

Can nutrient supplements modify brain function?¹⁻³

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ABSTRACT Over the past 40 y, several lines of investigation have shown that the chemistry and function of both the developing and the mature brain are influenced by diet. Examples are the effect of folate deficiency on neural tube development during early gestation, the influence of essential fatty acid deficiency during gestation and postnatal life on the development of visual function in infants, and the effects of tryptophan or tyrosine intake (alone or as a constituent of dietary protein) on the production of the brain neurotransmitters derived from them (serotonin and the catecholamines, respectively). Sometimes the functional effects are clear and the underlying biochemical mechanisms are not (as with folate and essential fatty acids); in other cases (such as the amino acids tyrosine and tryptophan), the biochemical effects are well understood, whereas the effect on brain function is not. Despite the incomplete knowledge base on the effects of such nutrients, investigators, physicians, and regulatory bodies have promoted the use of these nutrients in the treatment of disease. Typically, these nutrients have been given in doses above those believed to be required for normal health; after they have been given in pure form, unanticipated adverse effects have occasionally occurred. If this pharmacologic practice is to continue, it is important from a public safety standpoint that each nutrient be examined for potential toxicities so that appropriate purity standards can be developed and the risks weighed against the benefits when considering their use. *Am J Clin Nutr* 2000;71(suppl):1669S-73S.

KEY WORDS Polyunsaturated fatty acid, PUFA, folic acid, tyrosine, tryptophan, choline, brain, brain development, affective disorders, Parkinson disease, Alzheimer disease, dietary supplements

INTRODUCTION

The notion that constituents of the normal diet can influence brain function is not novel. Perhaps the best-known example is caffeine (and related methylxanthines), which is contained in coffee, tea, chocolate, and soft drinks. Caffeine is a mild stimulant that may improve mental alertness and performance (1). In the past few decades, it has become clear that many other constituents of the diet, from macronutrients to vitamins, influence brain function. For some, the effects so far noted are biochemical, whereas for others, functional and behavioral effects have been observed (and the underlying biochemical mechanisms are obscure). Because the field of diet and brain function is very young, it should not be surprising that large gaps exist at the biochemical, physiologic,

and behavioral levels in our knowledge of the effects of nutrients on brain function. Nevertheless, sufficient information is available to allow a glimpse of the promise of this area of investigation and its likely utility to human health. Of particular recent interest are observations in fetal and infant animals and humans linking dietary essential fatty acids and folic acid to brain development and function. Here, clear functional effects are evident, although underlying mechanisms are poorly understood. In contrast, the influence of amino acids on the synthesis and release of the brain neurotransmitters into which they are converted has been quite well documented, whereas the consequences of this relation for brain function are incompletely understood. I discuss these examples from the perspective of the conference goals, that is, to identify effects of nutrients and functional food components on health and aging as well as gaps in our knowledge of these relations, and to develop strategies for evaluating effects of food components on health and aging.

NUTRIENTS AND BRAIN DEVELOPMENT

Several avenues have been explored in the past 3 decades regarding the effect of dietary constituents on the developing brain. Prominent examples include protein, energy (2), and iron (3, 4). Two more recent examples are essential fatty acids [polyunsaturated fatty acids (PUFAs)] and folate.

Polyunsaturated fatty acids

The PUFAs linoleic acid (LA; 18:2n-6) and α -linolenic acid (α LA; 18:3n-3) are essential fatty acids in many mammals, including humans (5). Their biological importance derives in part from their role as precursors of important second messengers (prostaglandins, prostacyclins, and leukotrienes) (5, 6) and as constituents of structural lipids in cellular membranes, which influence the activities of membrane-linked functional molecules (receptors, enzymes, and transporters) (7, 8). Dietary deficiencies of either fatty acid, particularly during development, produce pathologic and functional deficits (5).

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α LA is the precursor of docosahexaenoic acid (DHA; 22:6n-3), a PUFA present in high concentrations in retinal and brain lipids. Deficits in central nervous system (CNS) function have been directly linked to dietary α LA deficiencies that reduce retinal and brain DHA content (6). In particular, DHA is known to be important in photoreceptor membrane function in the retina (a portion of the CNS). In the brain, DHA is most abundant in membranes associated with synaptic function (as opposed to membranes associated with neuronal insulation, ie, the myelin). DHA is accumulated in the CNS late in gestation and early in postnatal life. A dietary deficiency in α LA instituted soon after birth, therefore, can lead to changes in both photoreception and cortical functions related to the visual system. The most convincing evidence of this was shown in monkeys (6).

An interesting twist on this issue relates to the direct dietary intake of DHA. Makrides et al (9) reported that after birth the brain content of DHA in infants ingesting infant formula, which lacks DHA, falls below that in infants consuming breast milk, which contains DHA. The implication is that the presence of DHA in the diet could directly influence DHA accretion in the brain. These authors also linked this difference in postnatal feeding practice to a predicted difference in visual function: infants ingesting infant formula showed visual deficits relative to breast-fed infants (10). A tighter connection between dietary DHA and visual function was also made in premature infants. For example, Birch et al (11) showed that dietary supplementation with a source of long-chain PUFAs, including DHA, can produce a more normal visual profile in very-low-birth-weight infants compared with similar infants receiving supplements lacking DHA. This issue is a focus of controversy (12, 13), but it raises the important question of the optimal profile of essential fatty acids and their derivatives in the breast-milk substitutes and supplements provided to newborns and infants.

Although functional effects in the brain and retina of dietary variations in essential fatty acids (specifically, α LA) seem accepted, the underlying biochemical mechanisms are poorly understood and, unfortunately, are not currently an area of intensive study. This is surprising; because DHA is a component of synaptic membranes, a study could easily be conducted to determine whether modifications in the abundance of this PUFA in membranes affect any of a number of well-characterized aspects of synaptic function (eg, vesicular storage and release of neurotransmitters, neurotransmitter reuptake transporters, presynaptic and postsynaptic receptor function, and second messenger responsiveness). It is hoped that this oversight will not go unrecognized for long.

Folic acid

During the past decade, clinical observation has strongly linked folic acid to brain development. The incidence of neural tube defects (eg, spina bifida) is notably higher in children of women who are folate deficient during pregnancy and can be reduced by folic acid supplementation during pregnancy; ideally, supplementation should begin before conception (14). The clearest demonstration of this relation derives from a study by the Medical Research Council (MRC) Vitamin Study Research Group, which conducted a randomized, double-blind trial involving folate supplementation of women before conception (15). Initiating supplementation before conception is important because the fundamental construction of the CNS occurs during the first trimester, a time when many women are unaware they are pregnant. The MRC study involved administering 4000 μ g

folate/d, a dose much higher than the recommended daily intake. Nevertheless, no toxicity was evident and the outcome was remarkable. In women consuming the supplement, 6 infants (out of 593 births) developed neural tube defects, whereas in women receiving no folate supplement, 21 defects (out of 602 births) occurred. Indeed, the emergence of this difference led to early termination of the study. The authors concluded that folate supplementation produced a 72% protective effect against the occurrence of neural tube defects (15).

This and related findings indicate the importance of a vitamin (folate) in nervous system development. Little information is available to illuminate the mechanisms by which folic acid deficiency causes the improper formation of the spinal cord, however. Folate is important in 1-carbon metabolism (16), contributing carbon atoms to purines, thymidine, and amino acids. In addition, methylation reactions involving folate may be important in the formation and maintenance of neuronal and glial membrane lipids (17). A folate deficiency, by impeding DNA, protein, or lipid synthesis, could thus conceivably influence neuronal and glial growth and proliferation during critical points in neural tube development, leading in some cases to effects severe enough to induce neural tube defects. Folate is also involved in maintaining adequate methionine pools for the synthesis of *S*-adenosylmethionine (18), a cofactor in methylation reactions in catecholamine synthesis and metabolism (19). It has also been linked to the maintenance of adequate amounts of tetrahydrobiopterin (20), a key cofactor in the synthesis of serotonin and the catecholamine neurotransmitters (19). It is not presently known, however, which, if any, of these biochemical actions of folate might be involved in the production of neural tube defects.

NUTRIENTS AND ADULT BRAIN FUNCTION

Several nutrients, notably tyrosine, tryptophan, folic acid, and choline-lecithin, have important actions on the mature and aging brain. Each has been examined for its functional effects in human nervous system function and for possible use as a dietary supplement.

Tyrosine and tryptophan

Interest in the amino acids tyrosine and tryptophan centers on their role as precursors to neurotransmitters, molecules that allow neurons to transfer electrical impulses to other neurons as well as other cells. Tryptophan is the precursor to the neurotransmitter serotonin. Numerous studies showed that the availability of this amino acid to brain neurons that synthesize serotonin directly influences the rate at which it is converted to a neurotransmitter (21). Administering either the amino acid itself (22) or meals that raise tryptophan access to serotonin neurons (23, 24) rapidly stimulates serotonin production; tryptophan administration is also known to enhance serotonin release in neurons that are actively firing (25). These treatments can produce changes in brain function; for example, in humans, administration of oral tryptophan can modify sleep and mood via its actions to stimulate neuronal serotonin production and release (26, 27). Such functional effects are also reputed to accompany the ingestion of carbohydrates (28) and, in rats, are said to involve a known action of carbohydrate ingestion to stimulate brain tryptophan uptake and serotonin synthesis (24). The functional effects of administering tryptophan or carbohydrates are relatively small, however, compared with the actions produced by administering

potent drugs that enhance serotonin function in the brain, and it is not currently known whether the smaller effects of tryptophan and carbohydrates are functionally useful (ie, are the larger effects produced by drugs preferable in all therapeutic applications?).

The outbreak 10 y ago of a toxic response to nonprescription preparations of L-tryptophan diminished the availability of this amino acid and interest in studying it for its putative functional effects. The toxic response, termed *eosiniphilia myalgia syndrome* (EMS), was characterized primarily by an increased blood eosinophil count and an often debilitating myalgia (29, 30), with neurologic and pulmonary complications sometimes present (31). EMS was ultimately believed to have affected >1500 persons and to have caused a small number of deaths (32). Soon after the EMS outbreak was linked to nonprescription tryptophan preparations, these products were removed from the American market (33). Because the occurrence of the syndrome appeared to be correlated with the use of tryptophan from a single manufacturer, investigators thought that a contaminant in a production batch, not tryptophan itself, was responsible for EMS (32). The absence of EMS in subjects ingesting pharmaceutical-grade tryptophan, which meets high standards of purity, is consistent with this assessment (34). However, although several candidate compounds were identified from the suspect batches of tryptophan, thus far none has been convincingly shown in animal models to be responsible for producing EMS (35, 36), and considerable disagreement has emerged with regard to the validity of the association between nonprescription tryptophan and EMS (37). Regardless of the ultimate outcome, in our experience, pharmaceutical-grade tryptophan preparations in humans have never been associated with symptoms of EMS (34, 38), suggesting that pure tryptophan preparations are safe.

Tyrosine is the precursor to the catecholamine neurotransmitters dopamine, norepinephrine, and epinephrine. Analogous to the ability of tryptophan to stimulate serotonin production, elevating tyrosine concentrations in brain catecholamine neurons (particularly dopamine and norepinephrine neurons) can stimulate transmitter production. This effect occurs in actively firing neurons but not in catecholamine neurons that are quiescent or firing slowly (39, 40). This relation not only is observed when tyrosine is administered but also is readily observable in catecholamine neurons in both rat retina and brain in response to the large changes in tyrosine concentrations produced either acutely or chronically by the ingestion of protein-containing foods (41, 42). Physiologically, this relation is of interest for its potential as a signal that might inform the brain about the animal's success in acquiring protein in its diet (43).

From the standpoint of using tyrosine as a therapeutically beneficial supplement in human disease, however, work to date has been less than encouraging. This amino acid has been administered to depressed patients to improve their mood, but although catecholamine production was enhanced, the treatment did not elevate mood (44). Growdon et al (45) showed that tyrosine elevated dopamine production in the CNS of patients with Parkinson disease, a serious, debilitating disorder, the cause of which is thought to involve a loss of dopamine neurons and which is typically treated by administering the immediate dopamine precursor, L-dopa. Tyrosine was probably not effective as a therapeutic tool in Parkinson disease because no subsequent reports appeared from Growdon's group assessing tyrosine's efficacy as a treatment. Perhaps it is inappropriate to demand that a dietary amino acid be as potent as a drug and as effective in treat-

ing major diseases. If one looks for effects in healthy humans, reports of efficacy can be found. For example, tyrosine administration appears to improve cognition and performance in soldiers under stressful conditions (46, 47). Further work is required before the usefulness of tyrosine is established or accepted.

Folic acid

In addition to its use in reducing the occurrence of neural tube defects in newborns, folate has found application in the treatment of depression in adults. More than 30 y ago, a link was suggested between folate and psychiatric disturbances (48). The most unambiguous data supporting this link derive from patients with megaloblastic anemia; those having a clear folate deficiency in the absence of vitamin B-12 deficiency showed an incidence of affective (mood) disturbances of >50% (49). Similarly, other studies of nonpsychiatric patients showed changes in mood and mental function (48, 50, 51). Such results suggested the utility of assessing folate status in depressed subjects and possibly treating depression with folate supplements. Evidence was subsequently obtained indicating that depressed patients may indeed have low plasma and red blood cell folate concentrations (52–54). In addition, the efficacy of folate supplementation in the treatment of psychiatric illness was evaluated in 2 double-blind studies. Coppen et al (55) found that a 200- μ g/d supplement of folic acid improved the efficacy of lithium therapy in unipolar and bipolar illness. Godfrey et al (56) obtained evidence that folate supplementation (15 mg/d) for 6 mo improve, outcome in depressed and schizophrenic patients treated with standard pharmacotherapy. Intake of folic acid has been linked (although less convincingly) to other psychiatric conditions as well as to deficits in learning and memory, particularly in the elderly (57–59).

The mechanism by which folate modifies mood is hypothesized to be related to its role in 1-carbon metabolism (16). In the form of methylenetetrahydrofolate, the methyl donor in methionine synthesis from homocysteine, folate may help maintain adequate methionine pools for S-adenosylmethionine synthesis (18). The link to mood involves S-adenosylmethionine's role as a cofactor in methylation reactions in catecholamine synthesis and metabolism (19). Catecholamines are known to be important in maintaining mood, and exogenous S-adenosylmethionine is reputed to elevate mood (60). Folate has also been linked to the maintenance of adequate brain concentrations of tetrahydrobiopterin (20), a cofactor in the synthesis of serotonin and catecholamines (19). These transmitters, as indicated previously, are important in maintaining normal affective state (mood).

Although the evidence presented here suggests that a connection may exist between folate deficiency and abnormal mental function, the connection is not yet definitive. There is a clear need to evaluate folate supplementation further to make this connection more convincingly (57) and to determine the utility of folate supplementation in maintaining a normal affective state.

Choline-lecithin

Choline is the precursor to another neurotransmitter, acetylcholine. As with the transmitters discussed previously, the synthesis of acetylcholine is influenced by the availability of choline within the cholinergic neuron. Neuronal choline concentrations can be altered by dietary choline intake, in the form of either free choline or phosphatidylcholine (lecithin) (61, 62). Oral choline and phosphatidylcholine have found some application in human




disease and brain functions thought to involve cholinergic neurons. For example, they have been used successfully to treat movement disorders such as tardive dyskinesia (a drug-induced condition) (63, 64), but not Huntington disease (65, 66). Choline and lecithin have also been studied as potential memory enhancers, on the basis of the notion that acetylcholine neurons in the hippocampus play an important role in memory and that enhancing transmitter production might improve memory. Patients with Alzheimer disease are the group most studied; in general, the outcome has been that neither choline nor phosphatidylcholine offers much improvement in memory (67–70). This result is disappointing, but the choice of patient group may have been a factor. Subjects used in investigations of oral choline and lecithin were primarily those with chronic, degenerative nervous system diseases (such as Huntington chorea and Alzheimer disease). The extent of functional losses due to changes beyond those involving cholinergic neurons may be so great as to obscure any beneficial actions of choline or lecithin.

CONCLUSIONS

I have reviewed some of the evidence that particular nutrients may influence brain architecture, chemistry, and function. Although some avenues of investigation were negative, several identified important effects. Of interest are results indicating that deficiencies in particular nutrients during conception, embryogenesis, and early postnatal brain development can have a notable effect on the brain. Given this organ's vulnerability and the potential for lifelong deficits in brain function, more work is needed to identify which nutrients and micronutrients, when deficient in the diet, put the brain at risk. Furthermore, the identification of mechanisms of action might assist in correcting at least some mental deficits in persons subjected to such nutrient deficiencies in uterine and postuterine life. Almost no information currently exists, for example, to explain why the incidence of neural tube defects increases with in utero folate deficiency or why visual functions in retina and brain are modified by essential fatty acid deficiency during the third trimester of pregnancy and early postnatal life.

Several nutrients affect brain chemistry and function in the fully formed (adult) brain. Here, however, limited intervention appears not to produce major, presumably permanent alterations in structure and function (as is the case when such interventions are used during embryogenesis and early postnatal life). Thus, the nutrients are considered to be agents that induce short-term effects, implying that they must be administered on a continuing basis to maintain efficacy (eg, folate supplementation during antidepressant therapy). By and large, efficacy has not been convincingly shown in humans for most intended uses, and further work is needed to identify beneficial effects (and thus therapeutic utility). In this regard, it may be that the past focus on treating major, debilitating, and degenerative diseases with these agents was the wrong approach (because potent drugs are required to show efficacy) and that a new orientation toward milder or transient conditions would be productive.

Finally, too little is known about the potential toxicity of supplying nutrients in amounts above their known dietary requirements. If nutrients are to be used under pharmacologic conditions, toxicity profiles should be established for each so that the risks can be weighed against the benefits when evaluating whether and when these agents should be used. 

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