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DIET AND HUMAN BEHAVIOR: HOW MUCH DO THEY AFFECT EACH OTHER?[1]

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CONTENTS

> "Popular interest in food-behavior questions in the 1980's is a special case of the spread and confluence of two more general ideas: that human behavior has controllable organic determinants, and that man's physical environment is a controllable determinant of well-being. What brings these two ideas together in the case of food and behavior is the widespread conviction that diet and nutrition are parts of the environment that most people can understand and control if they will."
>
> Thomas E. Cooney (12)

It is a prevalent idea among the public that diet affects behavior, and scientific investigators have also become interested in diet and behavior relationships, in

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part because of evidence that the brain is more sensitive to nutrient supply than previously thought (2).

This review of nutrition and behavior is focused on human studies, although animal studies are cited to illustrate particular points. The behavioral effects of diet in specific metabolic disorders such as phenylketonuria are not covered.

Three behavioral roles are most often postulated for nutrients: (*a*) nutrients as etiologic for a particular behavior, (*b*) nutrients as therapeutic agents, and (*c*) nutrients as correlates of behavior. The last possibility does not imply a cause-and-effect relationship.

EVALUATION OF RESEARCH: GENERAL PRINCIPLES

The overall methodological level of most diet-behavior studies is extremely poor. For example, a review (32) of dietary factors alleged to influence delinquency criticized all studies on methodologic grounds, finding none adequate.

Research on diet and behavior consists of two general types: experimental and correlational or epidemiologic designs (2). Experimental designs involve manipulation of the variables (e.g. a dietary constituent such as caffeine) to examine their effect upon dependent measures (e.g. behavioral and/or cognitive factors such as continuous-performance test errors). Experimental designs permit causal relationships to be tested, whereas correlational studies do not. On the other hand, correlational studies have utility for hypothesis formation and experimental testing of relationships.

Subjects and Sampling

Both experimental and correlational studies may be influenced by the sample selected. A standardized selection process for subjects (inclusion and exclusion criteria and methods used) should be clearly described. Strategies for decreasing error variance include crossover and single-case designs, in which the subject serves as his own control. While baseline periods are helpful in estimating variance and controlling for initial differences between subjects, they introduce problems of practice and order effects. Therefore, treatment order must be counterbalanced or, if precluded by large numbers of treatment conditions, randomized or otherwise equated through the use of Latin squares or lattice designs.

Nutrient Manipulation or Dosage

Double-blind, controlled conditions are crucial in investigation of diet-behavior relationships. This is particularly true when the subject has strong beliefs about particular foods. In studies that involve challenges, subjects should be unable to discriminate between the placebo and the active substance

on the basis of taste or appearance. As the magnitude of dietary alteration increases, blinding becomes progressively more difficult. Large dietary changes such as the salicylate-free and dye-free diet, once (21) believed to benefit childhood hyperactivity, are not easily tested (4).

Blinding is crucial and often very difficult in diet-behavior studies. The critical nature of double-blind conditions is seen in a study by Jewett (46). "Clinical ecologists" put forth in their practice the idea that behavioral symptoms could result from food sensitivity and that this sensitivity could be detected and treated. Jewett studied intradermal injections of food extracts using doses small enough (underdoses) to avoid wheal and flare reactions. Subjects were selected by practitioners of the technique as being reliably and repeatedly hypersensitive to such injections. This would include single-blind conditions: the physician would know the contents of a particular syringe but the patient would not. When 18 such patients were tested under double-blind conditions, where neither the tester nor the subject knew whether the injection was placebo or active, not a single one could significantly identify the contents or demonstrate a reaction.

The duration and timing of the manipulation are important. Chronic effects may arise that are not apparent in acute-dose studies. For example, aggression in rats increases after 14 days of low-protein, high-carbohydrate diet, but not after one day (48). The lack of knowledge regarding the pharmacokinetics of compounds such as food dyes raises the possibility that crossover studies may employ treatments of insufficient duration (79). Mood and performance are subtly affected by the time of day a nutrient is given (82). For example, caffeine was shown to benefit the performance of certain personality types on a task similar to the Graduate Record Exam when given in the morning but not in the evening (73).

The greater context of any dietary manipulation must be kept in mind when evaluating research. A dietary component is unlikely to exert its behavioral effects in isolation (1); diets in which the percentage of protein is changed result in altered fat and/or carbohydrate intake. Thus such a study may be viewed as the effect of an increased carbohydrate/protein (CHO/Pr) ratio because CHO was substituted for the missing Pr. A concomitant of implementing the Feingold diet was a decrease in sucrose (70).

Prior nutritional state is another potential source of variation in acute-challenge studies of nutrient influence upon behavior (1). The types and amounts of food eaten previously will influence the metabolism of subsequent meals (45) and neuroendocrine functions (44, 81). Standardizing dietary intake prior to the acute challenge can control this variation.

The particular state that an individual is in is a part of the context in which a dietary challenge is carried out. For example, the restorative effect of caffeine can be measured only in a fatigued and/or bored individual and not in an alert

well-rested one (16). Cigarette smoking can almost double the rate of caffeine elimination via induction of metabolic enzymes (62).

One can attempt to monitor compliance by counting pills, weighing residual food, or keeping daily diaries. Ideally, assays are used for quantification of the biologically active and available substance (e.g. salivary caffeine concentration.)

GROSS DIETARY DISRUPTION

Chronic protein-calorie malnutrition is a gross nutritional insult affecting the biological substrates of behavior. Patel (63) summarizes the effects of malnourishment on the biochemical and structural maturation of the brain as follows: (*a*) distortions in the generation cycle of replicating neuronal or glial cells, (*b*) permanent deficits in total cell number and a distortion of the cellular composition, (*c*) retardation in biochemical and structural development of the brain, and (*d*) distortions in the normal coordinated pattern of transmitter systems. General agreement exists that malnutrition is associated with cognitive and behavioral deficits, particularly for infants and children. Children surviving early malnutrition are profoundly impaired in acquiring language and motor skills, in developing interpersonal relationships, and in learning adaptive and motivational behavior. However, interpretation of these close relationships is complicated by the confounding variables of socioeconomic and environmental conditions, which can affect brain and mental developmental in experimental animals as well as in man (14, 55, 63).

Moreover, environmental deprivation and malnutrition may be synergistic. Galler and colleagues studied children 5 to 11 years old in Barbados who suffered protein-energy malnutrition during the first year of life. Their IQs were significantly lower than those of matched controls (26). The children's classroom behavior was significantly worse as well, displaying attention deficits, reduced social skills, and emotional instability; these deficits in classroom behavior were independent of IQ although not independent of academic achievement (27). Galler et al concluded that malnutrition in the first year of life is a potential factor in causing attention deficit disorder (the diagnostic nomenclature for what used to be termed the hyperactive child syndrome or minimal brain dysfunction) (27).

These results are impressive because unlike most other studies, the investigators could control somewhat for socioenvironmental variables. For example, health care delivery in Barbados was good and documented records of obstetric care and subsequent medical records of the children were available. In order to exclude common determinants of mental deficiency, the following exclusionary criteria were applied: (*a*) birth weight less than five pounds, (*b*) antecedent of prenatal complications, and (*c*) history of high fever, con-

vulsions, head injury, or unconciousness. Moreover, multiple regression analyses using nutritional group and socioeconomic factors as independent variables indicated the relatively greater impact of nutrition in the first year of life compared to socioeconomic conditions.

However, in a more recent publication (28) the index of children's worse behavior at home appeared attributable to poor socioeconomic and home environment. Low maternal morale and adult involvement with the child, along with four other factors, significantly discriminated between the two groups. Thus even in this study some socioenviromental mediation is likely.

The choice of behavioral measures in older studies of malnutrition have been criticized (43) for relying on intelligence tests while running the risk of missing other effects. One example is a recent series of papers examining behavioral and cognitive sequelae of celiac disease, a lifelong malabsorption syndrome that starts in childhood (35–39). Adult patients, when first diagnosed, typically experienced a wide range of nutritional deficiencies. No consistent signs of cognitive impairment are found, but depressive symptoms severe enough to warrant disability pensions were seen.

Rumsey & Rapoport (75) point out that it may prove impossible to separate the effects of chronic malnutrition from the psychosocial concomitants by supplementation studies, where mother and/or infants at risk of malnutrition are given additional nutrition. Review of the past two decades of such studies concluded that nutrient supplementation of chronically and moderately malnourished infants in the prenatal and postnatal periods results in modest improvements in motor, language, and attentional skills (43). Only minor improvements in cognitive functioning were noted where the degree of malnutrition was marginal.

ACUTE MALNUTRITION: "FASTING" VERSUS "FED" STUDIES

An acute short fast or skipping a meal seem very subtle examples of undernutrition when contrasted with the chronic studies above, but are certainly more common in an affluent society! The powerful effect of public belief in nutrition-behavior relationships as well as the interests of the food industry have fostered research in this area. The idea that children perform better in school if they have eaten a good breakfast appeared a reasonable idea to test, given that as many as one third of children in developed nations are thought to have inadequate caloric intake at breakfast. Public perception has already influenced US public policy in the Child Nutrition Act of 1966 (PL80-642) (65). A 1978 review of US long-term studies of the effect of feeding programs on school performance and behavior found all the studies to be methodologically weak and inconclusive (65). However, short-term studies indicate an acute benefit of eating breakfast

compared to fasting. In 1983, two groups of investigators added support for an acute beneficial role of breakfast. When children skip breakfast, poorer performance and/or greater variability is seen on cognitive tests such as the matching familiar figures test (a skill having some correlation with educational achievement) (66), the continuous-performance test (an attentional task), and a task involving arithmetic problems (10).

Lunch effects have also received scrutiny; Craig (13) found evidence that lunch affects cognition more convincingly than does breakfast and in the opposite direction—impairment! A number of large epidemiologic studies have indicated a reduced work efficiency during the time period that follows lunch: error frequency in shift workers, the frequency of car drivers falling asleep, and the frequency of locomotive drivers compulsively braking all show increases following usual lunch times compared to preceeding or subsequent time periods. Specific effects of dietary constituents (alcohol, for example) and circadian effects may, of course, independently contribute to this pattern. Nonetheless, there is probably a more specific "meal effect" (13). Seven of the eleven studies reviewed found decrements in performance or perceptual sensitivity following the lunch condition (13).

Generally, fasting versus fed studies show the fed state to be better for mental performance, when the fast is of fairly long duration (e.g. overnight) (13). In addition to the breakfast studies in school children cited earlier, the only study (50) that found lunch to improve efficiency might more aptly be considered similar to the breakfast versus fast studies. Because breakfast was eaten between 4:30 and 5:30 in the morning in that study and the first test period was not until 1:30 in the afternoon, the test condition of "no lunch" represents at least an eight-hour fast. In this study of altitude tolerance, the time to complete a psychomotor task and the area of the visual blind spot were greater (worse) when lunch was skipped. However, obviously subjects could not be "blinded" to meal or fast conditions in these studies, and so the advantage of being fed might be psychological rather than nutrient based. In a study of food intake's effect upon reaction time during an eight-hour driving task, differences were seen in reaction time *prior* to the break in which food or no food was given (56). Poorer performance was seen on the no-food days. As this was a crossover design, anticipation or beliefs probably explain the finding.

Iron deficiency is believed to be the most common nutritional disorder. Three recent investigations have added support to earlier conclusions that iron deficiency results in behavioral impairment such as lassitude, decreased attention span, and irritability. Even in the absence of anemia, iron deficiency produced conditions that were ameliorated with parenteral iron (61). Developmental deficits occur in infants with iron-deficiency anemia even when socioeconomic level and general nutritional status are controlled (57). Additionally, reversible alterations in cognitive test performance were reported in mildly iron-deficient

preschoolers (67). Studies of iron-deficient adolescents and adults before and after iron therapy would also be interesting.

Whether chronic or acute (fasts of eight or more hours), lack of nutrition has some negative effects. The magnitude of that decrement, although significant, appears small except in the case of massive chronic undernutrition. Even then, the psychosocial accompaniments probably account for a great measure of the cognitive impairment. It may be that some sequelae of chronic nutritional deprivation are as yet unappreciated. For example, the response to an induced brain lesion differed between animals malnourished earlier in life and normally fed controls, even though performance of the two groups was the same before the brain lesion (6). This important study suggests that there may be silent sequelae of malnutrition that can be unmasked by later insult. Thus "confounding" socioeconomic factors may in fact be synergistic and most relevant, not just experimental artifact.

HYPERSENSITIVITY TO DIETARY SUBSTANCES

Dietary substances have been accused of being etiologic agents for many forms of behavioral distress and psychiatric illness. "Food allergy," a popular term often used in such claims, is a potential source of confusion in the recent literature. The term hypersensitivity is preferred here because it includes nonimmunologically mediated phenomena.

Sensitivity to gluten has been implicated in psychiatric illness. Dohan (17) postulated that peptides derived from gluten have a role in causing schizophrenia. Attempts have been made to add cereal-free diet regimens to standard pharmacologic treatments of schizophrenia. Two small studies with a combined total of 13 patients reported no worsening of symptoms with gluten challenges that followed periods of abstinence from milk, cereal grains, and gluten (60, 68). An earlier study did show a significant deterioration following double-blind gluten challenge (80). Two other approaches have been used to investigate this idea. A study of celiac patients found no cases of schizophrenia although it did find depression (37). Antibodies to food substances have been compared for psychiatric and control populations. Five of seven such studies (for references, see 74) found higher prevalences or higher titers of food antibodies in the psychiatric patients. While the data illustrating immunological differences between psychiatric patients and controls are intriguing, they do not constitute evidence for food allergy causing psychiatric illness; the findings may be results of the disorders or their treatment.

Of historical interest are the claims that food additives, particularly food dyes, caused hyperactivity in children. Meta-analysis (49) of the 23 controlled studies investigating this idea provides an emphatic negative conclusion: food dyes do not cause hyperactivity. There might be rare individual exceptions;

single-case studies have suggested that an occasional child may show behavioral sensitivity to food colors (58).

When properly "blinded," food-sensitivity studies have been negative. A double-blind study gave dried foods in capsules and bland foods disguised in a "milk shake" made from a soy-based milk substitute to 23 patients referred to a clinic because of suspected food allergy (64). Only four patients demonstrated actual food sensitivity. Sensitivity was assessed by (*a*) the skin test being positive and double-blinded sodium cromoglycate (which inhibits the release of histamine and other autocoids) blocking open provocation with the food, or (*b*) correctly identifying 5 out of 6 individual trials in a double-blind series. The four patients with actual food allergy had presenting symptoms associated with atopy: rhinitis, urticaria, asthma, or atopic eczema. Psychological symptoms were not among the presenting complaints of these four patients. In contrast, psychiatric symptom scores were much higher in the 14 patients who completed the allergy assessment and were not confirmed to have a food allergy.

Oligoantigenic diets are another rather complex approach to identification and treatment of behavioral reactions to foods. They go further than most exclusion diets because of the suspicion that multiple foods may provoke the same reaction(s). Recently, two trials of oligoantigenic treatment were carried out in London. Children with migraine and related symptoms (including behavior disorder in the first study and hyperactivity in the second) improved on a very limited diet (19, 20). Offending foods were later identified following their reintroduction into the diet. Subsequently this was confirmed by double-blind challenges. Indirect support comes from a double-blind, placebo-controlled trial in which oral sodium cromoglycate blocked the precipitation of migrane by food challenge (59).

Enthusiasm for these findings should be tempered. The improvement seen in hyperactive children was quite limited and other forms of management such as stimulant drug treatment continue to be required in those children. It is also not clear if all children went through all elimination maneuvers systematically. It appears that once something "worked" it was maintained. Most importantly, all food challenge studies have the problem of adequate blinding; for example, chocolate (to which over half of the hyperactive children in this study reacted) is so difficult to "blind" that results invite skepticism. Independent investigators need to reexamine this data, including examination of the success of the blind. Had a return to baseline occurred (no assessment was made), the trial would have been more convincing.

Even if these results were replicated, sensitization could still not be conclusively attributed to direct immunologic mechanisms. Learned histamine release has been demonstrated in animals using odors (76). Thus it is possible that behavioral reactions to foods, even if actually present, could also represent learned behaviors.

BEHAVIORAL STUDIES WITH SPECIFIC DIETARY CONSTITUENTS

Caffeine

In addition to its cognitive effects, caffeine has been well studied in relation to anxiety and childhood hyperactivity. "Caffeinism," a behavioral syndrome produced by high doses of caffeine, can produce symptoms indistinguishable from those of generalized anxiety disorder (30, 33). However, data are inconsistent as to whether caffeine intake in *moderate* doses potentiates anxiety.

Stimulant drugs are the medication of choice in treating children with attention deficit disorder with hyperactivity. In some settings, with high doses, these pharmacologic agents can also produce motor over-activity. Accordingly, studies have considered questions of behavioral toxicity of caffeine as well as the possibility of therapeutic benefit for pediatric populations. Interest and subsequent studies were spurred by an initial report that caffeine was as beneficial as Ritalin®, a frequently prescribed stimulant (78). Generally, the great majority of subsequent better-controlled studies found prescription drugs more beneficial (75). Furthermore, when caffeine was compared to placebo in hyperactive children, no significant benefit was seen (75). An exception to the apparent consensus is a recent study (77) that found very high doses of caffeine (600 mg/day) significantly ameliorated hyperactive behavior. While this trial compared varying doses of caffeine and/or amphetamine, it did not have a placebo comparison. The bothersome side effects seen with that dosage (stomach ache, nausea, insomnia) suggest that caffeine is unlikely to have clinical utility.

Other studies addressed whether caffeine might provoke childhood hyperactivity, and significant correlations were found between grade-school children's habitual caffeine consumption and teacher-rated classroom inattention and restlessness (71). Children reporting habitually high consumption (greater than 500 mg/day) had higher scores on the Conners teacher rating scale, higher scores on an anxiety questionnaire, and lower autonomic arousal than peers consuming low levels of caffeine, when both groups were assessed off caffeine. However, when challenged with caffeine (10 mg/kg/day), only children from the habitually *low*-intake group were more restless, while those with habitually high caffeine intake tended to be somewhat calmer. Similarly, only the low-intake children experienced side effects from caffeine. Thus caffeine was not shown to promote hyperactive behaviors and might possibly be self selected by children who tolerate or even benefit from it.

Sweeteners

SUCROSE AND OTHER CARBOHYDRATES In the US, sweeteners (notably sucrose and aspartame) have received a great deal of public attention, and

public concern that refined sugar may be linked to hyperactivity is widespread (15, 47, 83). Chiel & Wurtman (7) found that rats increased their motor activity as their dietary carbohydrate/protein ratio was raised, even though calories were held constant.

For scientists, particular impetus was given by human studies that found significant positive (70) correlations between dietary carbohydrate/protein ratios and directly observed restless and aggressive behaviors in a sample of 28 hyperactive children. Estimates of sugar intake based upon large categories of food correlated with the same behaviors of the hyperactives. Virkkunen (84) compared the insulin response to a glucose load seen in aggressive prisoners with that seen in nonaggressive men from the same institution and found greater insulin output among the more aggressive. As both of these studies are correlational, they do not address causality.

To date, eight double-blind, placebo-controlled challenge studies have been carried out examining the effects of sugar upon childrens' behavior and cognition. Four of the studies used versions of the Conners rating scale, which frequently demonstrates the effect of stimulant medication and differentiates hyperactives from normal children (3, 22, 52, 86). They did not find any significant behavioral difference between sucrose and the control conditions (5). Two of the studies, both negative, included parents as raters (34, 52). This is important because parents are most often the historians reporting a behavioral reaction to sugar. Seven of the studies used objective measures of activity to examine the possible motor effects of sugars. These are summarized in Table 1.

Behar et al noted a decrease in activity following sugar intake, but it only achieved statistical significance at one time point (two hours after challenge) when both sucrose and glucose were considered in comparison to saccharin (3). The two studies by Conners (10, 11) report opposite effects: the first found sugar increased activity and the second reported a decrease. Goldman et al (31) reported a sugar-induced increase in activity in eight preschool children. It is interesting to note that this study used a slightly higher dose than any of the others, which used body-weight-adjusted doses. On the other hand, three remaining studies (22, 52, 86) report no difference from placebo. These negative studies, the slight decrease observed by Behar (3), and Conners' conflicting results (10, 11) suggest that an acute challenge of sucrose or glucose, even in allegedly "sensitive" individuals, does not result in increased motor activity.

Cognitive effects of carbohydrates have received particular attention. Five of the challenge studies with children included cognitive measures. Three studies (3, 22, 86) found no difference in performance, one found improvements, and one found a decrement on the continuous performance testing (CPT) (31). (See Table 1). Similarly, a study in adults of meal composition and timing contrasted a high-carbohydrate meal with a high-protein one and found no difference on

Table 1 Challenge studies of sugar's effect upon activity and attention in children

Authors	Number of subjects	Sugars tested[a]	Dose(s) (g/kg)	Placebo/ Control[a]	Effect[b] of sugar on Activity	Effect[b] of sugar on Attention (CPT)
Behar et al (3)	21	S,G	1.75	X	−/=	=
Conners & Blouin (10)	13	F,G	50[c]	OJ	+	
Conners et al (11)	37(13)[d]	S,F	1.25	A	−	(+)[d]
Ferguson et al (22)	8	S	1.5, 1.0, 0.5	A	=	=
Goldman et al (31)	8	S	2	A+L	+	−
Kruesi et al (52)	32	S,G	1.75	A,X	=	
Woolraich et al (86)	32	S	1.75	A	=	=

[a]The code for sugars and placebo/control is as follows: S, sucrose; G, glucose; F, fructose; L, lactose; X, saccharin; A, aspartame; OJ, orange juice.
[b]Symbols used: + increased, = no significant difference, − decreased.
[c]Measured in grams.
[d]The ( ) indicate the subsample.

the CPT (82). However, Prinz & Riddle did find a significant negative correlation between habitual sucrose intake and continuous-performance test scores (69).

Cognitive effects have been noted when blood glucose is lowered significantly and/or with tasks of longer duration requiring sustained effort. Holmes et al studied juvenile diabetics for whom blood glucose was held at constant levels by means of a pump supplying both insulin and glucose (42). Hyperglycemic (300 mg/dl), euglycemic (110 mg/dl), and comparatively hypoglycemic (60 mg/dl) conditions were studied. Attention and fine motor performance required during a reaction-time task were slowed at both high and low glucose levels. However, other psychometric tests in that study did not reveal differences between conditions. Craig, in reviewing the acute effects of meals on perceptual and cognitive efficiency, noted that lunch-induced deficits seem related at least in part to carbohydrate content, and that tasks of longer duration appear more sensitive to meal effects (13). Spring et al found lower overall accuracy and greater omission errors during a 20-minute dichotic listening task following a high-carbohydrate meal compared to a high-protein meal (82). As noted earlier, the CPT, which only required 2–3 minutes to complete, did not show this effect.

There have been popular claims of sugar-induced changes in behavior, but most studies of diet and criminal behavior are methodologically so flawed as to prevent interpretation. Although the studies of Virkkunen (84) are well done, they offer correlations, not cause-and-effect data. These correlations have not yet been replicated in an independent laboratory. The NIMH challenge study did not show an increase in aggressive or destructive behavior in disturbed children following acute sugar challenges.

ASPARTAME Aspartame is a dipeptide used as a nonsugar sweetener. Soft drinks are probably the most frequently consumed form of aspartame; thus questions of behavioral and cognitive effects secondary to its ingestion apply to a broad population of adults as well as children. Questions of potential behavioral toxicity were raised by Wurtman in 1983 (87) because aspartame causes brain phenyalanine and tyrosine to rise and it blocks glucose-induced change in 5-hydroxyindoles (89).

Behavioral studies of aspartame with humans are limited. In most studies, aspartame was used as a "control" for sugar in an equivalent sweetness dose. Consequently, when no other artificial sweetner is used as a control, the possibility exists of effects being due to caloric differences or to the sugar itself. When sugar or saccharin are the compared substances, a difference in one could be interpreted as the activity of the other.

Aspartame has demonstrated little or no behavioral effect in most studies to date. Woolraich et al (86) studied 32 children with a battery of behavioral and cognitive measures and found no significant differences between aspartame (6.26 mg/kg) and sucrose (1.75 g/kg). Conners et al (11) reported that activity seen following 1.25 mg/kg of sucrose or fructose was less than after aspartame. If the sugars serve as reference points, then aspartame might be claimed to increase activity. Similarily the reported improvement in attention with the sugars in that subsample of 13 children might be viewed as a decline due to aspartame. Ferguson et al (22) found nonsignificant differences between aspartame (8.33, 5.6, 2.78 mg/kg) and sucrose (1.5, 1.0, 0.5 mg/kg). Unfortunately the dose of aspartame was small in these studies.

In a study with 32 preschoolers at the NIMH (52), a challenge of 30 mg/kg of aspartame (a daily dose estimated to be in the 90th percentile) was compared to glucose, sucrose, and saccharin. Motor activity as measured by an acceleration-sensitive device was significantly less than that seen after sucrose or glucose ingestion, and there was a trend ($P<0.06$, Bonferroni-corrected t test) for preschoolers to be less active after aspartame than after saccharin ingestion. However, other behavioral measures, including the behavioral ratings of the in-room observer during the playroom sessions, did *not* show any significant differences. Thus behavioral effects of an acute aspartame challenge, if present, are subtle. The children who were comparatively slowed down on aspartame had significantly higher "internalizing" scores on the Achenbach Child Behavior Checklist (often a measure of anxiety or depression) than children who were not slowed down. The intriguing possibility exists that the effects of aspartame, if present, might more clearly be seen by targeting internalizing as opposed to externalizing children (such as those with hyperactivity).

Goldman et al (31) used a sweetener containing aspartame and lactose and 2 g/kg of sucrose and found less activity and improved attention following

aspartame. This result can be interpreted as a sugar or an aspartame effect, although the low dose of aspartame make this unlikely.

In summary, acute sugar challenge does not cause hyperactivity and few or no cognitive effects are seen unless the magnitude of blood sugar change is sizable. Aspartame in high doses might have behavioral effects, although the NIMH study (with the exception of some equivocal findings) did not support the anecdotal reports of adverse behavioral reactions—usually increased activity and aggression.

Amino Acids

Proteins and their constituent amino acids are the major source of precursors for neurotransmitter synthesis. Fernstrom & Wurtman (24, 25) presented scientific rationale for dietary and behavioral effects and thereby stimulated more rigorous research. Fernstrom et al (23) demonstrated that central nervous system serotonin can be altered by dietary manipulations that change the ratio of tryptophan (tryp) to other large neutral amino acids (LNAA). High-carbohydrate meals cause insulin release, an attendant increase in plasma tryp/LNAA ratio (which increases tryp crossing the blood-brain barrier), and ultimately an increase in central serotonin synthesis. In part because of this work, tryptophan is the most frequently studied amino acid in diet-behavior research.

Tryptophan's (modest) sleep-inducing effects have been demonstrated repeatedly during the past 10 years. Sleep latency, that is the time it takes to fall asleep, is decreased by tryp (41). Similarly, infants fed tryp and glucose entered both quiet and active phases of sleep sooner than those fed commercially available formula (88). Valine (which competes with tryp for brain entry and which would therefore lower the tryp/LNAA) had the opposite effect. Although one may consider manipulations of single amino acids pharmacologic rather than "dietary" in nature, the ready availability of amino acids as "dietary supplements" for purchase by the general public is blurring the boundries between pharmacology and nutrition.

Prompted by serotonergic theories of depression, researchers gave tryp as an antidepressant but no consensus exists as to its efficacy. Young and colleagues found that mixtures of amino acids that were free of tryp, those that were tryp supplemented, and those that were a balance of amino acids in a slurry (reminiscent of the so-called liquid protein diet drinks) had little effect, although tryp depletion caused an acute and mild dysphoria (91).

Aggression in animals can be influenced by alterations of central serotonergic systems. Normal subjects did not show alterations in aggression, as assessed by the Buss Durkee Paradigm, with either tryp supplementation or depletion (90). Preliminary data suggest (12) aggressive schizophrenics may benefit from tryp supplementation (90).

Lieberman et al found that an acute 100 mg/kg oral dose of tyrosine, also a precursor for catecholamine synthesis, had no significant effect on a variety of measures including reaction time, manipulative dexterity, mood, and pain perception (53). Because of noradrenergic theories of depression, chronic tyrosine administration has been tried as antidepressant treatment but the encouraging pilot work by Gelenberg et al (29) has not been confirmed.

Glutamate has at least putative status as a neurotransmitter. While most reports have addressed its toxicity, a study of five adults with learning disabilities and five controls suggested 300 mg of monosodium glutamate daily improved oral reading speed in the learning-disabled group (51).

Vitamins

Vitamin deficiency is capable of producing behavioral change, which in some cases can appear as frank psychiatric symptoms such as depression and psychosis (55). The classical example, of course, is pellagra. A more subtle and less rare situation is vitamin insufficiency illness (5). Wernicke-Korsakoff syndrome, characterized by amnesia, disorientation, confabulation, ophthalmoplegia, and peripheral neuropathy, is an example. Although many alcoholics have poor nutritional intake, only a very few develop psychiatric illness. This may be explained by a variant of thiamine-dependent transketolase, in which the affinity of the apoenzyme for the cofactor was a tenth of the usual values (5). Thus, although these individuals may otherwise appear to have had unremarkable growth and development, their nutritional sensitivity may be unmasked by the stresses of chronic alcohol intake.

Vitamin supplements as treatment for behavioral problems in the absense of deficiency or demonstrated insufficiency seem less likely to be beneficial. As reviewed by Lipton & Golden, there is little well-controlled evidence to support the idea of vitamins as treatment for any psychiatric illness (54).

However, a recent rat study demonstrates that vitamin C enhances the antiamphetamine and cataleptogenic effects of haloperidol, an antipsychotic drug (72). Given the widespread availability of vitamins in large doses and the implication that vitamin C plays an important role in modulating the behavioral effects of antipsychotic drugs, further behavioral research would be interesting.

CONCLUSION

In conclusion, chronic nutritional deficiency can result in behavioral change, but not in all cases. Furthermore, the context, particularly psychosocial variables, interacts with nutritional effects in complex ways. Nonetheless, behavioral or cognitive changes following acute manipulations add credence to the view that diet can influence behavior. These acute effects of foods are subtle at best, and not of clinical magnitude. Consequently, future research should

focus on the much more difficult area of chronic exposure (or nonexposure in the case of depletion, hypersensitivity, or insufficiency) to nutritional factors.

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