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## The Effects of Aspartame on Locomotion and Body Weight in Rats

Linda Dianne Dykema Larsen

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THE EFFECTS OF ASPARTAME ON LOCOMOTION  
AND BODY WEIGHT IN RATS

by

Linda Dianne Dykema Larsen

A Thesis  
Submitted to the  
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I would also like to thank my husband and children for their support and patience.

I would like to dedicate this study to my father in gratitude for daring me to succeed.

Linda Dianne Dykema Larsen

THE EFFECTS OF ASPARTAME ON LOCOMOTION  
AND BODY WEIGHT IN RATS

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Western Michigan University, 1985

Nutrients, when ingested in isolation from other food stuffs or in excess, may produce drug-like action on neurotransmitter activity in the CNS. Administration of aspartame exclusively or in combination with d-amphetamine was found to produce weight loss and display of emotionality in rats as measured in an open field apparatus. The possible neurochemical action of aspartame was discussed relative to the well documented stimulatory effects on catecholamines of d-amphetamine and three putative mechanisms were explored: 1) formation of minor amines from the increased precursor pool, 2) increased synthesis of catecholamines in response to the increased precursor pool, and 3) decrease in CNS levels of the putative neuro-inhibitor serotonin due to competitive uptake at the blood-brain barrier.

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## CHAPTER I

### INTRODUCTION

In July of 1981 the United States Food and Drug Administration approved the nutritive sweetener Nutrasweet for use in cold cereals, drink mixes, sugarless gums, instant coffees, teas, geletins, and other dry food stuffs. In July of 1983 this approval was extended to use in carbonated beverages. Nutrasweet is J.D. Searle's name for aspartame which is a compound of dual amino acid composition: phenylalanine and aspartate. Soon after Nutrasweet use became wide spread, reports of undesirable side effects began to surface. Carbohydrate craving and irritability were among the most frequent and severe of these effects. This study was an attempt to assess the impact of the compound aspartame on the body weight and locomotor activity of rats.

In this study dietary intake was held constant in order to assess the impact of aspartame on body weight exclusive of fluctuations in carbohydrate intake. Carbohydrate concentrations in the blood and cerebral spinal fluids may effect the concentration of amino acid precursors in the brain thus altering neurotransmitter levels and the corresponding behaviors such as feeding mechanisms.

The second behavior to be assessed in this study is that of locomotion or exploratory behavior. Typically, when rats are exposed to an open field apparatus they display normal exploratory behavior. Freezing or absence of locomotion accompanied by urination or defecation is sometimes referred to as stereotypy or emotionality (Archer,

1973).

The concept of linking locomotor or exploratory behavior to emotionality in rats is not new (Archer, 1973). Research, however, associating emotionality with levels or activity of brain catecholamines is relatively recent (Morgan, 1982, Olson and Morgan, 1982). Test subjects subjectively scored as exhibiting emotional behavior were found upon histological examination to have consistently elevated levels of norepinephrine when compared to controls. A number of mechanisms through which aspartame may effect brain levels of neurotransmitters may be proposed. Central to all of these is the rise in tyrosine and phenylalanine relative to other precursors in the central nervous system (CNS). Secondary to the elevation of precursors is the change in neurotransmitter concentration which ensures.

It may be postulated that alteration of brain concentrations or balance of neurotransmitters may produce measurable changes in behavior. Chemical agents which are known to produce pharmacological effects in the central nervous system and on corresponding behaviors may therefore be of aid in determining the effects of dietary substances. D-amphetamine was employed in this study in order to elicit increased catecholamine activity in the test subjects. Amphetamine induced increased in release of newly synthesized catecholamines produce corresponding increases in locomotor activity (Seiden and Dykstra, 1977). In addition the affect of amphetamines on amine concentrations has long been employed to stimulate weight loss.

In this study an attempt was made to compare the behavioral effects of d-amphetamine to aspartame ingestion and to assess the

possible effects of the interaction between the two. Two dependent variables were employed; tabulated score of locomotor or exploratory behavior, and the total amount of body weight lost or gained over the ten day dosing period. The addition of the housing variable was an attempt to assess the impact of stress on aspartame ingestion.

## CHAPTER II

### MATERIALS AND METHODS

#### Subjects

Thirty-two male experimentally naive Sprague-Dawley rats served as subjects. Body weights ranged from 220 to 320 grams prior to initiation of the study.

#### Apparatus

Housing consisted of a standard metal cage measuring 22.9 cm by 30.5 cm (696.8 cm<sup>2</sup>). Subjects assigned to the aggregate experimental condition were housed in groups of four. The remainder of subjects were housed singly.

The open field apparatus consisted of a 114.3 cm by 114.3 cm (13064.49 cm<sup>2</sup>) plywood box. A grid divided into thirty-six equal (19.1 cm by 19.1 cm) squares was imposed on the black interior.

The original sides of the box measured 15.0 cm in height, however, in practice the height was raised to at least 91.5 cm on all sides.

#### Procedures

Thirty-two rats were assigned, through the use of a random number table, to eight experimental groups. Each group was exposed to a single or group housing condition and d-amphetamine and/or aspartame

were administered orally by feeding. In the group housed condition four animals were housed in a cage. The experimental conditions are listed in Table 1 for each group.

Table 1

Description of experimental conditions including group number, dosage amounts of aspartame and d-amphetamine in milligrams per kilogram of body weight, and housing condition.

TREATMENT GROUP	ASPARTAME mg/kg	d-AMPHETAMINE mg/kg	HOUSING <sup>a</sup>
I	0.0	0.0	Single
II	0.0	0.0	Aggregate
III	0.0	2.0	Single
IV	0.0	2.0	Aggregate
V	100.0	0.0	Single
VI	100.0	0.0	Aggregate
VII	100.0	2.0	Single
VIII	100.0	2.0	Aggregate

<sup>a</sup>Four rats were housed together under the aggregate condition.

Animals were allowed free access to water and the daily allowance of 20 grams of Purina Laboratory Chow per subject. A twelve hour light-dark cycle was maintained throughout the study.

Subjects were maintained on a controlled diet of twenty grams of rat chow per subject per day. The pellets were pulverized and the resulting powder was adulterated with the appropriate dosage of Equal

sugar substitute and/or d-amphetamine. Each of the subjects received the dosage amounts listed in Table 1 for ten consecutive days.

The rat chow was presented to the rats in metal feeders 8 cm in diameter and 6.5 cm in height which were fitted with metal lids. A circular hole in the lid allowed access to the food.

Subjects were weighed and the baseline data of the open field measure were gathered on day 1 of the study prior to the first drug administration. Weights were again taken and post dosage data was gathered on day ten of the study.

Exposure to the open field apparatus consisted of a five minute period during which the rat was allowed to explore freely. Each subject was placed in the corner square of the grid designated as square #15 at the initiation of the trial. Testing took place in a quiet, but not sound deadened room and the apparatus was cleansed of urine and fecal material between trials. Performance on the locomotor variable was tabulated as follows;

central square traversed - 1 square = 2 points

other square traversed - 1 square = 1 point

fecal material present - bolus = -2 points

urination present = -1 point

A measure of "emotionality" of rats can be derived from the locomotor behavior or exploratory behavior shown by the animals as well as from an index of autonomic activity based upon a count of fecal boli and urine output. Typically animals who are described as presenting "fear" or "anxiety" will freeze (remain immobile) and defecate and/or urinate. In the instance described here we measure the animal's

locomotor activity as well as counting the number of fecal boli and the presence of urine. These scores were combined to yield a measure of emotionality so that the data could be compared with other studies in this area which have used a combination score (Olson and Morgan, 1982).

## CHAPTER III

### RESULTS

#### Locomotor Scores

The locomotor score is the sum of the points awarded for movement within the area of the open apparatus. These data are presented in Figure 1 as a function of conditions. Three way analysis of variance of the locomotor scores revealed a significant omnibus  $F = 28.823$ ,  $p < .001$ .

The main effect of aspartame on locomotion was significant ( $p < .001$ ). Aspartame groups (V through VIII) were found to score much lower on the locomotor variable than either the controls (I and II) or the amphetamine groups (III and IV).

The main effect of d-amphetamine on locomotion was also significant ( $p < .001$ ). This effect was a result of the much higher locomotor scores of groups III and IV which received d-amphetamine but no aspartame.

The effect of the housing variable was not significant ( $p = .494$ ), nor was the interaction of d-amphetamine, aspartame and housing ( $p = .465$ ).

The interaction of d-amphetamine and aspartame was significant ( $p < .001$ ). The simple main effects of the interaction are presented in the first four comparisons of Table 2. Groups which received aspartame were found to score lower on the locomotor variable with or

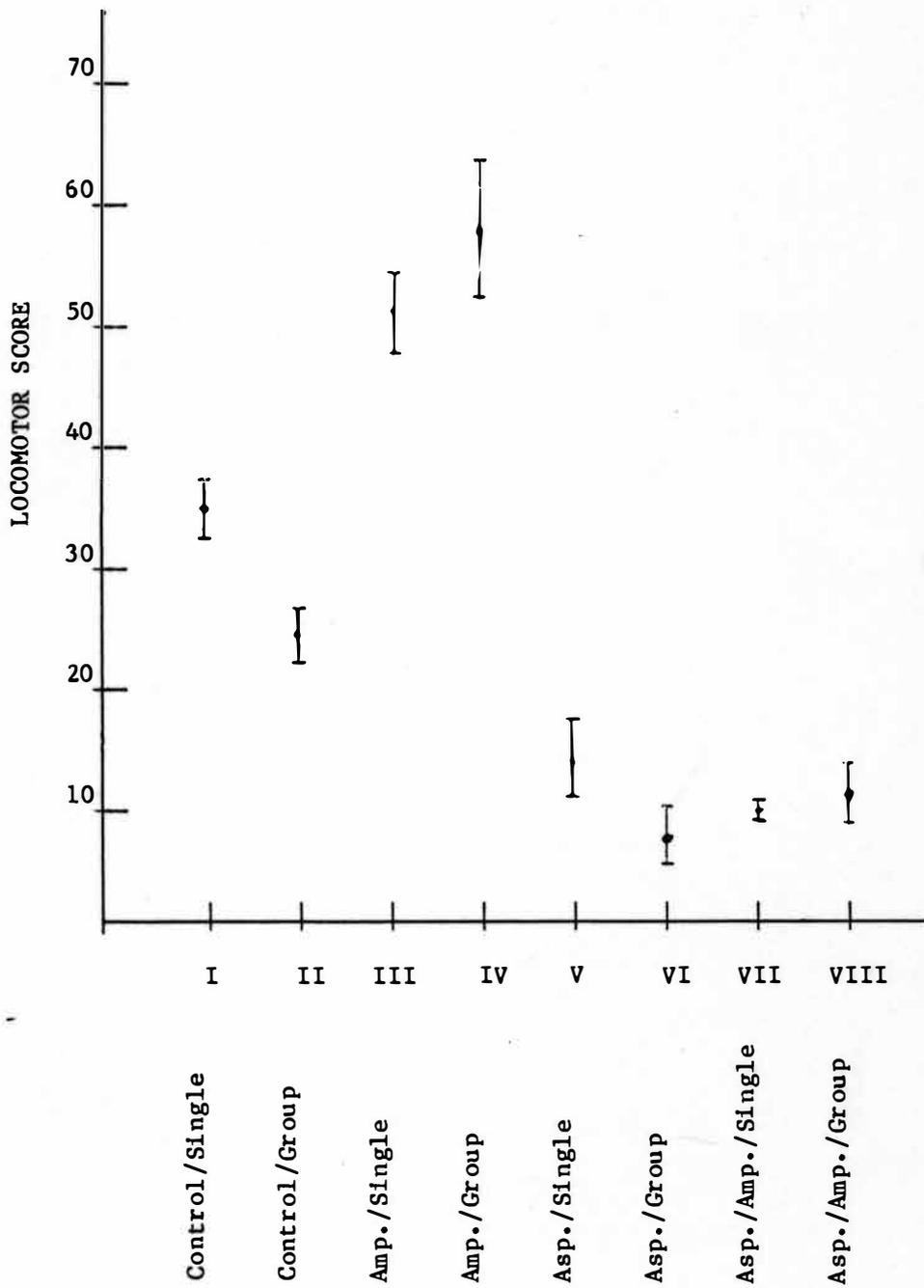


Figure 1. Locomotor Score Means for experimental groups. Bars indicate standard deviations of the means.

Table 2  
Locomotor Scores (Simple Main Effects)

---

Comparison of ASP/No ASP Groups	
No AMP (I & II vs. V & VI)	27.98*
AMP (III & IV vs. VII & VIII)	144.90*
Comparison of AMP/No AMP Groups	
No ASP (I & II vs. III & IV)	46.45*
ASP (V & VI vs. VII & VIII)	0.01
Comparison of AMP/No AMP Groups	
Single (I & II vs. III & VII)	27.27*
Crowded (II & VI vs. IV & VIII)	25.53*
Comparison of Single/Crowded Groups	
No AMP (I & V vs. II & VI)	5.16
AMP (III & VII vs. IV & VIII)	4.42

---

\* Bonferroni F Critical Value = 7.29,  $p = .05$ .

---

Note. Starred values indicate Bonferroni statistics greater than the critical value.

without the administration of d-amphetamine. Differences between groups which received amphetamines (III and IV) and those which did not (I and II) were found only in the absence of aspartame. No difference was found to exist in locomotor scores of groups which received amphetamines (VII and VIII) and those which did not (V and VI) in the presence of aspartame.

The interaction of aspartame and housing was not found to be significant ( $p = .653$ ).

The interaction of amphetamine administration and housing was significant ( $p < .032$ ). The simple main effects of this interaction are presented in the fifth through eighth comparisons of Table 2. Groups which received amphetamines were found to score higher on the locomotor variable under both single and crowded conditions. This effect was probably a result of the higher locomotor scores exhibited by groups III and IV. As expected by the lack of main effect by housing, single and crowded groups were not found to differ on the locomotor variable either with or without d-amphetamine.

#### Weight Gain Scores

The weight gain score was determined as the amount of body weight in grams gained or lost from day one to day ten of the dosing period. These data are presented in Figure 2. as the mean weight loss or gain per group as a function of conditions. Three way analysis of the weight gain scores revealed a significant omnibus  $F = 19.901$ ,  $p < .001$ . These data show a weight loss under all conditions with the exception of the single housed controls (group I). Each of the main effects of aspartame, amphetamine and housing were also significant ( $p < .001$ ). The overall interaction of the three variables, however, was not significant ( $p = .084$ ).

The interaction of aspartame and amphetamine was again found to be significant ( $p < .001$ ). The simple main effects of this interaction are presented in the first four comparisons of Table 3. Groups which

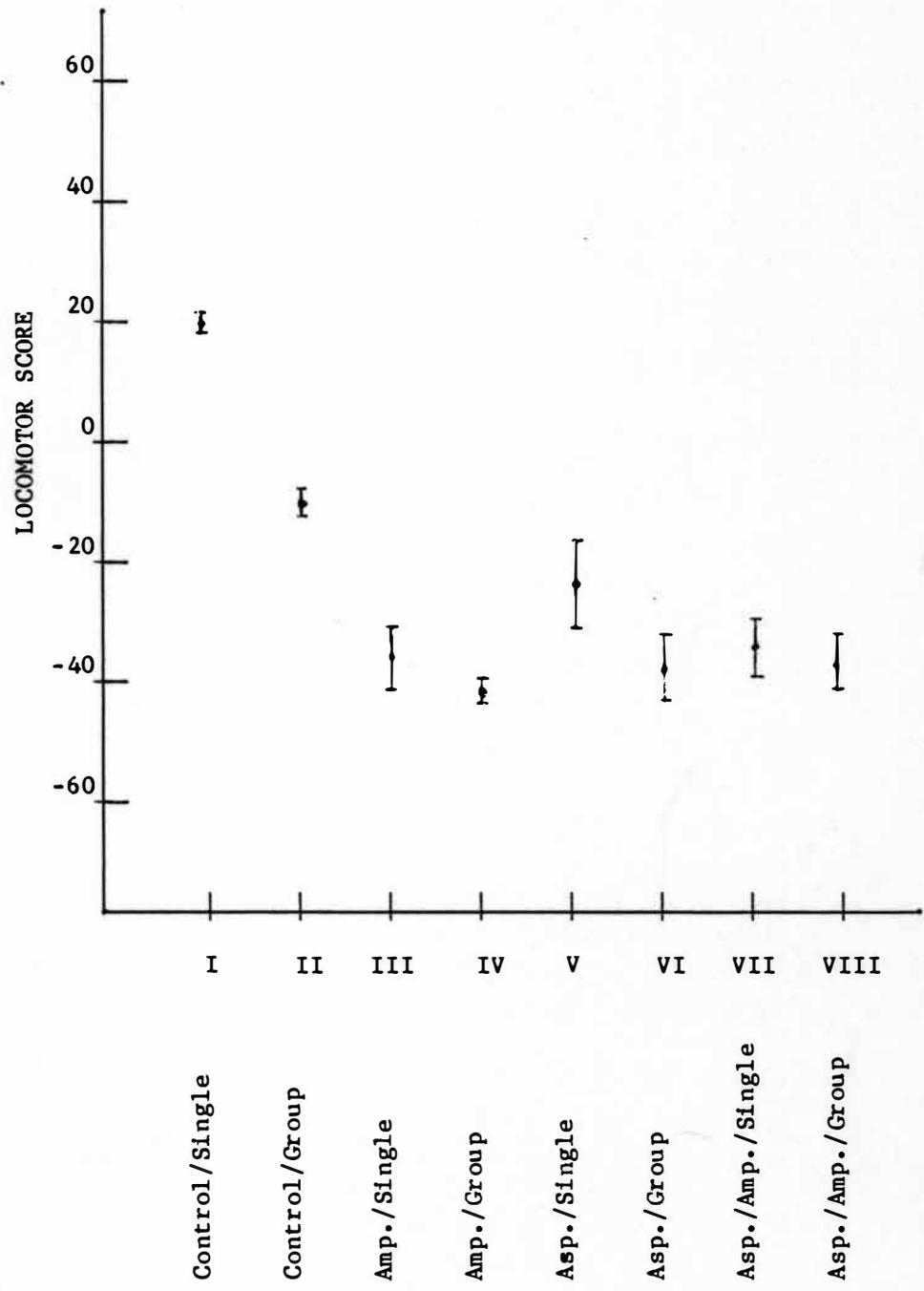


Figure 2. Weight gain means in grams for experimental groups. Bars indicate standard deviations of the means.

Table 3  
Weight Gain Scores (Simple Main Effects)

---

Comparison of ASP/No ASP Groups	
No AMP (I & II vs. V & VI)	54.50*
AMP (III & IV vs. VII & VIII)	5.84
Comparison of AMP/No AMP Groups	
No ASP (I & II vs. III & IV)	88.29*
ASP (V & VI vs. VII & VIII)	0.16
Comparison of AMP/No AMP Groups	
Single (I & II vs. III & VII)	48.72*
Crowded (II & VI vs. IV & VIII)	9.53*
Comparison of Single/Crowded Groups	
No AMP (I & V vs. II & VII)	24.67*
AMP (III & VII vs. IV & VIII)	1.15

---

\* Bonferroni F Critical Value = 7.29,  $p = .05$ .

Note. Starred values indicate Bonferroni statistics greater than the critical value.

received only aspartame (V and VI) lost more weight than controls (I and II). Also groups which received only amphetamine (III and IV) lost more weight than controls (I and II). No difference was found to exist in the amount of weight lost by these groups (III and IV, V and VI) and the amount lost by groups which received both aspartame and amphetamine (VII and VIII).

The interaction of housing and aspartame was not significant ( $p = 0.084$ ).

The interaction of amphetamines and housing was found to be significant ( $p < .011$ ). The simple main effects of this interaction are presented in the fifth through eighth comparisons of Table 3. Groups which received amphetamines lost more weight than those which did not under both single and crowded housing conditions. Groups housed in crowded conditions lost more body weight than those in single housing when no amphetamines were administered. This is a result of the inclusion of group I, which gained weight, in the comparison.

## CHAPTER IV

### DISCUSSION

Rats maintained on an aspartame adulterated diet exhibited less locomotion and lost more body weight than controls. Amphetamine administration in addition to aspartame did not significantly alter the locomotor activity and weight loss for either condition of housing (VII and VIII). Comparison of groups (VII and VIII) which received aspartame with amphetamine and those which received amphetamine alone (III and IV) showed less locomotor activity on the part of the former. No difference was found to exist, however, between groups which received aspartame with amphetamine (VII and VIII) and those which received aspartame alone (V and VI).

The behavior exhibited in the open field apparatus by the controls may be considered normal exploration. The amphetamine groups (III and IV) tended to move more frequently and more rapidly than controls. The aspartame groups (V through VIII) moved less frequently than both the controls and the amphetamine groups. Urination and defecation occurred infrequently for all groups.

In this study single housed control group I gained body weight. All other groups lost weight.

The stress factor of housing did not produce a significant interaction with aspartame for either dependent variable. The significant main effect of housing on weight loss did not appear to be a result of competition for food.

Three major monoamines are norepinephrine (NE), dopamine (DA), and serotonin (5-HT). Compounds which alter the metabolic balance of these substances in the central nervous system (CNS) may produce corresponding changes in behavior. One such substance is d-amphetamine, a known CNS stimulant. Amphetamines induce increases in locomotor activity in a dose-dependent manner. At dosage of 2.0 to 5.0 mg/kg of body weight locomotor activity is increased (Seiden and Dykstra, 1977). Such behavior has been shown to be accompanied by an increase in synthesis and turn over rate of NE and DA in the CNS (Olson and Morgan, 1982). At higher dosages, >5.0 mg/kg, amphetamines induce behaviors defined as stereotypical such as freezing or absence of forward locomotion accompanied by urination or defecation. These behaviors are also associated with heightened neurotransmitter activity in the CNS. The emotional or stereotypical behavior of aspartame fed rats as illustrated by significantly lowered locomotor scores suggests that aspartame may produce an alteration of neurotransmitter balance or activity in the CNS.

There are a number of possible mechanisms through which aspartame may alter the neurotransmitter balance of the CNS. Primary to the consideration of any of these is the role of precursor in the rate of metabolic synthesis. Amino acid precursors of monoamines are transported across the blood-brain barrier by the competitive amino acid transport carrier system. The capillaries of the brain are unlike those in other areas of the body in that they are unfenestrated, therefore inhibiting diffusion of compounds from circulatory fluids. Movement of metabolic substrates between the blood and the

brain is of necessity an active and selective process probably performed by transport systems located in the cerebral endothelial cell.

Movement of metabolic substrates via the transport system is dependent not only on the amount of amino acid in circulation but also on the relative levels of other amino acids. A single carrier molecule transports six large amino acids across the blood-brain barrier: tyrosine, phenylalanine, leucine, isoleucine, valine, and tryptophan. The amino acids compete with one another for attachment and transport by the carrier system (Wurtman, 1982). Ingestion of compounds which contain high levels of a particular amino acid, such as phenylalanine in the case of aspartame, produce corresponding increase in the brain's uptake of that amino acid and a proportional increase in neurotransmitter synthesis (Fernstrom, 1983, Weisburd, 1984).

Tyrosine is the amino acid precursor to the catecholamines, however, phenylalanine is converted to tyrosine in both brain and liver tissues. Following ingestion of large amounts of protein or amino acids, transport of tyrosine and phenylalanine into the brain is facilitated. Initially a rise in the rate of synthesis of NE and DA occurs. The rate limiting step in the synthesis of catecholamines is catalyzed by tyrosine hydroxylase. Research suggests that an interplay exists between substrate control and receptor mediated feedback inhibition of tyrosine hydroxylase activity. A rise in brain levels of NE and DA results in feedback inhibition on enzymatic activity thus limiting further catecholamine synthesis (Pardridge, 1977).

Tyrosine hydroxylase may also have an affinity for phenylalanine and in fact the rate of phenylalanine hydroxylation by tyrosine

hydroxylase in the brain may be as high as that of tyrosine. In addition, increased concentrations of phenylalanine may act to inhibit tyrosine hydroxylase (Pardridge, 1977). It is unlikely, therefore, that aspartame, by elevating serum and brain levels of phenylalanine, produces an actual increase of NE and DA in the CNS.

Tyrosine and phenylalanine may also be metabolized in the CNS through decarboxylation to form the minor amines phenethylamine and tyramine. These minor amines could act as false neurotransmitters producing corresponding alteration in behavior. Aspartame, by elevating the level of phenylalanine in the brain, may therefore produce an effect analogous to that of d-amphetamine. As previously stated the low dose of 2 mg/kg of body weight administered to rats in this study produced an increase in locomotor activity. The absence of forward locomotion observed in the aspartame fed rats may be similar to the stereotyped behavior at high doses of amphetamines (Seiden and Dykstra, 1977). The weight loss observed in aspartame fed rats may be due to an alteration in the balance of neurotransmitters (NE and DA to 5-HT) or as a direct result of the production of false neurotransmitters.

Another consequence of increasing the amino acid precursor pool may be abnormal transmethylation. This reaction may result in the production of hallucinogenic derivatives. Exogenous hallucinogens such as LSD have been found to inhibit neural activity in serotonergic cells of the raphe-nuclei in the midbrain. Raphe cells are primarily occupied in regulation of sleep and basic emotion, both of which may be affected by ingestion of large amounts of aspartame (Thompson,

1975). Disruption of the function of the raphe cells may produce the emotional behavior observed in aspartame fed rats.

A more probable explanation for the effects of aspartame on behavior is direct suppression of 5-HT. As stated earlier, tryptophan competes for transport into the brain via the amino acid transport system, Tryptophan is the amino acid substrate for serotonin production. When serum levels of the other neutral amino acids are elevated, uptake of tryptophan into the brain is blocked. Injection of phenylalanine into adult rats has been found to produce a corresponding depression of brain tryptophan levels. Even larger reduction of brain tryptophan may be produced by a diet containing excess amounts of phenylalanine (Ferstrom, 1983). Serotonin production is substrate limited unlike NE and DA which are enzymatically limited. When the ratio of tryptophan to other amino acids in the blood is altered there is a corresponding alteration of 5-HT synthesis in the CNS (Pardridge, 1977).

Tryptophan is unique among the neutral amino acids in that it is bound to the plasma protein albumin. Thus bound it is essentially immune to the effects of insulin. When a compound such as aspartame is eaten less tryptophan reaches the brain since there is less of it in protein than the other amino acids: tyrosine, phenylalanine, leucine, isoleucine, or valine. In addition, since the ratio of tryptophan to other amino acids is so low the competition at the blood-brain barrier is greater. A carbohydrate rich meal has the opposite effect because the resulting insulin secretion facilitates the uptake of amino acids across the cell membranes in tissues other than the CNS.

The relative plasma level of the albumin bound tryptophan rises allowing more tryptophan to reach the brain.

These mechanisms may be the basis for neuroregulation of protein intake. When rats are allowed free choice of protein diet, total protein consumed was found to be closely correlated with the ratio of serum tryptophan to the sum of all other competing neutral amino acids (Ashley and Anderson, 1975). The clinical observation of excessive carbohydrate intake by human users of aspartame may also be a result of these mechanisms. The carbohydrate "craving" may be a result of the tryptophan starved brains effort to minimize competition at the blood-brain barrier thus allowing more tryptophan to reach the brain. The weight loss observed in this study may be an affect of elevated dietary intake of phenylalanine and the resulting lowered tryptophan and serotonin levels in the CNS.

Decreases of 5-HT levels in the CNS have been associated with a variety of behaviors including sensitivity to heat and shock, increased wakefulness, increased aggressive behavior, and increased susceptibility to seizures. Evidence from clinical reports suggests that the users of aspartame may experience insomnia and irritability or difficulty with interpersonal relationships which may be a result of lowered 5-HT synthesis in areas of the CNS such as the raphe-nuclei. Further investigation of aspartame by histochemical methods may be of use to determine the effect in circumscribed areas of the brain.

Neurotoxicity of a compound may be described as structural or functional. The possibility of depression of 5-HT levels is a functional consideration. Aspartame may also produce structural

abnormalities in the CNS which are irreversible. This issue is of particular importance in view of the wide spread use of aspartame in products aimed at children. The margin of safety for aspartame of 40 mg/kg body weight per day set by the FDA is based upon data collected from mature subjects. This safety margin may be mathematically off a hundred fold for children (Hunter, 1983). In rats, the level of amino acids in the neonatal brain is much higher than in the adult brain. Restriction of movement of intracellular markers does not assume adult levels until approximately three weeks of age suggesting that the blood-brain barrier is immature at birth thus allowing greater influx of blood constituents (Pardridge, 1977). Newborn rats are, however, much less developed when compared to human infants. The period of susceptibility to an increased level of a single amino acid may occur prenatally rather than postnatally in humans.

The increased levels of phenylalanine and aspartate in the immature CNS may lead to irreversible brain damage in children. Aspartate has been implicated, along with glutamate, in the production of lesions in the arcuate nucleus of the hypothalamus when administered to neonatal rats (Hunter, 1983). Lesions of the arcuate nucleus produce a distinct syndrome characterized by obesity, shortness of stature, and genital abnormalities. These symptoms are thought to be a disruption of the normal patterns of release of hormones from the hypothalamus. The critical age and dosage amount required to produce arcuate lesions in humans has not been established, however, until firm data exists such compounds should not be approved for wide spread use in products likely to be consumed in large amounts by children.

The risk of brain damage presented by phenylalanine has been well established by research concerning phenylketonuria (PKU). Products containing aspartame are required by law to provide a warning statement on the package. PKU is a genetic condition in which phenylalanine is not metabolized and serum levels are elevated. The excessive phenylalanine in the brain produces a depression of neurotransmitter levels resulting in lack of formation of neural connections. PKU is a homozygous condition, however, the risk of high intake of phenylalanine for persons heterozygous for PKU has not been established. The mechanism through which excessive phenylalanine acts to produce the profound retardation observed in PKU subjects has been found to be alteration of amino acid transport into the brain resulting in lowered 5-HT synthesis. Phenylalanine may also act in high concentrations to inhibit tryptophan hydroxylase, the enzyme which is utilized in production of 5-HT (Fernstram, 1974).

Further research into the possible effects of aspartame ingestion should use advanced histological and histochemical techniques. In addition, inquires should be made into the safety of the breakdown products of aspartame such as diketopiperazine. The FDA decision seems to have been made on the basis of information provided by the manufacturer. These data were reviewed by the World Health Organization in 1980 and 1981. Unfortunately, no studies involving neonatal animals or prolonged life span periods were included. The FDA approval seems to have been made hastily in response to industry pressure and in the face of conflicting reports of safety.

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