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CHAPTER 13

# Effects of nutrients on brain function

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## Introduction

Nerve cells in the brain communicate with one another and with effector sites in the periphery using signals generated by chemical compounds termed neurotransmitters, neurohormones and neuromodulators. The synthesis, storage and release of these compounds must normally be subject to strict regulatory control mechanisms so as to maintain homeostasis in the face of constant challenges from the external environment. It is not surprising therefore to find that alterations in the levels of circulating neurotransmitter molecules in the periphery typically have little direct effect on the neurons contained within the central nervous system. However, all the precursor compounds that are eventually metabolized into these neurotransmitters derive from the diet. Thus, the possibility that diet can affect the rate of synthesis of neurotransmitters important in the control of many bodily functions requires investigation. In fact, studies have demonstrated the ability of various dietary manipulations including both macronutrient (e.g. carbohydrate, protein or fat) and micronutrient (e.g. vitamins, minerals and individual components of the diet) to influence the chemistry of the brain. Additionally, in other studies with animals and humans involving such dietary manipulations, certain behaviors believed to be associated with a particular neurotransmitter have been monitored and found to be changed. Therefore the potential of diet to influence brain chemistry and associated behaviors appears to be a fruitful avenue of investigation.

The measurement of chemical changes in the brains of experimental animals following dietary interventions has demonstrated, in some instances, powerful influences on the levels of neurotransmitter compounds. However the ability to demonstrate functional changes associated with such chemical changes has been more of a challenge, especially in humans. Although these changes tend to be subtle in nature, they may be of significance during times of altered homeostasis, e.g. stress, disease, etc. And, while most studies have investigated the acute effects of such dietary manipulations, few studies have looked at the effects of long-term exposure on body–mind interactions.

The present review will discuss the ability of specific amino acids found in the diet to influence the synthesis and release of their corresponding neurotransmitter compounds. A number of important functions of the brain are controlled by complex neuronal systems that utilize these chemicals and are messenger molecules. For instance, an individual's response to psychological and physical stress, changes in blood pressure, anxiety-provoking situations, painful stimuli, etc. are influenced by the catecholamine neurotransmitter norepinephrine. As norepinephrine is synthesized directly from its dietary amino acid precursor tyrosine, the availability of this amino acid in the diet may influence the individual's response to the above

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environmental stressors. Other situations that may have an endogenous neurochemical component, e.g. mood, depression, hypertension, may be influenced by treatments that alter the synthesis and/or release of norepinephrine. Other neurotransmitter systems to be discussed include serotonin derived from tryptophan, which is involved with sleep, mood, temperature regulation, pain sensations and appetite; nitric oxide derived from arginine, which is involved with learning and memory; and glycine derived from threonine which is involved with the central control of motor function.

## Nutrient entry into the brain: the blood–brain barrier

In order for any of the dietary components to influence chemical neurotransmission in the central nervous system they must traverse the blood–brain barrier (BBB). The BBB functions to effectively separate the peripheral chemical compartment from the central chemical compartment. Characterized by adjacent capillary endothelial cells with tight junctions (zona occludens), a paucity of micropinocytotic transport vesicles, and astrocytic foot processes, the BBB selectively determines which compounds pass between the periphery and the brain. Typically lipid-soluble (e.g. gaseous general anesthetics) and small molecular weight compounds (e.g. water, ions) are able to easily traverse the BBB. While most neurotransmitters, due to their water-soluble, polar characteristics, fail to pass the BBB, their precursor compounds, which are contained in the diet, are usually capable of passing the BBB via a facilitated diffusion process. A number of carrier-protein molecules have been identified that participate in the selective, competitive and saturable transport of amino acids, nucleic acids, amines and sugars across the BBB. The amino acids that are neurotransmitters themselves (e.g. glycine, glutamate, aspartate) typically have great difficulty passing the BBB. This is extremely important since consumption of protein that contains these amino acid neurotransmitters leads to elevations in their plasma concentrations, which if also were to lead to elevations in their levels in brain would most likely result in seizures, neurotoxicity and possibly death following a standard meal. However, some of the amino acids that are precursors for their respective neurotransmitters in the brain (e.g. L-tryptophan : serotonin; L-tyrosine : dopamine and norepinephrine; L-arginine : nitric oxide; L-threonine : glycine) do cross the BBB with greater ease. In this way the diet provides the precursor amino acids required by the brain for the synthesis of important neurotransmitters. The synthesis of these neurotransmitters is thus potentially influenced by the availability of these precursor molecules provided by the diet.

In order for an increased availability of a precursor substance to enhance neurotransmission in the brain, specific criteria must be met. First, if given orally as a bolus or in the diet, or if given parentally, as is usually the case in initial studies in experimental animals, the precursor molecule must reach the general circulation. The molecule must then be transported via the circulation to the neurons of interest. As many of the neurons of interest are located in the central nervous system, the BBB must be traversed in such cases. The precursor molecule must then be taken up into the neurons of interest and enzymatically converted into the neurotransmitter substance. This requires that the rate-limiting enzyme(s) be unsaturated with substrate at normal precursor concentrations. Once synthesized the neurotransmitter must be located in a releasable pool. Additionally, no negative feedback systems can be allowed to operate along the way that would blunt the ability of the enhanced precursor to accelerate synthesis and release.

## Tryptophan, carbohydrates and serotonin

Circulating levels of the precursor amino acids tryptophan and tyrosine are found to fluctuate depending on the composition of the diet (Glaeser et al., 1983; Maher et al., 1984). Ingestion of a high protein meal leads to increases in the plasma levels of the large neutral amino acids (LNAA) valine, leucine, isoleucine, phenylalanine, trytophan and tyrosine. Since the transport into the brain of these amino acids is competitive in nature and via facilitated diffusion at the BBB, the consumption of a high protein meal, which contains some trypto-

phan, but which also contains much more of the branched-chain amino acids (BCAA) valine, leucine and isoleucine, actually leads to a decrease in the flux of tryptophan into the brain. Studies indicate that to increase the flux of trytophan into the brain a carbohydrate-rich meal would need to be consumed (Glaeser et al., 1983). Carbohydrates elicit the release of insulin, which in addition to enhancing the uptake of glucose into peripheral sites, also enhances the uptake of the BCAA into muscle. The removal of a portion of the BCAA from the circulation results in a decrease in the competition tryptophan is exposed to for passage across the BBB. Thus, it is actually the ratio of the concentration of a particular amino acid in plasma to that of its competitors, the so-called 'plasma ratio', that determines the flux of that amino acid into brain.

Tryptophan is an essential amino acid, i.e. it cannot be synthesized by the body and must be consumed in the diet, that is the precursor for the neurotransmitter serotonin. The synthesis of serotonin occurs in two steps: initial conversion to 5-hydroxy-tryptophan followed by conversion to 5-hydroxy-tryptamine, or serotonin. The rate-limiting enzyme, tryptophan hydroxylase is normally unsaturated at typical brain concentrations of tryptophan, and thus the administration of tryptophan to animals leads to increases in the synthesis of serotonin. Additionally, diurnal variations in the levels of tryptophan in the circulation due to consumption of foods produces predictable changes in brain serotonin (Fernstrom and Wurtman, 1971). Numerous experiments have evaluated the ability of endogenously administered tryptophan to alter serotonergic neurotransmission. Tryptophan has been shown to reduce pain in animals and humans, reduce food intake (especially carbohydrates), improve depression, and decrease sleep latency (Van Praag and Korf, 1974; Hartmann, 1977; King, 1980). Additionally, animals given a diet deficient in tryptophan (e.g. certain types of corn), that results in reductions in brain serotonin, can increase pain sensitivity, a response that is reversed by tryptophan administration (Lytle et al., 1975).

Following the demonstration in experimental animals that the consumption of a meal high in carbohydrate enhances the synthesis of serotonin in the brain, studies were performed in human volunteers in an attempt to further explore the functional significance of these findings. Initial studies by Spring (1986) demonstrated that when men consumed a high-carbohydrate lunch, a significant increase in feelings of fatigue were noted. The high-carbohydrate lunch did not have to be composed of simple sugars to trigger fatigue; a high-starch, protein-poor meal was similarly effective. Others have demonstrated carbohydrate-craving by obese patients and suggested that this ultimately involves a serotonergic mechanism of food self-selection (Lieberman et al., 1986).

A number of studies have demonstrated the utility of various serotoninergic agents (e.g. fluoxetine, dexfenfluramine) to ameliorate the mood and cognitive distrubances associated with premenstrual syndrome (PMS). Because of the relationship between macronutrient consumption in the diet and serotonin synthesis, the ability of a specially designed carbohydrate-rich beverage to ameliorate some of the dysphoric symptoms of PMS in women was investigated in a placebo–controlled, crossover design study (Sayegh et al., 1995). Three isocaloric beverages were designed that would provide for different degrees of insulin release following consumption. One of the beverages containing dextrose and maltodextrin did adequately stimulate insulin release to increase significantly the ratio of tryptophan to LNAA by 29%, as compared with a placebo drink, and thus presumably would have enhanced serotonin synthesis in the brain. Women consuming this beverage had significantly lower scores for tension, anger, depression and confusion as compared with placebo. Additionally, their performance on a test of cognition (Auditory Consonant Trigrams Recognition test) was significantly improved. Two other drinks containing either protein or a carbohydrate with a much smaller glycemic index were also tested but both failed to alter the tryptophan to LNAA ratio. Neither of these drinks affected mood or cognition in the test subjects. While it is impossible to predict what proportion of those women suffering from PMS might realize symptomatic relief from such a dietary intervention, this approach appears to have associated with it essen-

tially no significant risk to the patient and thus should be tried in larger samples of women.

## Tyrosine and the catecholamines

Unlike tryptophan, which is an essential amino acid, the catecholamine precursor amino acid tyrosine, besides being obtained from the diet, can also be derived slowly from the hepatic hydroxylation of phenylalanine. The catecholamine norepinephrine is extremely important in our response to stress, whether the stress is psychological or physiological in nature, or a combination of both. Alterations in catecholaminergic neuronal function has been shown to influence a number of the responses to and consequences of stress.

While there is usually ample tyrosine to meet the biochemical and metabolic needs of an individual, during situations when catecholamine-containing neurons are made to fire rapidly, the availability of tyrosine may become limiting and compromise the rate of synthesis of dopamine, norepinephrine and/or epinephrine. Under resting conditions the rate-limiting enzyme in the biosynthesis of the catecholamines, tyrosine hydroxylase, is normally saturated with its substrate tyrosine, and it is the availability of its cofactor tetrahydrobiopterin that determines the rate of catecholamine synthesis (Lovenberg and Victor, 1974). However, when such neurons are made to fire rapidly, tyrosine hydroxylase is believed to become phosphorylated, resulting in a conformational change of the enzyme, and thereby making the availability of tyrosine the limiting factor. While normally feed-back inhibition of catecholamine synthesis keeps catecholaminergic neurotransmission carefully regulated, during periods of increased neuronal firing this feed-back inhibition appears to be inoperative. To explore this relationship between firing frequency of a group of neurons and their dependence on ample precursor supplies to support synthesis, a number of experiments have been performed which take advantage of the body's ability to selectively stimulate groups of neurons in response to pertubations of homeostasis.

When a portion of the neurons in the brain are damaged leading to a decrease in the release of neurotransmitter, as is seen in certain disease states or experimentally when neurotoxins are employed, the remaining neurons typically respond initially by increasing their firing frequency to maintain neurotransmitter homeostasis. This feed-back mechanism allows the organism to maintain neurotransmission at pre-perturbation levels. To demonstrate this point, the neurotoxin 6-hydroxydopamine, which selectively destroys dopaminergic neurons, was administered unilaterally in the striatum of rats to produce at least a 75% reduction in the number of nigrostriatal neurons (Melamed et al., 1980). The surviving neurons increased their firing rate as demonstrated by the increase in the major dopamine metabolite, homovanillic acid (HVA) on the lesioned side when compared with levels of HVA on the intact contralateral side. Administration of tyrosine via injection led to a further increase of HVA on the lesioned side, while failing to influence HVA levels on the intact, non-lesioned side. Similar dopamine synthesis-enhancing results could also be obtained by blocking postsynaptic dopamine receptors with haloperidol (Scally et al., 1977), or by depleting catecholamine stores with reserpine (Sved et al., 1979a).

Some of the more important homeostatic systems in the body that control blood pressure utilize selectively neurons that contain catecholamines. For example, when blood pressure is elevated central neurons in the brain stem increase their firing frequency to produce sympathoinhibition in an attempt to restore blood pressure back towards normal. The neurons that the released norepinephrine interact with are the same group of neurons that α-methylDOPA's (Aldomet) metabolite (α-methylnorepinephrine) acts on as a therapeutically useful antihypertensive agent. On the other hand, when blood pressure is decreased sympathoadrenal neurons are activated which result in increased peripheral resistance, heart rate, and thus blood pressure. During periods of hypotension, the depressor brain stem neurons are quiescent so as not to interfere with the adrenal responses, and similarly during periods of hypertension the pressor adrenal neurons are not activated. Thus, these reciprocal systems utilize catecholamines selectively to both increase and decrease blood pressure. As expected, administration of tyrosine to sponta-

neously hypertensive rats (SHR) decreases blood pressure (Sved et al., 1979b), while tyrosine increases blood pressure in rats made hypotensive by blood removal (Conlay et al., 1981). As predicted, the ability of tyrosine to decrease blood pressure in hypertensive rats was associated with an increase in the major norepinephrine metabolite, 3-methoxy-4-hydroxy-phenylethylglycol (MHPG) sulfate in the brain stem (Sved et al., 1979b). Additionally, since the hypotensive action of tyrosine requires its entry into the brain, coadministration of the LNAA valine, which competes for passage across the BBB and entry into the brain, attenuated the response. However, in animals made hypotensive by hemorrhage while tyrosine dose-dependently increased blood pressure, the response was not influenced by other LNAA administration, since this involves a peripheral mechanism not influenced by the BBB. Feeding rats a diet supplemented with tyrosine (five times the normal amount found in protein) has also been demonstrated to prevent the dramatic drop in blood pressure following intravenous administration of the nitrovasodilator agent hydralazine, and to significantly attenuate the rapid fall in blood pressure during a controlled hemorrhage, thereby prolonging survival (Moya-Huff et al., 1989).

Some sympathomimetic amines derive all or a portion of their activity via the release of stored catecholamines, with little or no direct interaction with adrenoceptors. One of the characteristics of such indirect-acting sympathomimetic drugs is the rapid development of tachyphylaxis, or a significant diminution in the observed response. When isolated perfused rat hearts are exposed to repeated doses of such a drug, e.g. tyramine, this tachyphylaxis is rapidly produced. However, when small amounts of tyrosine are included in the perfusion solution, a situation not typically employed with in vitro perfusion solutions for isolated tissues, the development of tachyphylaxis is completely prevented (Pinto and Maher, 1986). Similarly, the anorectic effects of several mixed-acting sympathomimetic amines, which produce a portion of their response via the release of stored catecholamines, e.g. *d*-amphetamine, *l*-ephedrine, *dl*-norephedrine, are enhanced by tyrosine administration in hyperphagic rats (Hull and Maher, 1990). Tyrosine itself had no anorectic effects in this model.

The ability of opioids such as morphine and codeine to produce analgesia is also partly dependent upon the release of norepinephrine in the central pain-pathways. Administration of tyrosine significantly potentiated the centrally mediated analgesic effects of these opioids (Hull et al., 1994). Additionally their duration of action was significantly prolonged. The response was not mimicked by the unnatural enantiomer, D-tyrosine, and the response was attenuated by co-administration of the LNAA valine. The degree of potentiation correlated with the magnitude of the increment in brain tyrosine, and co-administration of the tyrosine hydroxylase inhibitor alpha-methyl-*p*-tyrosine prevented the potentiation. Opioids also have well known peripherally-mediated effects such as decreased gastric motility and altered body temperature. Neither of these responses were influenced by increased tyrosine availability since these responses are not catecholamine-dependent. These studies have now been extended to include dietary supplementation of tyrosine (five and 10 times the normal amount for five days) in which it was found that tyrosine was still effective at enhancing the potency and prolonging the duration of action of morphine in the tail-flick analgesia assay (Hollenbach and Maher, 1998). While it was possible that the inclusion of tyrosine in higher than normal amounts in the diet might have led to an activation of tyrosinase, an enzyme that would divert the metabolism of tyrosine away from catecholamine synthesis, these studies suggest that this did not occur at least to an extent that tyrosine availability was still appropriately enhanced when needed for supporting the actions of these opioids.

Stress is known to activate catecholamine-containing neurons in the locus coeruleus. Experiments performed in rats exposed to restraint and electric shock stress demonstrated the protective effects of tyrosine added to the diet (Lehnert et al., 1984). As stress is known to rapidly deplete stores of norepinephrine in this brain area, the supplementation of tyrosine in the diet was associated with a maintenance of norepinephrine levels and an increase in its major metabolite MHPG. Further studies involving stress have been

performed in human volunteers subjected to high altitude (4700 meters) and cold temperature (15°C) stress with the aid of an environmental chamber (Banderet and Lieberman, 1989). Tyrosine supplementation (100 mg/kg, orally over a 40 minute period) significantly diminished the normal reactions to this hypobaric, hypoxic cold stress (e.g. headache, distress, muscular discomfort, fatigue, hostility, tension, feelings of cold, confusion) and prevented the cognitive deficits (e.g. poor performance on pattern recognition tests, vigilance) normally observed in subjects exposed to such severe stress. Tyrosine may find utility in modifying function in a number of catecholamine-dependent systems.

## Arginine : nitric oxide

Arginine is a basic amino acid that serves as the precursor of the free radical nitric oxide (NO) (Bredt and Snyder, 1992). Besides its long-time recognized role in the immune system, NO also plays a significant role in the peripheral regulation of blood pressure and in the central nervous system mediation of memory and learning. In the periphery NO appears to be identical to the previously described endothelium-derived relaxing factor (EDRF), which functions to relax many vascular beds via an activation of guanylyl cyclase (Palmer et al., 1987). Studies have demonstrated the utility of arginine to prevent or delay the development of hypertension in SHR and also to decrease blood pressure in animals with existing hypertension (Calvier et al., 1990). These effects of arginine are generally prevented if one of the NO synthase inhibitors (e.g. L-NAME, L-NOArg) is employed, suggesting that the effects of arginine occur via NO production. Arginine has a promising therapeutic role in modifying cardiovascular function.

Within the central nervous system NO appears to function as a retrograde neuromodulator which is associated with long-term potentiation (LTP) and learning/memory formation (Bohme et al., 1991). The process of LTP involves an increase in the efficiency of neuronal neurotransmission associated with repeated traffic through a neuronal circuit. The administration of arginine (50–400 mg/kg, i.p.) has been demonstrated to improve learning and memory in rats tested in a Morris water maze (Sato and Maher, 1995). The beneficial effects of arginine were dose-dependent and attenuated by the coadministration of NO synthase inhibitors. Interestingly, very high doses of arginine led to a decrement in performance in this behavioral task. This could have been the result of the formation of two other arginine metabolites, agmatine and the polyamine spermine, both of which are known to interfere with mechanisms associated with memory formation, or due to an overall toxic response to an exaggerated amino acid imbalance (Maher, 1994).

## Threonine : glycine

The inhibitory amino acid neurotransmitter glycine plays an important role in the control of motor function in the brain and spinal cord. Early attempts to increase central nervous system glycine concentrations by administering large doses of glycine peripherally failed since the transport of this amino acid across the BBB is very poor. Using the precursor approach, Maher and Wurtman (1980) demonstrated the ability of threonine administration to enhance central glycine concentrations in rats. Threonine was then tried in patients with spasticity and found to have beneficial effects (Barbeau et al. 1982; Lee et al., 1990; Growden et al., 1991). Currently, threonine has 'orphan drug' status with the Food and Drug Administration.

## Summary and conclusions

While many of the above examples support a role of these dietary components in modifying the synthesis, storage, release and actions of various neurotransmitter molecules in the central nervous system, most of the responses to eating everyday foods are expected to produce subtle changes in physiological and/or behavioral parameters. However, the observed subtle changes may have significant consequences when present in individuals with altered homeostasis as might be present in various disease states or certain environmental situations (e.g. depression, PMS, stress). Studies in the future should investigate the effects of various diets, e.g. vegetarian, macrobiotic, traditional Eastern, etc. on physiological and psychological

functioning. Care should be taken to differentiate between the responses of subgroups of subjects, e.g. male vs. female, old vs. young, and lean vs. obese, as some differences in the rate of neurotransmitter synthesis and receptor dynamics have been reported in some studies. Chronic consumption of these diets may lead to long-term alterations in the neurotransmitter systems' dynamics, or as is often the situation with long-term pharmacological treatments, may result in adaptive changes to minimize the acute effects of such treatments. To date, no such studies have been performed that have systematically addressed many of these issues.

Future studies will require careful design so as to enhance the chances of detecting such alterations in function. However, the most significant alterations in function occur when a dietary component is administered in a purified form, separate from the normal diet. In this case the compound should be treated more like a pharmacological agent than a nutrient since adverse (i.e. antinutritive) effects may result. The most difficult studies however will use everyday foods with the aim of detecting changes based on the underlying biochemical changes.

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