

Neurotransmitters and Nutrition

Elsa Colby-Morley, Ed.D., Ph.D.¹

Over the past decade, preclinical research has opened the promise of a new link between nutrition and neuropsychiatry — the use of dietary precursors of neurotransmitters to treat brain disorders. Alan J. Gelenberg, 1980

There is a body of evidence (Wurtman and Fernstrom, 1974; Growdon and Wurtman, 1977, 1980; Gelenberg, Wojcik and Growdon, 1980) that ingesting large quantities of naturally occurring dietary constituents that are precursors for neurotransmitters can produce sequential elevations in blood and brain levels of the neurotransmitters themselves. The relationship of dietary intake to brain function has been the focus of recent research, especially that of Richard J. Wurtman, M.D. and colleagues at the Massachusetts Institute of Technology; and a number of laboratories have begun to utilize the brain's dependence on dietary precursors to learn more about normal brain function as well as disease states. It is thought that certain disease states may result from inadequate release of

precursor-dependent neurotransmitters. Some very exciting and innovative concepts have been identified in the relationship between neurotransmitters and nutrition.

In their recent article, **Nutrients and Neurotransmitters**, Drs. J.H. Growdon and R.J. Wurtman (1980) assure us that recent evidence indicates that a view of the brain as an autonomous organ, independent of metabolic processes elsewhere in the body, is no longer tenable. They see the composition of the recent meal, the concentration of amino acids and choline in the blood, as affording the brain neurons the ability to make and release several of their neurotransmitters — serotonin, acetylcholine, and perhaps the catecholamines dopamine and norepinephrine. To satisfy its needs for neurotransmitter synthesis, the brain is unable to make sufficient quantities of amino acids and choline and therefore must obtain these precursor molecules from the peripheral circulation. Each meal, depending on its composition, can modify choline and plasma amino acid contents, alter the brain levels of choline and tryptophane; and thereby the rate at which serotonin and acetylcholine, respectively, are synthesized by the neurons will be affected. Dr. R.J. Wurtman asks, "Why does it come

1. P.O. Box 1195 Beverly Hills California 90213

as a surprise that what we eat can directly influence the brain?" And yet, it is surprising that food choice should influence such an important process as neurotransmitter synthesis; however, the full biological significance of this "open-loop" control system remains obscure (Growdon and Wurtman, 1980).

Neurotransmitters (molecules) are the chemical link whereby one neuron, or a group of neurons, communicate with another. Neurotransmitters are water soluble, low molecular weight compounds which are ionized at the pH of body fluids. They are synthesized in nerve terminals primarily and stored, partly within vesicles, in the presynaptic terminus. Neurotransmitter molecules are released into the synaptic cleft when the presynaptic neuron is depolarized, and they come into contact with specific receptors on the surface of the next distal postsynaptic cell. Many thousands of presynaptic neurons may send impulses to a given postsynaptic neuron. The given postsynaptic neuron's cell membranes somehow determine whether or not to depolarize after summation of all these excitatory and inhibitory stimuli.

Drs. Growdon and Wurtman (1980) explain that in order to demonstrate that a particular neurotransmitter is subject to nutritional control, five types of evidence must be obtained: (1) brain neurons must be unable to synthesize adequate amounts of the transmitter's precursor from glucose or any other energy source; (2) the brain must be able to obtain the precursor by taking it up from the circulation by a low affinity uptake system that allows the rate of uptake to increase or decrease when plasma levels of the precursor rise or fall; (3) plasma levels of the precursor must normally rise and fall (for example, in response to eating or secretion of hormones); (4) a low affinity enzyme must catalyze the key step in converting the precursor to the transmitter; and (5) no closed feedback loops should operate within the neuron to keep its neurotransmitter levels constant. Drs. Growdon and Wurtman assure us that the relationship between the amino acid tryptophane and the transmitter serotonin, between choline and acetylcholine, and between tyrosine and the catecholamines fulfill these criteria.

The precursor for the neurotransmitter

serotonin is tryptophane. Tryptophane consumed as part of dietary protein is the only source of the precursor for brain serotonin synthesis because tryptophane cannot be synthesized in the body. In response to meals, brain tryptophane levels, as well as the levels of most other amino acids, fluctuate characteristically during each 24-hour period. As an inverse function of the protein content of each meal, plasma amino acid composition can be monitored by neurons that contain serotonin, and thereby provide information to modify production and release of their transmitter. Administration of the amino acid tryptophane has been shown to increase synthesis and release of central serotonin (Fernstrom and Wurtman, 1971).

Drs. J.D. Fernstrom and R.J. Wurtman describe the interesting discovery that the secretion of a hormone — insulin — could increase plasma concentration of tryptophane relative to the plasma concentration of other large neutral amino acids with which it competes for transport into the brain, thereby increasing tryptophane entry into the brain. Therefore, tryptophane uptake by the brain and the acceleration of serotonin synthesis will follow a meal rich in carbohydrates which will stimulate insulin secretion. By contrast, Drs. Fernstrom and Wurtman explain, decreased tryptophane uptake into the brain, which will lower the brain's potential for synthesizing serotonin, follows a meal laden with protein which lowers the ratio of tryptophane to other amino acids.

With dietary strategies, brain serotonin levels have been increased and patients whose diseases resulted from deficiencies of serotonergic transmission have been helped. Tryptophane administration can reverse insomnia and suppress myoclonus; it has been used to treat depression successfully in some, but not all, patients and may also suppress migraine headaches in a few patients (Growdon, 1979). Dr. Growdon also suggests that by increasing CNS serotonin levels tryptophane may have a role as a hypnotic.

Ascorbic acid and Pyridoxine (B6) have often been given with L-tryptophane on the assumption that they were necessary cofactors in indoleamine synthesis (Coppen et

al., 1972). Orthomolecular physicians have established the fact that there is a difference seen in the therapeutic results when these vitamins have been added. Pyridoxine can work in one of two ways or both according to Dr. Abram Hoffer (1981). He explains that it is essential for the conversion of tryptophane into nicotinamide adenine dinucleotide (NAD). It is also required to replenish the Pyridoxine removed from the body of patients who have too much kryptopyrrole (KP). This is a substance first discovered by Irvine (1969) primarily in schizophrenic patients under the direction of Hoffer and Osmond (1963). Dr. Hoffer explains that later Pfeiffer (1975) and Pfeiffer et al. (1974) developed a quantitative assay and demonstrated that KP bound irreversibly with zinc and Pyridoxine causing a double deficiency.

Oxidized adrenaline rapidly continues to be oxidized to adrenochrome in the absence of enough NAD; Dr. Hoffer assures us that this reaction is not reversible. Oxidized adrenaline is reduced to adrenaline when there is enough NAD. Dr. Hoffer believes this is the normal process, and that the deficiency of NAD should therefore cause or, if it is already present, intensify schizophrenic symptoms; and that pellagra is the best natural model of schizophrenia.

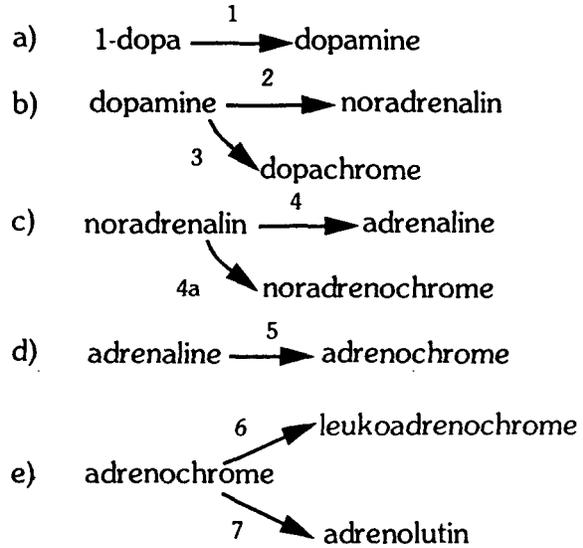
In the Vitamin B3 deficiency disease pellagra, a deficiency of NAD is present. A diet which is too low in tryptophane, deficient in Vitamin B3 and absorbable Vitamin B3 and too rich in leucine causes pellagra. Too much B3 is lost in the urine when too much leucine is present. This is reversed by isoleucine, i.e., isoleucine is an antidote against the pellagra producing property of leucine (Hoffer, 1981).

In 1954, Hoffer, Osmond and Smythies published **The Adrenochrome Hypothesis of Schizophrenia**. The adrenochrome hypothesis can be described biochemically by a series of reactions as follows:

- a) Noradrenalin + methyl → adrenaline
- b) Adrenaline + oxygen → adrenochrome
- c) Adrenochrome ↗ leukoadrenochrome
 ↘ adrenolutin

They suggested that any reaction which diverted adrenochrome into adrenolutin rather than leukoadrenochrome would cause or aggravate schizophrenia.

The complete hypothesis:



Abram Hoffer, 1981

Dr. Abram Hoffer explains that reactions 1, 2 and 4 are essential as we cannot live without noradrenalin and adrenaline. He suspects that reaction 5 and reactions such as 3 are also essential when under proper control. He has suggested (Hoffer and Osmond, 1963) that the ratio of leukoadrenochrome to adrenaline helps to control anxiety. Reaction 6 would be therapeutic but reaction 7 is toxic.

The adrenochrome hypothesis immediately called attention to Vitamin B3 and ascorbic acid and potential treatments for schizophrenia and helped point to the catecholamines as significant facts in the etiology of schizophrenia.

We now know that the production and release of catecholamine neurotransmitters dopamine and norepinephrine can also be influenced by physiologic variations in brain levels of their dietary precursor tyrosine (Growdon and Wurtman, 1980). Dopaminergic neurons have been implicated in the etiology of Parkinson's disease and schizophrenia; norepinephrine - containing neurons are thought to be involved in blood pressure control and depression. Philip B. Applewhite (1981) suggests that regardless of the cause or causes of

depression, the best current guess of what is happening is that there is not enough of the neurotransmitter molecule norepinephrine at the right place in the brain. He suggests that if norepinephrine molecules are not present in selected nerve cells in sufficient quantity, nerve signals will not be transmitted from one nerve cell to another at a fast enough rate to maintain a normal level of behavior. He assures us that diet may be an important consideration in assuring the availability of the chemical precursor of norepinephrine. Norepinephrine is synthesized from the amino acid tyrosine — if tyrosine is present in too low an amount in the diet, not enough norepinephrine will be synthesized and depression may result. Administration of the amino acid tyrosine has been shown to elevate plasma tyrosine concentrations, thereby increasing the brain uptake of tyrosine and synthesis of the catecholamines dopamine and norepinephrine (Sally, Ulus and Wurtman, 1978). If there is a gene for depression would it act by suppressing the production of norepinephrine? While the molecular specifics of major depression are by no means firmly established, they tie in nicely with another mental illness at the other end of depression — mania (Applewhite, 1981). To indicate its shifting nature, psychiatrists now call mania-depression a bipolar disorder. Dr. Applewhite suggests, "if depression is produced by a lack of the norepinephrine molecule, it would be reasonable to guess that mania is produced by an excess of the norepinephrine molecule."

Drs. J.H. Growdon and R.J. Wurtman (1980) express astonishment to find that cholinergic neurons were vulnerable "to the vagaries of food choice" as were the neurons releasing serotonin. They explain that acetylcholine is synthesized when a molecule of choline joins a molecule of acetylcoenzyme A in a reaction catalyzed by the enzyme choline acetyltransferase. Since this enzyme has a low affinity for its substrate and is not fully saturated under normal conditions, it seemed possible that the synthesis of acetylcholine, like that of serotonin, might be accelerated by treatments that increased the levels of precursor in the brain. Drs. E. Cohen and R.J. Wurtman (1976) found that administration of choline,

either by injection

or as a constituent of the diet, caused major sequential elevations in serum choline, brain choline and brain acetylcholine levels. Subsequent studies have shown that as a function of dietary choline content in humans, blood and choline levels normally vary. The effects of dietary choline provided as lecithin, the form in which it usually is ingested, was found by Drs. J.H. Growdon and R.J. Wurtman (1980) to be far greater than those observed when choline itself is administered; that the acetylcholine-forming enzyme is not subject to end-product feedback controls; and that increases in acetylcholine levels are, in fact, associated with parallel changes in the amount of the transmitter that are released into synapses to act on postsynaptic receptors.

L. Galzigna (1970) has suggested that there may be a relationship between the neurotransmitter acetylcholine and catecholamines. A complex which does not change to adrenolutin in ascorbic acid medium is found when acetylcholine interacts with oxidized noradrenaline. With dopamine it reacts similarly. Dr. Abram Hoffer (1981) explains that both acetylcholine and nicotinamide increase the auto-oxidation of noradrenaline but the complex reacts differently with ascorbic acid. Dr. Galzigna expresses the idea that aminochrome could form if a central catecholamine leaks into the synapse; acetylcholine would stabilize it and nicotinamide would increase its removal. "The leak of catecholamine and the stabilization of its oxidation products could produce an aberrant communication, which on the one hand might be the chemical event leading to a short circuit between adrenergic and cholinergic systems, and on the other hand might be the origin of irritative foci of stabilized psychotogenic agents at cortical level. Both effects could possibly explain the onset of mental illness" (Hoffer, 1981).

The neurotransmitter choline and its precursor lecithin have been used successfully to suppress involuntary movements in patients with tardive dyskinesia — a choreiform movement disorder caused by antipsychotic medication. The employment of choline and lecithin to suppress the abnormal movements of tardive dyskinesia constitutes the most impressive use of

dietary therapy to date (Growdon, Hirsch, Wurtman et al., 1977; Galenberg, Wojcik and Growdon, 1979). These substances presumably increase central nervous system acetylcholine tone. For the same reason, lecithin is being tested for the treatment of mania (Cohen, Miller, Lipinski et al., 1980). Studies are also underway to evaluate lecithin's ability to augment memory in normal subjects (Davis, Mohs and Finklenberg et al., 1980) and to improve cognitive function in patients with dementia (Christie, Blackburn and Glen, 1979).

We know now that eating certain foods can raise the level of brain neurotransmitters, the chemicals that carry messages between brain cells. There is direct evidence that higher levels of these chemicals actually increase the amplitude of the message sent to the next cell — with probable consequences for behavior (Wurtman, 1978). This has major implications for understanding healthy persons and therefore for mental illness and perhaps other forms of disease. It is conceivable that we will eventually know enough about how diet affects brain chemistry to lessen pain and control our moods, to suppress or stimulate our appetites for certain foods, to be more alert by day or sleep by night, and even to improve our memory and circulation (Wurtman, 1978).

As times goes by we may see more and more psychological disorders being removed from the classification of mental illness and being called what they are — genetic, nutritional, metabolic or infectious disorders of the brain. Dr. Philip B. Applewhite notes, "... their molecular origin is acknowledged." As we learn more about the brain, i.e., neurotransmitters and the role nutrition plays, the role of the psychosocial environment in causing mental illness is being replaced with attention to the role of the chemical and physical.

Opiatlike substances which reside in the brain have only recently been discovered. They are protein molecules called endorphins morphine, or the morphine within us. They are found in B lipotropin from the anterior pituitary gland — they are found in all areas of the brain and in cerebro spinal fluid (Hoffer, 1981). Endorphins are noted for their ability to alter moods as well as for their pain killing properties. There is now some speculation that endorphins

may create the moods experienced by schizophrenics. The notion that the brain contains an in-built supply of opioid chemicals has been particularly seductive to psychiatrists — and one awaits the scientific evaluation of the efficacy of their potential in psychiatric disorders.

As far as mental health is concerned, it has been suggested that the endorphins may play such a major role in regulating moods that disturbances in these molecules could lead to any number of mental illnesses. Dr. Applewhite (1981) suggests that endorphins may serve to increase eating. Naturally occurring endorphin molecules in the brain can be released into the bloodstream targeted for the stomach. Here the endorphins may block the nerve impulses from the stomach that tell the brain the stomach is full, and we continue to eat. Norepinephrine applied to the brain will cause hunger in "full" animals (Applewhite, 1981). Eating has its own control center in the hypothalamus and an injection in this area (in rats) with a neurotransmitter molecule like norepinephrine stops even hungry animals from eating (in other brain areas it causes eating). "It is difficult to imagine that anorexia nervosa is caused by anything other than a malfunction in the eating center of the hypothalamus" (Applewhite, 1981). Given the potential implications that endorphins and neurotransmitters both play a role in moods and depression and in eating there is the possibility that we may find an important relationship between them; and that endorphins, like neurotransmitters, are somehow controlled by nutrition.

It is too soon to tell yet, but the endorphins may bring us an important step closer to the cause of molecular madness.

Philip B. Applewhite, 1981

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