Dietary Phenylalanine and Brain Function

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CHAPTER 20

Aspartame and Human Behavior: Cognitive and Behavioral Observations

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Little is known regarding the possible cognitive and behavioral effects of the artificial sweetener aspartame in humans. Few, if any, studies have addressed the issues raised by the potential elevation of brain phenylalanine levels which may be induced by aspartame ingestion and the concomitant depletion in specific neurotransmitter supplies which may result. In this chapter, the relevant literature addressing this topic is reviewed, the results of a new double-blind, acute study are briefly summarized, and findings from the pilot phase of a new chronic exposure study are reviewed.

Formal reports concerning possible behavioral alterations in association with ingestion of the artificial sweetener aspartame are most notable either for their paucity or for the complete absence of careful measurement either of behavioral changes or cognitive functioning. This is surprising given the potentially powerful effects which aspartame may be capable of producing in human brain. These alterations occur via the intermediary effects of phenylalanine, a large neutral amino acid, on tyrosine and tryptophan, which have been discussed in detail in other chapters of this book. The conclusion to be drawn from the neurobehavioral perspective is that aspartame ingestion may alter neurotransmission as a result of its potential effect on serotonin, dopamine, and norepinephrine. Specific experimental studies have demonstrated that the administration of pure amino acids, like tryptophan or tyrosine, or of foods that change plasma amino acid levels results in behavioral effects in humans such as decreased alertness, altered sleep, depressive mood, and increased aggressivity. Clinically, meanwhile, these neurotransmitters have been shown to be important for the mediation of numerous functions and have been associated with disorders of motor control, of abstraction, of inhibition and problem-solving,

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of sleep, of mood, and, in particular, of depression and may play a role in various psychiatric disorders.

These findings are not particularly surprising considering, for example, that dopaminergic pathways have significant temporolimbic and orbitofrontal projections and that these areas have been independently identified to have important behavioral specializations in the control of emotion, social behavior, arousal, attention, and mental flexibility. Furthermore, these brain regions contain neurons sensitive to other important behavioral neurotransmitters. Given recent findings that a single neuron may respond to as many as three different neurotransmitters, it is possible to conceive of a situation where neuronal populations that react to aspartame may contain cells with overlapping sensitivity, for example, to hormones, which have been shown to be highly represented in these regions, and which clearly can alter behavior.

While metabolic studies have generally indicated that the aspartic acid component of aspartame does not cross the blood-brain barrier, it is important to recognize that aspartate and glutamate are excitatory amino acids. The recent identification of binding sites for these substances, such as the *N*-methyl-D-aspartate (NMDA) receptor, has led to research suggesting that these excitatory amino acids are probably critical to the brain's ability to learn and remember new information. In addition, these excitatory amino acids probably act as neuromodulators by opening slow potential intracellular channels which may, in turn, contribute significantly to the potentiation of excitatory states that result in epilepsy or produce morphological alterations resulting in neuronal loss after cerebral insult. Even though it may be unlikely that aspartame alters aspartic acid levels in normal human brain, this issue has not been adequately addressed, and little is known regarding the possible effect of raising brain concentrations of excitatory amino acids in potentially vulnerable individuals. The influence which such substances may exert on human behavior is obviously substantial, particularly given that the anatomic distribution of NMDA receptors identified by autoradiographic techniques involves most major limbic structures and certain hypothalamic nuclei, linking these substances to hormonal regulation as well. The question, therefore, appears to be not how aspartame might influence human behavior, as the mechanisms for such effects are clearly available, but rather whether it, in fact, does, and what research needs to be done before it can be concluded that it does not.

Before proceeding to consider the literature on aspartame and human behavior, it is worth considering what the structure of an adequate clinical investigation into this question might entail. Precedent certainly exists for such studies, and the literature which has evolved on the relative effects of the various anticonvulsant medications is most instructive. Ideally, such an investigation should begin with some theoretical understanding of the neural mechanisms potentially affected by the substance in question, and a double-blind, placebo-controlled design should be used with administra-

tion of the substance for an equivalent period of time and in a comparable dose to the manner in which it is expected to be consumed when freely available. Plasma levels of the substance should be monitored and cor related with outcome variables which, at the very least, should include specific measures of cognitive functioning administered before, during, and after the trial and independent measures of cognitive functioning, such as school or job performance where available. Additionally, specific measures of mood or psychological state administered at regular intervals, as well as independent blind behavioral observations or ratings of mood or psychological state, and monitoring of the subjective complaints reported by participants should be included in the investigation. No study even approaching this fundamental design has ever been conducted to investigate the relationship between aspartame and human behavior. Studies reported in the late 1970s evaluated plasma concentrations of phenylalanine and aspartate and their relation to various physiological parameters in acute dosing, acute dosing at abuse levels, and chronic dosing with aspartame in apparently healthy children and adults, in young persons during weight reduction, and in certain special populations such as phenylketonurics (see Visek 1984). In the study of apparently healthy children and adults maintained on aspartame for 13 weeks, the only comment and report regarding behavioral factors was that "the subjective complaints which were recorded in biweekly interviews were not clinically important" (Visek 1984, p. 499). In the study of overweight young adults maintained on aspartame for 13 weeks, the participants' subjective complaints were recorded but apparently were not systematically elicited or reviewed, and such factors as sleep and mood were not examined. Furthermore, cognitive functioning was not formally evaluated in any of these studies, nor was any attempt made to ascertain whether subjects experienced any change in their memory or concentration skills. Essentially, these two studies constituted the entire body of human neurobehavioral literature on aspartame prior to its approval by the Food and Drug Administration.

Previously, a study investigating the effects of phenylalanine on learning in nonhuman primates had demonstrated deficits on some of the more difficult tests available for the Wisconsin General Testing Apparatus (WGTA) (Waisman and Harlow 1965). These deficits were not replicated in a later study using the WGTA (Suomi 1984), but in this second paradigm the primates were exposed to phenylalanine only during infancy with a lengthy withdrawal prior to testing, whereas in the original study the animals were maintained on phenylalanine during the actual learning performance evaluations.

Since approval for aspartame was granted, three reports have appeared which provide somewhat more information, while at the same time raising some cautionary signals. The first of these did not actually administer aspartame but examined the effects of elevated plasma phenylalanine on the neuropsychological performance of patients with treated phenylketon-

uria (PKU) (Krause et al. 1985). The literature on the cognitive performance of children who follow phenylalanine-restricted diets has thus far supported a subtle but positive effect of the diet in improving cognitive performance, and it is well known that if this syndrome is untreated in infancy, it can lead to irreversible mental retardation, often accompanied by seizures. Adolescent or early-adult presentations of PKU are rare but typically involve a clinical picture with a prominent psychosis. In brief, this experiment used a double-blind, crossover design in which subjects served as their own control on a battery of repeatable neuropsychological tests selected to evaluate both higher integrative and more fundamental cognitive functions. The most difficult task was a Computerized Forced-Choice Reaction Time procedure which assessed visual-perceptual discrimination. While simpler tests of motor speed and dexterity and of visual-spatial sequencing did not show any effect in relation to dietary manipulation of phenylalanine, slower performance on the Forced-Choice Reaction Time test was correlated with increased phenylalanine plasma levels. The authors also examined urinary dopamine excretion and found that there was a clear inverse correlation between this variable and performance on the Reaction Time test. As urinary dopamine fell, choice reaction time increased; that is, performance worsened.

In a similar attempt to examine the effects of increased plasma phenylalanine levels on the cognitive performance of normal, nonphenylketonuric humans, Lieberman et al. (1987) administered aspartame to normal, healthy, male, young adult volunteers and assessed their performance on a battery of tests shown to be sensitive to the effects of tryptophan and tyrosine, of other food constituents, of caffeine, and of sedative-hypnotic medications. They also had subjects fill out two mood scales and a measure of drowsiness. A double-blind, placebo-controlled, crossover design was used, and aspartame was administered in a single, acute, low or high dose, either alone or in combination with carbohydrates. Carbohydrates depress the levels of other amino acids that usually compete with phenylalanine and therefore potentially facilitate phenylalanine transport across the blood-brain barrier. None of these conditions resulted in any change in the subjects' cognitive performance or mood state, even though plasma phenylalanine levels were clearly elevated by the aspartame.

While the results of this study might be taken to suggest that aspartame ingestion in healthy individuals is likely to produce few acute adverse effects, several issues have still not been addressed. The study was restricted to males, and it is not known whether these findings can be generalized to women. All of the subjects were healthy and were chosen because they reported no known sensitivity to aspartame. Consequently, these results cannot be generalized to an undifferentiated sample of individuals who have no history of exposure to aspartame or who either may have a reported vulnerability to this substance or may be at risk for such a vulnerability given other neurodevelopmental deficits or medical conditions. The

method of administration of the aspartame was via oral capsules which may not parallel the time course for phenylalanine effects when this substance is ingested in foods or beverages. It should also be remembered that this was an acute dosing study, a situation which is unlikely to mimic the consumption pattern for this substance, and it is unclear what the effect of chronic phenylalanine elevation may be following prolonged daily aspartame intake. Finally, while the cognitive measures used here may have been shown to be sensitive to other substances, they may be insufficiently difficult to detect subtle alterations in higher integrative functions and may not require complex perceptual judgments, decision-making or problem-solving skills, or memory at a level at which these functions may be more likely to be impaired.

The third study to investigate any relationship between behavior and aspartame assessed the response of male college students to a single dose of aspartame or phenylalanine (Ryan-Harshman et al. 1987). Cognitive functions were not tested. Using visual analog scales, the subjects rated their "stomach sensations" of emptiness, rumbling, ache, and nausea, their "head sensations" of headache, dizziness, and faintness, and their "general sensations" of feeling drowsy, weak, nervous, tense, drugged, depressed, alert, and mentally slow. There was no effect of either the aspartame or phenylalanine in producing any consistent changes in the subjects' ratings of these "sensations." This study, obviously, is subject to the same criticisms as the preceding one but is further compromised by failing to assess any cognitive functions objectively.

In summary, the experimental investigation of the potential effects of aspartame on human behavior and cognitive functioning remains inconclusive at this time and can perhaps best be characterized as inadequate. Those studies which have failed to show any effect for this substance both used acute exposure to a single dose of aspartame and preselected subjects to avoid individuals who might be more likely to show some vulnerability to aspartame consumption. The study with positive results, meanwhile, was the only study in which there was chronic elevation of blood phenylalanine. However, this study also preselected subjects for an inborn error of metabolism in relation to phenylalanine and did not actually use aspartame as the means for elavating plasma phenylalanine levels. Other studies examining chronic exposure to aspartame in healthy children and adults unfortunately did not systematically collect behavioral or cognitive data. Consequently, the potential effect of aspartame in altering human behavior and cognitive functioning remains entirely unknown at this time. What is perhaps most striking is the lack of investigation of this topic and the outstanding need which exists for a comprehensive study of this problem both in normal individuals and those potentially at risk. While it might be argued that the successful introduction of aspartame into the consumer market without apparent major repercussion may indicate that this substance is safe for human consumption, the absence of proof cannot be taken

TABLE 20.1 Neurobehavioral complaints related to aspartame consumption reported to the Center for Brain Science and Metabolism and the Massachusetts Institute of Technology (CBSM/MIT) and to the Centers for Disease Control (CDC) as reported by Bradstock et al. (1986).

CBSM/MIT	CDC
Headache	Headache
Dizziness	Dizziness
Sleep disturbance	Insomnia
Visual impairment	Visual impairment
Abdominal pain	Abdominal pain
Hyperactivity	Hyperactivity
Light-headed	Nausea
Autonomic symptoms	Fatigue
Blackouts	Numbness
Seizures	Depression
Hallucinations	Anxiety
Memory loss	Irritability
Speech deficit	Altered menses

as proof of absence. Furthermore, a recent report from the Centers for Disease Control (Bradstock et al. 1986), as well as our own experience in collecting information from individuals who have had adverse reactions to this product, suggests that aspartame may have more widespread and diverse effects on human behavior than has heretofore been contemplated. It has been suggested that the variety of symptoms reported by individuals in response to aspartame mitigates against a neurobehavioral effect of this substance because no unitary constellation of symptoms is constant to all complainants. Such a conclusion seems unjustified given the wide range of individual biological variation in response to chemical agents. For example, it could similarly be stated that there is no uniform constellation of symptoms which appears in response to low or even moderate alcohol consumption; however, one would be hard pressed to maintain that alcohol has no neurobehavioral consequences, even in minimal doses. To date, we haviors reported are summarized in Table 20.1. The types of symptoms reported to us are somewhat similar to those reported to other groups, but there is probably a greater representation of seizures in our population. In fact, our interest in the potential relationship between epilepsy, or a lowered seizure threshold, and aspartame consumption led us to design a study to investigate the effects of chronic aspartame exposure on several neurobehavioral parameters. Prior to obtaining approval for a population of complainants with seizure manifestations to go through the protocol, however, the Institutional Review Board of the Massachusetts Institute of

Technology required that we first examine a population of normal subjects. This sample yielded some surprising data which then led us to study another population of normal control subjects. We will present here the preliminary results of these two groups.
preliminary results of these two groups.

Essentially, normal volunteers were recruited from the undergraduate and graduate schools of MIT and the local Cambridge, Massachusetts area. They were screened to meet the following criteria prior to admission to the study. Subjects had to be free of any active or past history of neurological disease, have no other active physical disease, and have no history of seizures, no history of psychiatric hospitalization, and no history of developmental learning disability. Subjects could not be taking any prescription medications and had to have results within normal limits on EEG, neurological and physical examination, and neuropsychological screening and could not have any abnormal lab values on a routine battery of chemistry, hematology, and amino acid profiles. Furthermore, subjects had to have a history of moderate exposure to aspartame without any reported adverse effect. This was defined as a daily minimum of two to three cans of aspartame-sweetened soda; however, we actively sought to enroll subjects whose consumption history exceeded a liter of aspartame-sweetened soda per day. In summary, we made a conscious effort to preselect individuals who we felt would be unlikely to experience any effect from chronic aspartame exposure.

In a first phase, five subjects were admitted to an open protocol in which they were informed that they would receive aspartame up to a daily equivalent of 50 mg/kg of body weight, administered in three divided doses, in capsule form. Subjects were maintained on a controlled diet with an upper limit restriction of proteins and carbohydrates, as well as a 2-liter daily fluid restriction. Subjects were admitted to the Clinical Research Center at MIT and slept on site but were allowed to carry out their normal daily activities. They were observed for a 3-day baseline and then started on aspartame for 12 days, followed by 3 days of observation off aspartame, discharge from the Clinical Research Center, and follow-up one week later.

Subjects completed a daily symptom diary and had interval EEG telemetry, neurological and physical examinations, amino acid profiles, chemistry, hematology, and urinalysis screens, and neuropsychological testing during the baseline, aspartame exposure, and follow-up phases of the protocol. In a second phase, still in progress as of this writing, five additional normal volunteers, loosely matched for age, sex, and academic background, have been entered into the same protocol but are blind with regard to whether they are receiving aspartame or placebo. In fact, they are all receiving placebo in order to act as controls for the first five subjects. The nursing staff responsible fo the daily care of the subjects and for administering the substance is also blind for this phase. Placebo and aspartame capsules are identical in appearance and taste.

While there is much we have not yet analyzed from this protocol, we will report briefly here on the results of the cognitive, neuropsychological testing in the four, matched pairs of subjects on whom data are currently available. First, what cognitive functions were measured? Intelligence quotient estimates were obtained at baseline, but this was primarily for the purpose of matching subjects, and this type of test is recognized to be a poor measure of state-dependent effects. More important, from our perspective, given the role of serotonin, dopamine, and norepinephrine in the central nervous system, were functions such as attention and response set flexibility. More particularly, we were interested in evaluating the subjects' attention and response set by means of tasks requiring some sustained behavioral output, or alternation between various performance strategies on the same task, rather than by a simple, reactive response in a passive, signal detection paradigm. To this end, we selected tests such as Word List Generation, Form B of the Trailmaking Test, and the Stroop Color Word Naming Test which place a premium on these functions. We were also interested in memory and, finally, we wanted a task that combined attention, skilled motor output, and some immediate memory load with shifting stimuli and response demands, that is, we wanted a task that approximated the complexity at which the brain has to function in everyday life. We were fortunate in finding just such a measure in a MacIntosh software application developed in the educational realm called "Think Fast" (S. Steffin and D. Harris for Brainpower Corp., Calabasas, Calif., 1985). "Think Fast" requires the subject to alternately match, copy, or recall sequences of letters and patterns of block designs in a self-governing, self-scoring, progressively difficult series of levels. Once the program is engaged, the examiner has no influence on the pacing or selection of stimuli, which are randomly generated and time limited.

The results presented in Table 20.2 are the mean difference scores between the baseline and exposure testings on each of the measures used for four subjects under each of the two conditions, aspartame (open) and placebo (blind). The use of difference scores utilizes each subject as his own control, establishes each subject's own baseline performance as the zero point, and eliminates the effect of any baseline differences between individuals or groups. Statistical comparisons (t test) of the difference between the mean changes in performance during placebo versus aspartame exposure showed a trend toward significance for the Trailmaking, Stroop Interference, and all Think Fast trials, and yielded significant comparisons for the Stroop Word Reading and Motor Response Set tasks. Learning and memory for simple stimuli and more passive attentional tasks showed no significant difference between the two exposure groups.

In addition to these cognitive measures of neurobehavioral functioning, we reviewed the behavior and subjective complaints of the participants during the two exposure conditions based on their daily symptom diary and the nurses' notes. Summarizing this information and taking into consid-

TABLE 20.2 Average change in performance from baseline to exposure conditions for placebo- and aspartame-exposed subjects.[a]

Measure	Average change for subjects receiving: Placebo	Aspartame	*t*-Probability
Learning			
Mean increase in words recalled during learning trials	0.4	0.375	N.S. >0.25
Mean increase in words recalled during memory trials	0.19	1.19	N.S. >0.25
Attention			
Mean increase in total span	2.3	1.71	N.S. >0.25
Mean increase in words generated	4.75	1.00	N.S. >0.25
Response set			
Mean decrease in time to complete:			
Trails A	5.38	10.83	N.S. >0.25
Trails B	18.38	−1.4	$p<0.16$
Stroop Word Reading	1.62	−13.13	$p<0.002$
Stroop Interference	10.25	−8.25	$p<0.17$
Mean decrease in reciprocal motor program errors bilaterally	6.75	1.88	$p<0.04$
Think Fast			
Mean improvement in score for:			
Condition A	397.38	−140.25	$p<0.13$
Condition B	351.25	−181.25	$p<0.08$
Mean decrease in number of errors:			
Condition A	2.25	−0.75	$p<0.12$
Condition B	1.38	−0.38	$p<0.14$

[a] Pilot data: $n = 4$/group; 2 male, 2 female.

eration only those symptoms that represent a change from behaviors observed or reported during the baseline phase, it can be seen that none of the placebo subjects reported or were observed to have any significant neurobehavioral changes whereas three of the five aspartame subjects reported the appearance of at least two of the following symptoms during the exposure period. Subjects developed focal pains, autonomic symptoms, nausea, lightheadedness, sleep disruption, frontal headaches, photophobia, and visual disturbances, apparently in response to chronic, daily exposure to aspartame. Furthermore, the nursing staff spontaneously noted that two of the aspartame-exposed subjects became irritable, anxious, and complaining whereas none of the placebo-exposed subjects were ever described in these terms.

These results were somewhat surprising to us. Initially, this study was designed as a pilot project, restricted to low-risk subjects, to test the safety

and efficacy of this protocol prior to examining a population of complainants who maintained that they had developed seizures in response to aspartame exposure. However, the finding of positive results in this normal group of subjects, which presumably cannot be attributed to the structure of the protocol, to dietary habits, or to taking up residence at the Clinical Research Center, has realigned our priorities. It seems that aspartame may be capable of producing significant neurobehavioral effects, some of which may not even be within the subject's awareness. This issue requires further research and must be investigated under more rigorous conditions using a double-blind, crossover design. While it would certainly be premature to conclude that chronic, high-dose aspartame ingestion interferes with cognitive functioning, it would seem wise, based on the present report, to keep an open mind to such potential brain-behavior relationships.

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