and the severe seizure genetically epilepsy-prone rat (GEPR-9) (Dailey et al., 1989a; Mishra et al., 1988; Mishra et al., 1989; Reigel et al., 1986). Both GEPR-3s and GEPR-9s were obtained from the resource colonies maintained at the University of Illinois College of Medicine in Peoria. Non-epileptic rats were also obtained from the colony of these animals maintained at the same facility (Reigel et al., 1986). For each dose within a given experiment 10–15 animals were utilized, resulting in a total of 420 animals (approximately equal number of males and females). Within any given experiment, comparisons between aspartame and vehicle treated subjects were made using rats randomly selected from the same pool of animals so that no bias relative to sex, weights or ages was introduced. All animals had free access to food (Teklad-LM485) and water until the night before an experiment when food but not water was withdrawn. Fasting continued from this point until the experiment was concluded, approximately 19 hours later.

The vivarium in which the animals were housed was environmentally controlled. Temperature and humidity settings were approximately 21°C and 50%, respectively. Lights in the vivarium were activated at 6:00 A.M. and terminated at 6:00 P.M.

Drugs

The vehicle used throughout our study consisted of 0.5% methylcellulose (Sigma Chemical Company, St. Louis) and 0.1% Tween 80 (City Chemical Corporation) in deionized water. The aspartame (The NutraSweet Company) used throughout these studies contained impurities in small concentration. These were (w/w%): 0.15% diketopiperazine, 0.08% alpha-aspartyl-phenylalanine and 1.26% beta-aspartame. Either vehicle or aspartame in vehicle was administered to rats by gavage, using an 18 gauge × 3 inch curved intubation needle, one hour before an electroshock seizure was induced. Aspartame suspensions were prepared so that any given dose of the sweetener was contained in either 2, 4 or 10 ml of vehicle, depending on the particular experiment. The rationale for choosing the doses of aspartame we employed (0–3000 mg/kg) and the relationship of these doses to aspartame intake in humans (Koch and Wenz, 1984) is described in detail by Dailey et al. (1989b).

Seizures

Supramaximal electroshock was used to induce seizures throughout the present study. Three factors prompted us to choose this particular seizure producing stimulus. First, non-epileptic controls, GEPR-3s and GEPR-9s are each susceptible to seizures produced by this stimulus. As a result, the effects of aspartame could be assessed in all three types of animals. Second,

pharmacologically-induced changes in noradrenergic and serotonergic activity cause reciprocal alterations in the magnitude of the convulsive responses to supramaximal electroshock (Browning, 1987). Third, the severity of the responses to supramaximal electroshock is amenable to precise quantitative assessment (Swinyard, 1972).

Seizures were induced using a supramaximal current of 150 mA administered for 0.2 seconds via ear clip electrodes (Swinyard, 1972). This stimulus was obtained from a constant current electroshock seizure apparatus (ME-5300: Metro Scientific, Incorporated, Farmingdale, N.Y.). The stimulus parameters employed were selected to produce tonic convulsions, commonly referred to as "full tonic extensor seizures." More descriptively, the overt motor manifestations of these seizures are characterized by ventriflexion of the neck and trunk, tonic flexion of the shoulder joint and tonic extension of the elbow, hip, knee, talocrural and phalangeal joints. In some rats, tonic extension of the joints of the pelvic limbs does not occur despite the use of a supramaximal stimulus. Initially, these partial responders exhibit the same convulsive movements as do the complete responders in that the electrical stimulus causes the pelvic limbs to be drawn into bilateral tonic flexion. A partial response becomes evident as tonic flexion fails to progress into tonic extension.

Convulsive severity was assessed by determining the ratio between the duration of tonic hindlimb extension and flexion. A high ratio is indicative of seizure facilitation, whereas a low ratio is indicative of seizure suppression (Swinyard, 1972). The durations of extension and flexion were obtained by simultaneously recording each stimulus, subsequent convulsion and the passage of time, in tenths of seconds, on video tape. With this technique, play-back through a monitor provided simultaneous display of the convulsive movements and the elapsed time from the stimulus. Combining this approach with an infinitely variable controller for increasing, decreasing or stopping frame advancement, enabled us to determine accurately the duration of tonic flexion and extension. Our experiments were designed so that the person responsible for reading and noting the elapsed times during the play-back procedure was unaware of whether the animals were treated with vehicle or aspartame.

Each day of an experiment, the electroshock stimulus was administered between 9:00 and 12:00 noon. These time constraints were utilized to minimize any diurnal factors that might influence seizure responses.

Amino acid assays

We determined plasma concentrations of selected amino acids as a means of verifying the dietary consequences of aspartame administration. The aspartame moiety itself is not absorbed intact after oral administration (Ranney et al., 1976). Rather, it is rapidly hydrolyzed to phenylalanine, aspartic acid and methanol, whereupon these compounds enter the blood. Once absorbed, phenylalanine may be converted via hydroxylation to tyrosine.

In the event that aspartame might fail to produce effects on electroshock seizures, we believed that it would be important to have independent verification that our doses of the sweetener had actually been delivered and absorbed into the blood. Plasma amino acid measurements were used to obtain this information.

The relative amounts of phenylalanine, tyrosine and tryptophan were determined in our experiments as described by previous investigators (Fernstrom, 1983). We also calculated transport ratios, namely, the ratio of the plasma concentration for each of these three specific large neutral amino acids (LNAA) divided by the sum of the remaining LNAAs. These ratios serve as predictors of the competitive effect of other LNAAs on the brain uptake of the specific amino acid in the numerator. Determination of these transport ratios required that we measure not only the plasma concentrations of the amino acids involved in monoamine neurotransmitter synthesis, but also those of the other large neutral amino acids commonly found in plasma; namely, valine, methionine, isoleucine and leucine.

Procedurally, trunk blood samples were obtained from rats sacrificed by decapitation 1 hour after gavage with aspartame or vehicle. The samples were collected between 9:00

A.M. and 12:00 noon. Immediately following collection in heparinized tubes, the blood was cooled and centrifuged to separate the cells from the plasma. After collection and before amino acid analysis, the plasma was maintained at −70°C. For analysis, the plasma was thawed, ultrafiltered (to remove protein) and the resultant free amino acid containing ultrafiltrate derivatized with phenylisothiocyanate (PITC). Subsequent quantitative determinations were made on a Water's Pico Tag Amino Acid Analysis System (Bidlingmeyer et al., 1984). Samples from vehicle and aspartame treated rats were processed in an interdigitated manner so as to avoid any systematic error that might be introduced by analytical variation.

Experimental design

Three experiments were undertaken: *Experiment 1*, a study in which the doses of aspartame ranged from 0 to 1000 mg/kg; *Experiment 2*, a study of 2000 mg/kg of aspartame versus 0 mg/kg; and *Experiment 3*, a study in which the doses of aspartame ranged from 0 to 3000 mg/kg.

In addition to differences in the doses of aspartame used, these three studies also diverged in other ways. The desired mg/kg dose of aspartame was administered in an injection volume of 2 ml/kg in Experiment 1, 4 ml/kg in Experiment 2 and 10 ml/kg in Experiment 3. The change from 2 ml/kg to 4 ml/kg was made to facilitate injection of the 2000 mg/kg dose by producing a less viscous mixture. The 10 ml/kg volume was used to accommodate the larger 2000–3000 mg/kg doses and to hasten stomach emptying. Comparisons were made only within experiments and it was not our purpose to test the effect of different injection volumes.

The experiments also differed in terms of the design for experimental processing of aspartame doses and/or animal types. In Experiments 1 and 3, animals were treated so that the vehicle and the different doses of aspartame would be completely interdigitated sequentially with regard to time within a given animal type. According to this design, animals were processed in repetitive cycles consisting of 1 to 2 vehicle treatments followed immediately by 1 to 2 treatments with each dose of aspartame. A sufficient number of cycles were employed so that a desired number of animals entered the vehicle and treatment groups. This design allows decisions as to whether the different doses of aspartame caused changes in seizure endpoints or in plasma amino acid concentrations and/or ratios in any of the three types of animals studied. However, it does not provide the optimal means for determining whether responses of non-epileptic controls, GEPR-3s or GEPR-9s differ from each other.

Experiment 2 differed from Experiments 1 and 3 in that it was characterized by a more complete interdigitated design in which sequential processing of all vehicle treatments, aspartame doses and animal types was utilized. Thus, Experiment 2 provides a means for determining whether non-epileptic controls, GEPR-3s and GEPR-9s differ in their responses to supramaximal electroshock.

As an additional point relative to experimental design, the animals used for each of the three experiments were different animals so that none of the subjects used in one experiment were used for either of the other two and any given animal received only one dose of aspartame. Yet, within any particular experiment, the various analyses were obtained using the same pool of animals throughout that particular experiment. Accordingly, in Experiment 1 the pool of test subjects used for determining extension/flexion ratios was the same pool used to determine plasma amino acid concentrations and ratios. Similarly, the animal pool used for any one measurement in Experiment 3 was the same pool used for any of the other measurements in that experiment. In Experiment 2, a comparative analysis of amino acids was not undertaken. Consequently, the pool of animals for this experiment was used only for ascertaining extension/flexion ratios.

Data from any one of the vehicle-treated control groups used in our three experiments were compared statistically only to the responses of aspartame-treated subjects from the same experiment. This restriction was imposed because previous experience in our laboratory has shown that extension/flexion ratios obtained from different pools of the same strain

or colony of rats may differ across experiments over several months. Such variations in electroshock seizure severity have also been noted by other investigators (Ronald A. Browning, personal communications). Consequently, we concluded that treatment-data must be compared only with vehicle data when both are obtained from animals drawn randomly from a common pool and processed temporally in an interdigitated fashion. Failure to integrate this principle into work with maximal electroshock seizures would breach the fundamental tenants of experimental design.

Despite the fact that each experiment utilized its own pool of experimental subjects, the sample sizes were not in every instance identical for one part of an experiment as compared to the other parts of that same experiment. For example, in some instances within a given experiment and dose of aspartame, the sample size for the amino acid ratios was smaller than the smallest sample size for the amino acid concentrations. This occurred since in order for a valid ratio (calculated as [AA]/[LNAA]) for a specific animal to be calculated, all of the large neutral amino acids in the denominator and numerator must be present.

Statistical Analyses

The effects of aspartame on mean extension/flexion ratios and amino acid concentrations were statistically treated using Analysis of Variance with a posthoc Scheffe procedure for multiple dose experiments and the *t*-test for single dose experiments. The quantitative relationship between aspartame dose and amino acid concentrations was determined by calculation of the Pearson's R correlation coefficient. The relation between plasma amino acid concentrations and extension/flexion ratios was determined by comparison of individual values. This approach was used as a way to obviate some of the potential distortions in mean values and standard errors that might have arisen from experimental variables other than the predetermined aspartame doses. For example, influences that might have occurred if an animal received a partial dose of aspartame or if a given animal absorbed amino acids at a rate different from that of another experimental subject in the same group would be precluded.

Results

The effects of aspartame on extension/flexion ratios are set forth in Table 1. Regardless of dose, no statistically significant changes occurred in these ratios in response to aspartame treatment either in non-epileptic controls or in GEPR-3s or GEPR-9s.

Table 1 also documents the differences between extension/flexion ratios that exist between non-epileptic controls, GEPR-3s and GEPR-9s. Experiment 2 which was specifically designed to test for differences between the responses of these three types of animals shows that the ratios were higher in GEPR-3s than in non-epileptic controls and that the highest ratios were found in GEPR-9s. Experiments 1 and 3 show qualitatively these same relationships.

The effects of aspartame on mean amino acid concentrations in plasma are shown in Tables 2–4. Both phenylalanine and tyrosine concentrations rose in response to aspartame administration. At the highest dose of aspartame (3000 mg/kg), phenylalanine concentrations were 732%, 580% and 813% of the corresponding vehicle value for nonepileptic control rats, GEPR-3s and GEPR-9s, respectively. The analogous tyrosine values were between 400% and 500%.

Small, statistically significant decrements in plasma valine, methionine, isoleucine and leucine occurred at the 2500 and 3000 mg/kg doses of aspartame. Significant alterations in mean tryptophan levels were not detected at any dose of aspartame used.

Table 1. Effects of aspartame on mean extension/flexion ratios in non-epileptic and epileptic rats[a]

Experiment	Aspartame Dose (mg/kg)	Extension Flexion Ratios Mean ± SEM with N in Parentheses		
		Non-Epileptic	GEPR-3	GEPR-9
1	0	1.53 (5) ±0.59	3.90 (7) ±0.35	32.98 (9) ±3.78
	50	1.28 (7) ±0.24	3.48 (9) ±0.25	35.76 (10) ±4.23
	100	2.29 (7) ±0.96	4.21 (10) ±0.28	34.62 (10) ±3.30
	250	1.78 (2) ±1.04	3.82 (9) ±0.35	27.70 (10) ±2.87
	500	1.48 (7) ±0.24	4.20 (8) ±0.21	30.50 (10) ±2.37
	1000	1.75 (6) ±0.44	4.60 (9) ±0.51	29.00 (10) ±1.87
2	0	1.58 (9) ±0.31	3.20 (9) ±0.26	31.42 (8) ±1.59
	2000	1.98 (9) ±0.40	4.49 (9) ±0.31	30.46 (10) ±2.14
3	0	2.62 (8) ±0.60	3.86 (14) ±0.30	37.27 (11) ±4.56
	2000	3.64 (10) ±0.63	4.27 (11) ±0.43	38.21 (14) ±3.24
	2500	3.45 (12) ±0.54	4.89 (12) ±0.43	33.03 (12) ±2.41
	3000	3.30 (10) ±0.63	4.50 (12) ±0.30	37.45 (13) ±3.34

[a] Extension/flexion ratios were determined 1 hour after vehicle or aspartamed gavage. Numbers of animals that exhibited tonic extension are indicate in parentheses. Doses from 50 to 1000 mg/kg were in 2 ml of vehicle. The 2000 mg/kg dose was in 4 ml of vehicle. Doses from 0 to 3000 mg/kg were in 10 ml of vehicle. Statistical comparisons (Analysis of Variance with a *post hoc* Scheffe procedure for multiple dose experiments and the *t*-test for the single dose study) were made with the appropriate vehicle control. No statistically significant differences were found between vehicle and aspartame-treated groups. However, in all instances, the ratios for GEPR-3s and GEPR-9s were greater than the corresponding ratios for non-epileptic controls. Similarly, the GEPR-9 ratios were significantly greater than the corresponding GEPR-3 values.

The effects of aspartame on mean transport ratios for the large neutral amino acids are shown in Tables 5–7. With the higher doses of aspartame, statistically significant increases occurred in the transport ratios for tyrosine and phenylalanine in nonepileptic rats, GEPR-3s and GEPR-9s. In contrast, significant decrements in the transport ratios for tryptophan were observed in all three types of animals.

Table 2. Effects of aspartame on mean amino acid concentrations in plasma of non-epileptic control rats[a]

Experiment	Aspartame Dose (mg/kg)	Plasma amino acid concentrations Mean in nmol/ml ± SEM with N in parentheses						
		Valine	Methionine	Isoleucine	Leucine	Tryptophan	Phenylalanine	Tyrosine
1	0	180.87 (7) ±7.22	63.47 (7) ±3.18	95.39 (6) ±4.99	111.60 (7) ±4.13	129.55 (7) ±8.59	74.33 (7) ±2.67	82.52 (7) ±2.44
	50	172.17 (7) ±7.83	60.85 (7) ±3.08	94.95 (7) ±5.05	110.32 (7) ±5.33	121.26 (7) ±6.12	88.61 (7) ±4.23	101.76 (7) ±4.58
	100	167.76 (7) ±4.34	63.16 (7) ±3.20	89.09 (7) ±2.28	106.17 (7) ±4.24	108.99 (7) ±5.99	106.31 (7) ±8.13	139.21 (7) ±5.37
	250	158.65 (7) ±8.19	59.28 (7) ±1.76	84.01 (7) ±4.83	98.70 (7) ±5.75	109.31 (7) ±6.66	145.81 (7) ±6.15	189.85 (7) ±18.48
	500	155.47 (7) ±2.98	57.68 (7) ±1.32	81.83 (7) ±1.73	92.14 (7) ±2.56	113.38 (7) ±10.80	191.82 (7) ±7.66	321.60[cd] (7) ±32.73
	1000	148.36 (6) ±8.31	51.61 (6) ±2.13	77.44 (6) ±5.19	86.53 (6) ±5.27	113.00 (6) ±17.02	533.96[b–f] (6) ±170.38	407.75[c–e] (6) ±69.40
3	0	201.32 (8) ±5.16	74.21 (6) ±4.72	107.74 (7) ±2.99	137.29 (8) ±5.05	134.98 (7) ±11.19	90.52 (8) ±3.21	88.23 (8) ±4.23
	2000	201.34 (8) ±5.54	65.88 (7) ±1.21	104.72 (8) ±3.31	122.50 (8) ±4.96	138.04 (7) ±8.51	613.45[b] (7) ±47.21	429.78[b] (8) ±13.42
	2500	182.70 (8) ±5.72	57.63[b] (8) ±2.34	91.79[b] (8) ±3.73	103.36[b] (8) ±4.98	120.61 (8) ±7.79	628.09[b] (7) ±29.03	417.36[b] (8) ±18.83
	3000	193.97 (8) ±7.18	61.42[b] (7) ±2.50	97.07 (8) ±4.04	110.15[b] (8) ±4.51	126.58 (8) ±5.66	662.52[b] (8) ±35.06	398.28[b] (8) ±14.82

[a] Animals were subjected to supramaximal electroshock (150 mA; 0.2 sec), observed and then immediately sacrificed 1 h after aspartame or vehicle gavage; [b] Indicates significant difference ($p < 0.05$; Scheffe) from zero dose mean; [c] Indicates significant difference ($p < 0.05$; Scheffe) from 50 mg/kg dose mean; [d] Indicates significant difference ($p < 0.05$; Scheffe) from 100 mg/kg dose mean; [e] Indicates significant difference ($p < 0.05$; Scheffe) from 250 mg/kg dose mean; [f] Indicates significant difference ($p < 0.05$; Scheffe) from 500 mg/kg dose mean.

Table 3. Effects of aspartame on amino acid concentrations in plasma of moderate seizure genetically epilepsy-prone rats[a] (GEPR-3s)

Experiment	Aspartame Dose (mg/kg)	Plasma amino acid concentrations Mean in nmol/ml ± SEM with N in parentheses						
		Valine	Methionine	Isoleucine	Leucine	Tryptophan	Phenylalanine	Tyrosine
1	0	173.41 (7) ±10.74	47.40 (7) ±1.75	96.13 (7) ±6.66	114.92 (7) ±8.49	84.55 (7) ±7.27	76.95 (7) ±5.50	75.28 (7) ±2.88
	50	165.78 (7) ±8.74	46.29 (7) ±1.33	92.88 (7) ±5.05	112.40 (7) ±5.71	79.29 (7) ±6.95	81.18 (7) ±2.50	101.0 (7) ±6.78
	100	172.07 (7) ±11.23	49.18 (7) ±1.41	92.53 (7) ±6.80	110.56 (7) ±8.64	86.37 (7) ±6.66	90.60 (7) ±3.79	123.41 (7) ±12.32
	250	163.00 (7) ±6.56	45.91 (7) ±1.73	88.72 (7) ±4.28	102.58 (7) ±5.46	86.85 (7) ±6.65	125.33 (7) ±7.92	219.0 (7) ±25.23
	500	155.26 (7) ±7.62	43.88 (7) ±2.29	84.29 (7) ±5.61	97.01 (7) ±7.11	76.46 (7) ±5.35	150.89 (7) ±13.12	282.05[bc] (7) ±36.89
	1000	168.33 (7) ±11.37	46.87 (6) ±2.68	90.79 (7) ±5.19	104.84 (7) ±6.11	78.92 (7) ±3.10	301.98 (7) ±50.40	494.77[b–f] (7) ±39.32
3	0	179.00 (7) ±4.55	55.17 (6) ±2.27	94.29 (7) ±3.38	121.98 (7) ±2.77	98.08 (7) ±6.94	90.21 (7) ±2.99	89.09 (7) ±4.00
	2000	164.30 (7) ±4.28	47.37 (7) ±2.66	89.17 (7) ±2.13	99.90 (7) ±4.00	105.36 (7) ±3.86	484.14[b] (6) ±15.11	419.77[b] (7) ±15.00
	2500	167.62 (7) ±5.33	48.61 (8) ±2.68	83.67 (7) ±3.44	92.22[b] (7) ±4.85	103.20 (7) ±6.73	560.52[b] (8) ±38.62	419.83[b] (8) ±12.01
	3000	154.20[b] (7) ±2.93	49.06 (8) ±2.77	81.08[b] (7) ±2.35	97.19[b] (8) ±7.52	95.16 (7) ±6.53	523.59[b] (6) ±33.18	438.17[b] (8) ±8.67

[a] Animals were subjected to supramaximal electroshock (150 mA; 0.2 sec), observed and then immediately sacrificed 1 h after aspartame or vehicle gavage; [b] Indicates significant difference ($p < 0.05$; Scheffe) from zero dose mean; [c] Indicates significant difference ($p < 0.05$; Scheffe) from 50 mg/kg dose mean; [d] Indicates significant difference ($p < 0.05$; Scheffe) from 100 mg/kg dose mean, [e] Indicates significant difference ($p < 0.05$; Scheffe) from 250 mg/kg dose mean; [f] Indicates significant difference ($p < 0.05$; Scheffe) from 500 mg/kg dose mean.

Table 4. Effects of aspartame on mean amino acid concentrations in plasma of severe seizure genetically epilepsy-prone rats (GEPR-9s)[a]

Experiment	Aspartame Dose (mg/kg)	Plasma amino acid concentrations Mean in nmol/ml ± SEM with N in parentheses						
		Valine	Methionine	Isoleucine	Leucine	Tryptophan	Phenylalanine	Tyrosine
1	0	143.11 (7) ±13.23	45.80 (7) ±2.41	72.69 (7) ±8.86	87.49 (7) ±12.18	110.97 (7) ±8.84	68.10 (7) ±5.34	72.30 (7) ±3.42
	50	143.04 (7) ±7.69	54.68 (7) ±3.31	71.69 (7) ±4.55	85.63 (7) ±5.90	124.45 (7) ±8.59	74.36 (7) ±2.77	84.87 (7) ±6.09
	100	138.52 (7) ±5.88	54.95 (7) ±4.32	67.55 (7) ±3.43	81.32 (7) ±4.45	118.70 (7) ±4.12	77.61 (7) ±4.59	95.63 (7) ±5.80
	250	127.81 (6) ±5.02	50.19 (6) ±3.65	63.07 (6) ±3.77	73.59 (6) ±5.17	118.84 (6) ±5.79	88.75 (6) ±4.53	138.96 (6) ±10.73
	500	141.08 (7) ±14.46	50.29 (7) ±4.82	71.46 (7) ±9.27	85.12 (7) ±11.64	124.26 (7) ±5.15	102.50 (7) ±8.09	172.08 (7) ±15.02
	1000	137.47 (7) ±9.47	47.71 (7) ±3.82	68.89 (7) ±5.14	79.78 (7) ±7.30	124.19 (7) ±6.60	198.85 (7) ±88.51	205.48 (7) ±35.77
3	0	173.85 (7) ±4.91	53.48 (6) ±3.73	94.18 (8) ±2.20	116.33 (8) ±4.12	124.94 (6) ±5.48	80.29 (8) ±2.39	82.29 (8) ±5.88
	2000	164.51 (7) ±8.47	47.44 (6) ±3.05	83.52 (6) ±4.00	101.67 (7) ±5.80	125.81 (6) ±7.38	678.69[b] (6) ±34.85	296.90[b] (7) ±29.98
	2500	155.73 (8) ±2.36	48.69 (8) ±2.16	84.38 (8) ±2.23	93.60[b] (8) ±2.46	129.52 (8) ±6.04	688.53[b] (7) ±40.19	281.46[b] (8) ±29.90
	3000	155.42 (7) ±5.19	46.07 (7) ±2.99	84.02 (7) ±4.15	94.89[b] (7) ±4.27	117.65 (7) ±5.51	652.74[b] (7) ±37.06	329.17[b] (7) ±33.21

[a] Animals were subjected to supramaximal electroshock (150 mA; 0.2 sec), observed and then immediately sacrificed 1 h after aspartame or vehicle gavage; [b] Indicates significant difference ($p < 0.05$; Scheffe) from zero dose mean.

Table 5. Effect of large doses of aspartame on plasma amino acid ratios in non-epileptic control rats[a]

Experiment	Aspartame Dose (mg/kg)	Mean plasma amino acid ratios ± SEM with N in parentheses							
		Tyr/ LNAA	% of 0 Dose Aspartame	Phe/ LNAA	% of 0 Dose Aspartame	Phe/ Tyr	% of 0 Dose Aspartame	Trp/ LNAA	% of 0 Dose Aspartame
1	0	0.1275 (6) ±0.0018	100	0.1116 (6) ±0.0020	100	0.9005 (7) ±0.0168	100	0.2134 (6) ±0.0122	100
	50	0.1585 (7) ±0.0089	124	0.1346 (7) ±0.0063	118	0.8774 (7) ±0.0443	97	0.1927 (7) ±0.0062	90
	100	0.2174 (7) ±0.0062	170	0.1569 (7) ±0.0096	137	0.7628 (7) ±0.0504	85	0.1618 (7) ±0.0061	76
	250	0.2894 (7) ±0.0263	226	0.2111 (7) ±0.0128	185	0.8114 (7) ±0.0853	90	0.1482[b] (7) ±0.0053	69
	500	0.4649[b–d] (7) ±0.0447	363	0.2355 (7) ±0.0111	206	0.6324 (7) ±0.0626	70	0.1257[bc] (7) ±0.0107	59
	1000	0.4127[b–d] (6) ±0.0350	322	0.5510[b–f] (6) ±0.1220	482	1.1736[f] (6) ±0.1906	130	0.0920[b–e] (6) ±0.0129	43
3	0	0.1233 (5) ±0.0049	100	0.1187 (5) ±0.0020	100	1.0356 (8) ±0.0386	100	0.1923 (5) ±0.0161	100
	2000	0.3484[b] (5) ±0.0264	283	0.5841[b] (5) ±0.0537	492	1.4344 (7) ±0.1301	139	0.0889[b] (5) ±.0072	46
	2500	0.3576[b] (7) ±0.0235	290	0.6573[b] (7) ±0.0320	554	1.5450[b] (7) ±0.1261	149	0.0799[b] (7) ±0.0048	42
	3000	0.3187[b] (7) ±0.0179	258	0.6854[b] (7) ±0.0403	577	1.6823[b] (8) ±0.1157	162	0.0822[b] (7) ±0.0055	43

[a] Animals were subjected to supramaximal electroshock (150 mA; 0.2 sec), observed and then immediately sacrified 1 h after aspartame or vehicle gavage; [b] Indicates significant difference ($p < 0.05$; Scheffe) from zero dose mean; [c] Indicates significant difference ($p < 0.05$; Scheffe) from 50 mg/kg dose mean; [d] Indicates significant difference ($p < 0.05$; Scheffe) from 100 mg/kg dose mean; [e] Indicates significant difference ($p < 0.05$; Scheffe) from 250 mg/kg dose mean; [f] Indicates significant difference ($p < 0.05$; Scheffe) from 500 mg/kg dose mean.

Table 6. Effect of large doses of aspartame on plasma amino acid ratios in moderate seizure genetically epilepsy-prone rats[a] (GEPR-3s)

Experiment	Aspartame Dose (mg/kg)	Mean plasma amino acid ratios ± SEM with N in parentheses							
		Tyr/ LNAA	% of 0 Dose Aspartame	Phe/ LNAA	% of 0 Dose Aspartame	Phe/ Tyr	% of 0 Dose Aspartame	Trp/ LNAA	% of 0 Dose Aspartame
1	0	0.1292 (7) ±0.0074	100	0.1303 (7) ±0.0052	100	1.0225 (7) ±0.0623	100	0.1443 (7) ±0.0081	100
	50	0.1743 (7) ±0.0056	135	0.1371 (7) ±0.0047	105	0.8173 (7) 0.0384	80	0.1312 (7) ±0.0067	91
	100	0.2030 (7) ±0.0091	157	0.1454 (7) ±0.0082	112	0.7598 (7) ±0.0489	74	0.1352 (7) ±0.0060	94
	250	0.3566 (7) ±0.0358	276	0.1791 (7) ±0.0119	137	0.6102 (7) ±0.0623	60	0.1184 (7) ±0.0109	82
	500	0.4578[b-d] (7) ±0.0405	354	0.2059 (7) ±0.0145	158	0.5621 (7) ±0.0547	55	0.0946[b] (7) ±0.0031	66
	1000	0.6108[b-d] (6) ±0.0623	473	0.3399[b-d] (6) ±0.0762	261	0.6533 (7) 0.1424	64	0.0689[b-d] (6) ±0.0031	48
3	0	0.1415 (6) ±0.0083	100	0.1403 (6) ±0.0068	100	1.0209 (7) ±0.0442	100	0.1530 (6) ±0.0115	100
	2000	0.4317[b] (6) ±0.0202	305	0.5200[b] (6) ±0.0248	371	1.1438 (6) ±0.0651	112	0.0824[b] (6) ±0.0028	54
	2500	0.4148[b] (6) ±0.0118	293	0.5923[b] (6) ±0.0505	422	1.3351[b] (8) ±0.0806	131	0.0742[b] (6) ±0.0062	48
	3000	0.4541[b] (6) ±0.0171	321	0.5462[b] (5) ±0.0296	389	1.1656 (6) 0.0619	114	0.0697[b] (5) ±0.0032	46

[a] Animals were subjected to supramaximal electroshock (150 mA; 0.2 sec), observed and then immediately sacrificed 1 h after aspartame or vehicle gavage; [b] Indicates significant difference ($p < 0.05$; Scheffe) from zero dose mean; [c] Indicates significant difference ($p < 0.05$; Scheffe) from 50 mg/kg dose mean; [d] Indicates significant difference ($p < 0.05$; Scheffe) from 100 mg/kg dose mean.

Table 7. Effect of large doses of aspartame on plasma amino acid ratios in severe seizure genetically epilepsy prone rats[a] (GEPR-9s)

Experiment	Aspartame Dose (mg/kg)	Mean plasma amino acid ratios ± SEM with N in parentheses							
		Tyr/ LNAA	% of 0 Dose Aspartame	Phe/ LNAA	% of 0 Dose Aspartame	Phe/ Tyr	% of 0 Dose Aspartame	Trp/ LNAA	% of 0 Dose Aspartame
1	0	0.1392 (7) ±0.0061	100	0.1335 (7) ±0.0176	100	0.9588 (7) ±0.1038	100	0.2314 (7) ±0.0205	100
	50	0.1527 (7) ±0.0065	107	0.1322 (7) ±0.0036	99	0.8887 (7) ±0.0344	93	0.2457 (7) ±0.0205	106
	100	0.1767 (7) ±0.0053	127	0.1389 (7) ±0.0042	104	0.8124 (7) ±0.0117	85	0.2340 (7) ±0.0151	101
	250	0.2663 (6) ±0.0203	191	0.1547 (6) ±0.0049	116	0.6470 (6) ±0.0290	67	0.2208 (6) ±0.0141	95
	500	0.3019 (7) ±0.0194	217	0.1596 (7) ±0.0030	120	0.6028 (7) ±0.0270	63	0.2082 (7) ±0.0174	90
	1000	0.3375 (7) ±0.0691	242	0.3167 (7) ±0.1522	208	1.0776 (7) ±0.4810	112	0.1806 (7) ±0.0198	78
3	0	0.1335 (6) ±0.0121	100	0.1273 (6) ±0.0034	100	0.9952 (8) ±0.0426	100	0.2075 (6) ±0.0139	100
	2000	0.2637 (4) ±0.0297	198	0.8080[b] (4) ±0.0486	107	2.6277[b] (6) ±0.4033	110	0.0950[b] (4) ±0.0091	86
	2500	0.2298 (7) ±0.0341	172	0.8833[b] (7) ±0.0710	693	2.8735[b] (7) ±0.4671	289	0.0991[b] (7) ±0.0041	48
	3000	0.2906[b] (7) ±0.0345	218	0.8200[b] (7) ±0.0974	644	2.2440 (7) ±0.4432	225	0.0863[b] (7) ±0.0035	42

[a] Animals were subjected to supramaximal electroshock (150 mA; 0.2 sec), observed and then immediately sacrificed 1 h after aspartame or vehicle gavage; [b] Indicates significant difference ($p < 0.05$; Scheffe) from zero dose mean.

A quantitative analysis of two relationships is shown in Table 8: (1) aspartame dose versus amino acid concentrations or transport ratios in plasma; and (2) amino acid concentrations or transport ratios in plasma versus extension/flexion ratios. For non-epileptic controls, GEPR-3s and GEPR-9s, numerous positive and negative, statistically significant correlation coefficients were found for the relationships between aspartame dose and the concentrations (and transport ratios) of phenylalanine and tyrosine.

In general terms, significant correlations between aspartame dose and plasma tryptophan concentrations were not detected in our studies. The significant, negative correlation in the 0 to 2000 mg/kg aspartame dose-effect study in non-epileptic controls was the single exception to the prevailing observations. In contrast, the correlation coefficients for the relationship between tryptophan transport ratios and aspartame dose were all negative and significant at $p < 0.0002$.

Only one significant relationship between plasma amino acid levels and extension/flexion ratios was found. In the 0–2000 mg/kg study, the correlation coefficient for tryptophan concentrations and extension/flexion ratios was equal to -0.401 and significant at $p < 0.0467$ (Table 8).

Discussion

Our current observations indicate that single aspartame doses between 50 and 3000 mg/kg do not facilitate supramaximal electroshock seizures either in non-epileptic control rats or in GEPRs. Despite 3 separate studies using a total of 3 groups of animals treated with vehicle and another 9 treated with aspartame, we detected no dose of this sweetener which caused significant alterations in mean extension/flexion ratios. Also, the linear regression analysis of individual values of extension/flexion ratios and amino acids did not reveal any evidence of aspartame-induced seizure facilitation. Thus, whether derived from a statistical examination of mean values or from a regression analysis using individual values, the conclusion was the same: bolus doses of aspartame are not proconvulsant.

Failure of aspartame to facilitate seizures occurred throughout our current investigations despite the marked increments in plasma phenylalanine and tyrosine concentrations and transport ratios which occurred in response to administration of this sweetener. Absence of a proconvulsant effect also occurred despite aspartame-induced decrements in tryptophan transport ratios.

According to Wurtman et al. (1985), these aspartame-induced increases in transport ratios for phenylalanine and tyrosine as contrasted with the decrements in tryptophan ratios, would be predictive of corresponding changes in the brain concentrations of these amino acids. Although not measured in our current experiments, we have demonstrated in another study that the effects of aspartame on brain phenylalanine, tyrosine and tryptophan largely parallel the transport ratios for these three amino acids both in non-epileptic control rats and in GEPRs (Dailey et al., 1991; Lasley et al., 1988). Thus, transport ratios appear to be indices of the competitive uptake of large neutral amino acids into the brain not only of normal rats but also for non-epileptic controls and for GEPRs.

Table 8. Relationship between aspartame dependent alterations in plasma large neutral amino acids and the propensity to supramaximal electroshock seizures in genetically epilepsy-prone rats (GEPRs) and in non-epileptic controls

Type of animal	Study Aspartame dosage range (mg/kg)	N	Amino acid variable tested for relation to E/F or APM dose	Coefficient of correlation and probability of significance			
				APM	Probability	E/F	Probability
Control	0–2000	25	[Phe]	0.839	<.0001	0.158	0.4509
		25	[Tyr]	0.908	<.0001	0.194	0.3540
		25	[Trp]	−0.513	0.0088	−0.401	0.0467[a]
		25	[Phe]/[LNAA]	0.856	<.0001	0.243	0.2416
		25	[Tyr]/[LNAA]	0.889	<.0001	0.269	0.1938
		25	[Trp]/[LNAA]	−0.929	<.0001	−0.383	0.0589
		25	[Phe]/[Tyr]	−0.076	0.7189	−0.031	0.8837
		25	[Phe]/[Trp]	0.797	<.0001	0.335	0.1016
	0–3000	24	[Phe]	0.787	<.0001	0.293	0.1640
		24	[Tyr]	0.713	0.0001	0.003	0.9896
		24	[Trp]	0.205	0.3372	−0.031	0.8868
		19	[Phe]/[LNAA]	0.850	<.0001	0.280	0.2449
		19	[Tyr]/[LNAA]	0.681	0.0013	−0.067	0.7858
		19	[Trp]/[LNAA]	−0.757	0.0002	−0.264	0.2750
		23	[Phe]/[Tyr]	0.698	0.0002	0.394	0.0624
		21	[Phe]/[Trp]	0.817	<.0001	0.307	0.1760
GEPR-3	0–2000	49	[Phe]	0.708	<.0001	−0.073	0.6192
		49	[Tyr]	0.876	<.0001	−0.146	0.3157
		49	[Trp]	−0.274	0.0566	−0.075	0.6063
		49	[Phe]/[LNAA]	0.712	<.0001	−0.025	0.8627
		49	[Tyr]/[LNAA]	0.896	<.0001	−0.107	0.4664
		49	[Trp]/[LNAA]	−0.868	<.0001	0.087	0.5539
		49	[Phe]/[Tyr]	0.279	0.0523	−0.065	0.6551
		49	[Phe]/[Trp]	0.688	<.0001	−0.044	0.7658
	0–3000	27	[Phe]	0.469	0.0136	0.158	0.4287
		27	[Tyr]	0.803	<.0001	0.244	0.2188
		27	[Trp]	−0.253	0.1987	0.192	0.3376
		20	[Phe]/[LNAA]	0.729	0.0003	0.320	0.1690
		20	[Tyr]/[LNAA]	0.817	<.0001	0.329	0.1566
		20	[Trp]/[LNAA]	−0.783	<.0001	−0.235	0.3189
		24	[Phe]/[Tyr]	0.313	0.1360	0.238	0.2620
		22	[Phe]/[Trp]	0.786	<.0001	0.170	0.4495
GEPR-9	0–2000	48	[Phe]	0.555	<.0001	−0.121	0.4115
		48	[Tyr]	0.712	<.0001	−0.139	0.3450
		48	[Trp]	−0.021	0.8860	−0.081	0.5837
		48	[Phe]/[LNAA]	0.528	0.0001	−0.110	0.4570
		48	[Tyr]/[LNAA]	0.476	0.0006	−0.129	0.3838
		48	[Trp]/[LNAA]	−0.691	<.0001	−0.002	0.9882
		48	[Phe]/[Tyr]	−0.017	0.9094	−0.034	0.8188
		48	[Phe]/[Trp]	0.565	<.0001	−0.123	0.4049
	0–3000	28	[Phe]	0.655	0.0002	−0.007	0.9700
		28	[Tyr]	0.695	<.0001	0.176	0.3695
		28	[Trp]	0.283	0.1450	−0.025	0.8980
		22	[Phe]/[LNAA]	0.701	0.0003	0.033	0.8834
		22	[Try]/[LNAA]	0.567	0.0060	0.203	0.3658
		22	[Trp]/[LNAA]	−0.780	<.0001	−0.197	0.3807
		26	[Phe]/[Tyr]	0.403	0.0413	−0.221	0.2789
		23	[Phe]/[Trp]	0.741	0.0001	0.174	0.4625

[a] This single significant correlation pertaining to E/F ratios is inconclusive and may be attributed to variation in the random sampling process. Such a correlation does not exist for the other five [Trp]: Extension-Flexion relationships shown.

If plasma transport ratios are predictors of brain amino acid concentrations, should we also anticipate that the ratios would serve as indices of the relevant neurotransmission within the brain? Other investigators have argued in favor of this concept (Pinto and Maher, 1988; Wurtman, 1985). Accordingly, if an increase in plasma phenylalanine ratio causes an increase in brain phenylalanine concentration at the expense of brain tyrosine, we might anticipate that neuronal synthesis of norepinephrine would decrease so that the amount stored would also be diminished. A reduced amount of norepinephrine available for release would possibly result in a decrease in the amount of norepinephrine released into the synapse by an action potential. According to a parallel line of reasoning, decrements in tryptophan transport ratios would lead to decrements in the neuronal release of serotonin.

Interestingly, out of the four brain areas assayed in both GEPR-3s and GEPR-9s in our laboratory, persuasive evidence that aspartame causes either serotonergic or noradrenergic deficits was not forthcoming (Dailey et al., 1991). Contrary to the idea that increases in the phenylalanine ratio would result in noradrenergic deficits, we found either normal or elevated concentrations of norepinephrine in the various brain regions assayed in both GEPR-3s and GEPR-9s. More specifically, norepinephrine concentration deficits were absent despite the aspartame-induced elevation of phenylalanine and tyrosine transport ratios to 820% and 220% of the corresponding values for vehicle treated subjects, respectively. Also, despite our detection of aspartame-induced decrements in plasma tryptophan ratios and brain tryptophan levels, predictable and broadly represented alterations in brain serotonin concentrations did not occur. These observations do not support the concept that aspartame decreases noradrenergic or serotonergic activity in the brain.

Our present experiments showing that single bolus doses of aspartame do not facilitate supramaximal electroshock seizures in non-epileptic control rats, GEPR-3s and GEPR-9s extends our earlier data showing that this sweetener does not facilitate audiogenic seizures in GEPRs (Dailey et al., 1991). The work of Tilson et al. (1989) undertaken with electroshock in neurologically normal rats provides corroborating evidence for our observations made in non-epileptic control rats.

In contrast, as pointed out earlier, several investigators have suggested that aspartame does exert proconvulsant effects. Yet, the very small seizure facilitating effects detected in CD-1 mice treated with the convulsant drug pentylenetetrazol (Pinto and Maher, 1988), were not confirmed in our laboratory even though we used the same type of mice and seizure inducing drug (Dailey et al., 1989b). The proconvulsant effect of aspartame in neurologically normal rats treated with pentylenetetrazol (Guiso et al., 1988) were similarly not confirmed either by our laboratory (Dailey et al., 1988) or that of Tilson et al. (1989). Also, large doses of aspartame have failed to produce detectable facilitation of seizures induced by microinjection of quinolinic acid directly into the hippocampus (Guiso et al., 1988) or of seizures induced by limbic kindling in rats (Tilson et al., 1989). Finally, Meldrum and colleagues (1989) observed that bolus doses of aspartame do not cause proconvulsant effects in genetically epileptic baboons despite sharp increases in plasma phenylalanine concentrations.

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