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Review

Non-nutritional uses of nutrients

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ABSTRACT

Nutrients are generally conceived as dietary substances which the body requires more-or-less continuously, within a particular dosage range, to protect against developing the characteristic syndromes that occur when they are deficient. However some nutrients – when given apart from their usual food sources or at higher doses than those obtained from the diet – can also exercise pharmacologic effects, particularly on the CNS. Some, like folic acid, can promote neuronal development; others, like the neurotransmitter precursors tryptophan, choline, and histidine, can modulate the rates at which their products are synthesized; yet others, like uridine and omega-3 fatty acids, can increase the production of synaptic membrane, and thus promote synaptogenesis. In order for the nutrient to produce such effects, its plasma levels must be allowed to increase substantially when larger amounts are consumed; an unsaturated or competitive system must exist for transporting the nutrient across the blood–brain barrier; and the enzymes that convert the nutrient to its pharmacologically-active form must also be unsaturated with substrate. Nutrient mixtures chosen for their pharmacologic effects (and general lack of serious side-effects) are presently used for ameliorating several conditions, and more such uses can be anticipated.

Contents

1. Introduction

This article describes the ability of some nutrients to produce pharmacological effects, particularly involving the central nervous system, when administered alone or when given in doses above their recommended dietary allowances. Nutrients are generally conceived as food constituents which prevent development of the clinical syndromes that appear when they are deficient. Their usual sites of action are biochemical pathways, in which they serve as substrates or cofactors of enzymes. By enabling these pathways to operate at normal rates they sustain growth and metabolism. Other chemicals naturally present in some foods – for example caffeine – can produce pharmacological effects involving, for example, cardiac contractions or neurotransmission; however these compounds are not essential for normal growth or metabolism and thus are not classified among the nutrients.

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Drugs, in contrast to both nutritive and non-nutritive food constituents, are not endogenously present in foods, nor are their intake essential for preventing clinical deficiency syndromes. Their pharmacologic actions can involve a variety of sites, including for example enzymes, neurotransmitter receptors, other types of proteins, and even multicellular systems.

This classification of the biologically-active chemicals that people ingest as belonging within either the nutrient, non-nutritive food constituent, or drug categories fails to account for compounds which can function as both nutrients and drugs. For example, the vitamin folic acid is, at low doses, a nutrient, which protects against developing a characteristic type of anemia; however when taken at higher doses by normally-nourished pregnant women, folic acid is a medication which decreases the incidence of neural tube defects in fetuses. (Moreover a large recent study (N>40,000) (Magnus et al., 2006) indicates that folic acid supplements taken before and after conception can significantly decrease the risk that offspring will develop severe language delay, as assessed by Maternal Report at age 3 (C. Roth and E. Susser, personal communication, 2010.) Or the amino acid tryptophan (Cansev and Wurtman, 2007); which functions as an essential nutrient, enabling the synthesis of albumin (Munro, 1968) and other endogenous proteins, but when taken alone as a dietary supplement acts as a drug, enhancing serotonin production in (Fernstrom and Wurtman, 1971a) and release from (Schaechter and Wurtman, 1990) brain neurons, and thereby promoting, for example, sleep. Dietary carbohydrates also increase brain tryptophan levels when they are consumed along with little or no protein (Fernstrom and Wurtman, 1971b), and thereby produce pharmacologic effects on mood, sleep propensity, and appetite (Lieberman et al., 1986) which are similar to those that follow administration of the pure amino acid (Demisch et al., 1987; Lieberman et al., 1985; van Praag, 1981). Similarly choline, taken alone, increases the production (Cohen and Wurtman, 1975; Haubrich et al., 1975) and release (Bierkamper and Goldberg, 1980; Ulus et al., 1977) of brain acetylcholine without affecting the synthesis of phosphatidylcholine; however when taken along with two other food constituents – uridine and an omega-3 fatty acid – choline increases membrane phosphatidylcholine production (Wurtman et al., 2009a, 2009b) and can thus facilitate synaptogenesis (Wurtman, 2009). Thus some nutrients can have important, non-nutritional effects even among normally-nourished people.

2. Processes that enable dietary nutrients to affect CNS functions

2.1. "Open-loop" control of plasma levels of the nutrient

In order for administration of a nutrient to exert a pharmacological effect on the brain, its plasma concentration (which, unlike concentrations of drugs being administered for the first time, never starts at zero) must be "allowed" to rise, in relation to the dose that has been consumed, i.e., its concentration must be under "open-loop" regulation, and not kept within a more-or-less constant range by feedback mechanisms. (This is generally the case for nutrients, even those without pharmacologic actions. For example, plasma levels of leucine and the other branched-chain amino acids normally vary over a six-fold daily range depending on the protein content of the meal most recently ingested; Fernstrom et al., 1979).

2.2. Blood–brain barrier transport of hydrophilic nutrients

Since most nutrients, unlike most drugs, are hydrophilic, a mechanism must exist, based on an energy-requiring transport process or on facilitated diffusion, for ferrying them across the hydrophobic, lipid-rich membranes that comprise the blood–brain barrier. Moreover the protein or proteins that mediate this process should, in general, be unsaturated with nutrient-substrate, such that a rise or fall in the nutrient's plasma concentration will produce parallel changes in its transport into, and its levels within the brain. It should be noted that the transport rates of some nutrients, e.g., the large neutral amino acids (LNAA) like tryptophan or tyrosine, depend not simply on their own plasma levels but also on those of other LNAA (Fernstrom and Faller, 1978; Fernstrom and Wurtman, 1972) which compete with them for attachment to a common site, the L-system LNAA transport protein complex (LAT1-4F2hc) (Boado et al., 1999). This transport system, unlike others that carry nutrients across the blood–brain barrier, is saturated with its amino acid substrates, so the rate at which any single LNAA is transported into the brain depends not on its plasma concentration, per se, but on the ratio of that concentration to the summed concentrations of its competitors (e.g., the "plasma tryptophan ratio"). Hence a protein-rich meal which significantly elevates plasma tryptophan levels (Fernstrom et al., 1979) will fail to elevate brain tryptophan if it produces proportionately greater increases in plasma levels of the other, more abundant LNAA and thus lowers the plasma tryptophan ratio.

The facilitated-diffusion mechanism that transports tryptophan and other LNAA into the brain also transports several other amino acids that are neurotransmitter precursors (Pardridge, 1977), and whose concentrations in the brain control the rates at which their neurotransmitter products are formed. These include, among others, tyrosine (for brain dopamine and norepinephrine, Wurtman et al., 1974); glutamine (for GABA, Wang et al., 2007); threonine (for glycine, Maher and Wurtman, 1980); and histidine (for histamine, Schwartz et al., 1972). Moreover this mechanism also transports circulating amino acids – valine, leucine, and isoleucine (Fernstrom and Faller, 1978; Pardridge, 1977) – which are not themselves neurotransmitter precursors but which can slow brain serotonin or dopamine synthesis by competing for blood–brain barrier transport with tryptophan or tyrosine (Gessa et al., 1974; Wurtman et al., 1974). Not surprisingly, the LNAA in dietary protein also suppress the uptake into brain of the amino acid drug L-dopa, also an LNAA, thus diminishing a dose's therapeutic efficacy (Mena and Cotzias, 1975), while consumption of a carbohydrate-rich meal – which via insulin, lowers plasma levels of the competing LNAA – increases the dose's neurochemical and clinical effects (Berry et al., 1991) sometimes to the point of inducing dyskinesias.

2.3. Subsaturation of low-affinity enzymes that activate the nutrient

The brain enzyme that controls the overall rate at which the nutrient is converted to its pharmacologically-active product must also be unsaturated with substrate, and capable of generating more product when brain levels of its substrate rise. This is indeed the case for the acetyltransferase enzyme that converts choline to the neurotransmitter acetylcholine (Blusztajn and Wurtman, 1983); or the kinases that phosphorylate uridine (Cansev, 2006; Skold, 1960) to form the P2Y receptor agonists (Arslan et al., 2000; Burnstock, 2007) UDP or UTP; or the enzyme that hydroxylates tryptophan (Hufton et al., 1995) to form 5-hydroxytryptophan, an intermediate in serotonin synthesis ; or the enzymes that control the conversion of tyrosine, glutamine, threonine, or glutamine to their neurotransmitter products, described above. The activity of tyrosine hydroxylase, the enzyme in catecholaminergic nerve terminals that hydroxylates tyrosine to form dopa and, subsequently, dopamine or norepinephrine, may or may not be affected by tissue tyrosine levels, depending on its own state of phosphorylation: If the neuron has been quiescent, the activity of its tyrosine hydroxylase is limited by the enzyme's poor saturation with tetrahydrobiopterin, its cofactor (Lovenberg et al., 1975); however when the neuron fires repeatedly, the enzyme becomes phosphorylated, causing its cofactor affinity to rise several hundredfold and its net activity to depend instead on its saturation with tyrosine (Melamed et al., 1980; Wurtman et al., 1974). This enables the oral administration

of tyrosine to increase the net neurotransmitter outputs of some catecholaminergic neurons selectively – the ones that happen to be firing frequently – without affecting dopamine or norepinephrine release from neurons that happen to be quiescent (Conlay et al., 1981; Gibson et al., 1983).

Few CNS-active drugs require biotransformation within the brain in order to become active, nor do pharmacologically-active non-nutritive compounds like caffeine; however the pharmacologically-active nutrients – like tryptophan, uridine, or choline – usually must first be metabolized, e.g. by phosphorylation, acetylation,or hydroxylation, to produce these effects.

3. Examples of nutrients that have non-nutritive therapeutic effects

The remainder of this report describes two examples of nutrients which can produce therapeutically-useful pharmacologic effects: Sugars and starches, which by eliciting insulin release, raise brain tryptophan and, consequently, the synthesis, levels and release of serotonin; and a triad of nutrients – uridine, choline, and docosahexaenoic acid – which, when given together, enhance the synthesis of brain phosphatides, the activation of brain P2Y receptors controlling neuronal differentiation, and the formation of new dendritic spines and glutamatergic synapses.

3.1. Dietary carbohydrates, serotonin release, and disorders affecting mood

3.1.1. Carbohydrate effects on human brain: biochemical mechanisms

Consumption of a snack or meal that is rich in carbohydrates but contains little or no protein increases serotonin-mediated neurotransmission and, as a result, the likelihood that serotonin-dependent behaviors will occur. Intake of carbohydrates is soon followed by an increase in brain tryptophan levels (Fernstrom and Wurtman, 1971b); this increases the substrate-saturation of tryptophan hydroxylase, the enzyme that initiates and limits serotonin synthesis, causing more serotonin to be formed, brain serotonin levels to rise, and the release of serotonin into synapses to increase, basally and in response to neuronal depolarization (Schaechter and Wurtman, 1989, 1990).

The carbohydrates act via insulin, and independent of whether or not they also happen to taste sweet. This hormone substantially decreases plasma levels of most of the large, neutral amino acids (LNAA, e.g., leucine; isoleucine; valine; tyrosine; phenylalanine) by increasing their uptakes into skeletal muscle, however it causes only minor changes in plasma tryptophan levels (Fernstrom et al., 1979). The difference between tryptophan's response to insulin and the responses of the other LNAA results from tryptophan's propensity, unique among amino acids, to bind loosely to circulating albumin (about 80% of total plasma tryptophan) (McMenamy and Oncley, 1958). This binding is competitive with the albumin-binding of circulating free fatty acids (Lipsett et al., 1973; Madras et al., 1973) and since insulin also lowers plasma levels of these compounds, it enables more tryptophan to bind to the albumin. This causes total plasma tryptophan levels – free plus bound – to fall only slightly or even to rise while levels of the other, competing LNAA are falling. Yet since tryptophan's binding to albumin is of low affinity, both the albumin-bound and "free" tryptophan in the blood readily traverse the blood–brain barrier (Pardridge and Fierer, 1990) enabling brain tryptophan and then serotonin levels to rise after insulin is secreted.

Dietary proteins, virtually all of which contain tryptophan and raise plasma tryptophan levels (Maher et al., 1984) have, paradoxically, opposite effects on brain tryptophan and serotonin from those of dietary carbohydrates, all of which lack tryptophan: Protein consumption suppresses the increases in brain tryptophan and serotonin that carbohydrate consumption would otherwise produce (Yokogoshi and Wurtman, 1986). This is because most proteins contain only about 1.0–1.5% tryptophan, but 20–30% of the other LNAA, and thus produce much greater increases in plasma levels of the other LNAA than in tryptophan. Hence as described above, eating carbohydrates, which selectively lowers plasma LNAA other than tryptophan, increases the "plasma tryptophan ratio" (the tryptophan concentration divided by the summed concentrations of competing LNAA; a measure of the rate at which tryptophan enters the brain), but eating proteins, which raises plasma LNAA more than tryptophan, decreases this ratio (Fernstrom et al., 1979), hence less tryptophan enters the brain.

Many people learn to associate the consumption of carbohydrates – often as high-carbohydrate, low-protein snacks – with decreased appetite, increased sleepiness, improved mood, or diminished anxiety, and elect to consume such snacks at times of day that they feel "low" (Wurtman et al., 1981). Among patients with disorders like SADS (Seasonal Affective Disorder Syndrome) (Rosenthal et al., 1984) or the Late Luteal Phase Disorder Syndrome (severe PMS) (Sayegh et al., 1995; Wurtman et al., 1989) this behavior is often exaggerated, and patients may describe severe "carbohydrate-craving" as a presenting symptom. If the carbohydrate-rich foods chosen for consumption also happen to be rich in fats, patients can become obese. Among another group of patients severe carbohydrate-craving develops while they follow weight-loss diets that allow ad libitum protein and fat consumption but strictly limit carbohydrate intake (Wurtman and Frusztaler-Marquis, 2006); similar carbohydrate-craving is observed among rats given high-protein, low-carbohydrate diets (Wurtman et al., 1983). Such diets may thereby predispose to manifestations of reduced serotonin release, including depressed mood, insomnia, and emotional lability (Wurtman and Frusztaler-Marquis, 2006).

Not a great deal of carbohydrate – approximately 25 g – is required to increase the plasma tryptophan ratio in humans by an amount – 30–50% or more (Martin-Du-Pan et al., 1982) – which, in experimental animals, is sufficient to increase brain tryptophan (by 39%), and the spontaneous or depolarization-induced release of serotonin by 28% or 14%, respectively (Schaechter and Wurtman, 1989, 1990). Among overnight-fasted subjects who, on separate days, consumed each of two common American-style breakfasts – one containing about 70 g carbohydrate and 5 g protein, and the other 15 g carbohydrate and 47 g protein – the plasma tryptophan ratio was on average 54% higher after the carbohydrate-rich meal (Wurtman et al., 2003), suggesting that meal choice had indeed affected brain serotonin synthesis.

3.1.2. Tryptophan, dietary carbohydrates, and behaviors

The brain controls not only total food and calorie intake but also the proportions of the macronutrients – proteins and carbohydrates – that are chosen for consumption (Musten et al., 1974; Wurtman and Wurtman, 1979) Moreover, the mechanisms mediating macronutrient choice involve the decreases or increases these nutrients induce in serotonin-mediated neurotransmission (Wurtman and Wurtman, 1979). Evidence that people perhaps-unwittingly select the proportions of macronutrients that they eat, and that this process involves brain serotonin, includes the propensity of most Americans - even those with little or no knowledge of food composition – to consume about 13–14% of total daily calorie intake as proteins (Wurtman and Wurtman, 1989); or the ability of a carbohydrate premeal to diminish the proportion of carbohydrates subsequently chosen for dinner (Wurtman et al., 1983); or the selective increase in carbohydrate intake among animals given a drug that suppresses serotonin-mediated neurotransmission (Wurtman and Wurtman, 1979); or the inverse phenomenon: suppression of elective carbohydrate intake among humans given a drug that enhanced serotonin-mediated neurotransmission (Wurtman et al., 1981). This mechanism of appetite control apparently is impaired in a group of disorders in which patients manifest both affective and appetitive symptoms e.g., depression or anxiety, or excessive carbohydrate-craving, or excessive

weight gain. Indeed, the observation that a patient exhibits both depressive and appetitive symptoms - particularly carbohydrate-craving – should raise the possibility that serotonin-mediated neurotransmission is involved in his or her disorder, and that a therapy directed towards enhancing that transmission may be useful.

Such disorders include, as above, the Seasonal Affective, Disorder Syndrome, or "winter blues", in which patients may exhibit signs of major depression between November and March, severe carbohydrate-craving, weight gain, and a propensity towards social isolation (O'Rourke et al., 1989; Rosenthal et al., 1984); the Late Luteal Phase Dysphoric Syndrome (LLPDS), a severe form of the premenstrual syndrome, characterized by emotional lability with anger, anxiety, and signs of depression, as well as by carbohydrate craving and weight gain during the last days of the luteal phase (Sayegh et al., 1995) and Obesity Associated with Severe Carbohydrate-Craving, most commonly observed in female patients (Wurtman and Frusztaler-Marquis, 2006).

Patients with LLPDS have been successfully treated with serotonin-uptake blockers including fluoxetine (Wurtman, J.J., Wurtman, R. J., Composition for Treating the Premenstrual or Late Luteal Phase Syndrome, US Patent # 4971998) or dexfenfluramine (Brzezinski et al., 1990), and those with the milder premenstrual syndrome with a mixture of dietary carbohydrates (Sayegh et al., 1995) ("PMS Escape") formulated to sustain insulin secretion for a number of hours. Those with SADS are often well treated with supplemental lighting, not known to have specific effects on serotonin-mediated neurotransmission; those with carbohydrate-craving obesity have been effectively treated with an agent that releases serotonin directly, suppresses its reuptake, and activates particular serotonin receptors (Wurtman et al., 1981). Tryptophan has been used extensively, alone or with an antidepressant drug, to treat major depression (Coppen et al., 1972), and LNAA mixtures that deplete brain tryptophan and serotonin as provocative challenge tests for diagnosing depression (Delgado et al., 1991). The use of supplemental tryptophan terminated abruptly in the United States and elsewhere in 1989 because batches of amino acid that had been synthesized using a novel chemical reaction (and found subsequently to contain previously-unknown impurities) caused a sometimes-lethal disease, the eosinophilia-myalgia syndrome, among dozens of Americans who had taken it to relieve insomnia or mild depressive symptoms (Centers for Disease Control, 1989. Eosinophilia-myalgia syndrome: New Mexico. Morb Mortal Wkly Rep 38:765–767); only recently has oral tryptophan returned to the pharmacy.

3.2. Uridine, supporting nutrients, and synapse formation

Circulating uridine, like dietary carbohydrates, is used by cells in two ways: As a nutrient it is incorporated into compounds like RNA and uridine diphosphoglucose (UDP-glucose) which are needed for cellular differentiation and metabolism. And via its phosphorylated products uridine diphosphate (UDP), uridine triphosphate (UTP), and cytidine triphosphate (CTP) it activates receptors and proteins that control the syntheses of the phosphatides and of specific signaling proteins in synaptic membranes (Wurtman et al., 2009b, 2010) (Neither the phosphatides nor, of course, any proteins actually contain uridine itself.)

The UTP formed from uridine is the precursor for most of the CTP in brain (Cansev et al., 2005) (almost all, in humans), levels of which can control the overall production of phosphatides via the Kennedy Cycle (described below). Uridine, UTP, and uridine's other phosphorylated products also act via P2Y receptors (Arslan et al., 2000; Burnstock, 2007) to influence neuronal differentiation, stimulating neurite outgrowth in vitro (Pooler et al., 2005), and, when consumed with choline and the omega-3 fatty acids docosahexaenoic acid (DHA) or eicosapentenoic acid (EPA), stimulating the syntheses of synaptic proteins (e.g., PSD-95; GluR-1; Synapsin-1; Actin; NF-70) (Wurtman et al., 2006) and the formation of specialized synaptic membranes in vivo (Wurtman et al., 2009a, 2009b). This treatment also increases the production, in hippocampus and cerebral cortex, of dendritic spines (Sakamoto et al., 2007) — the anatomic precursor of glutamatergic synapses (Alvarez and Sabatini, 2007; Barbosa et al., 2008; Diano et al., 2006; Knott et al., 2006; Nimchinsky et al., 2004). Since more than 90% of all new dendritic spines are believed to develop into functioning synapses (Toni et al., 2007), and since the treatment also enhances cognitive functions in experimental animals (Holguin et al., 2008a, 2008b) the possibility arises that the administration of this nutrient triad might provide a useful adjunct for managing diseases that cause synaptic loss and, consequently, cognitive disturbances (Wurtman et al., 2010). These might include, for example, neurodegenerative disorders like Alzheimer's Disease (Scheltens et al., 2010), or Parkinson's Disease with dementia; vascular insufficiency causing strokes; brain trauma causing multiple concussions in athletes; or "blast injuries" in combat veterans.

In the Kennedy Cycle (Kennedy and Weiss, 1956), three circulating nutrients — choline, uridine, and a fatty acid (e.g., DHA or EPA) are converted to a phosphatide, phosphatidylcholine (PC), which is the major constituent of synaptic membranes. The choline is phosphorylated by the enzyme choline kinase to form phosphocholine, and the uridine is sequentially phosphorylated by kinase enzymes to form UTP. Some of the UTP is then converted to CTP, which can combine with the phosphocholine to form cytidydyl-diphosphocholine (CDP-choline, also known as citicoline). Finally, the CDP-choline combines with a diacylglycerol molecule – preferentially one containing an omega-3 fatty acid like DHA or EPA (Araki and Wurtman, 1997) – to yield the PC. Importantly, all of these kinase enzymes exhibit low-affinities towards their substrates (Wurtman et al., 2009a, 2009b), hence increases in, for example, intracellular choline or uridine concentrations are followed by increases in the formation of their phosphorylated products in brains of humans (measured using magnetic resonance spectroscopy; Babb et al., 2004) as well as experimental animals (Cansev et al., 2005; Millington and Wurtman, 1982). This substrate-dependence underlies the ability of treatment with uridine, DHA, and choline to affect phosphatide levels per brain or per brain cell, which can increase by 30% or more after four weeks of daily treatment (Wurtman et al., 2006). Similar increases are noted in the other major brain phosphatides phosphatidylethanolamine (PE, also formed by the Kennedy Cycle) and phosphatidylserine (PS, formed by base-exchange of serine for the ethanolamine in PE or the choline in PC) — as well as in other membrane phospholipids (phosphatidylinositol; sphingomyelin). Moreover levels of synaptic membrane proteins such as those listed above are also increased (probably a consequence of P2Y receptor activation by uridine phosphates and, possibly also, of DHA acting on syntaxin-3; Darios and Davletov, 2006). Hence the stoichiometric relations among key synaptic membrane constituents tend to be preserved. The choline needed for PC synthesis can derive from consumption of choline-rich foods or from its synthesis in and secretion from the liver; this synthesis can be enhanced by administering vitamins B12, B6, and folic acid to generate the required methyl groups.

In humans, the plasma contains abundant uridine but virtually no cytidine – even after consumption of cytidine-rich compounds like citicoline (Wurtman et al., 2000) – because the cytidine is deaminated to form uridine in the liver. Plasma uridine – unlike cytidine – readily crosses the blood–brain barrier, via redundant low-affinity and high-affinity transport systems (Cansev, 2006; Pastor-Anglada et al., 1998), and can be converted, via UTP, to CTP, as described above. Consumption of citicoline shares with uridine–DHA–choline mixtures the ability to elevate plasma uridine and choline levels (Wurtman et al., 2000), however it fails to raise those of plasma DHA or of DHA-rich diacylglycerol in the brain. Hence though it can accelerate the Kennedy Cycle to the point of increasing brain CDP-choline levels, citicoline administration has not been shown to increase synaptic

membrane nor dendritic spine formation. Unlike humans, rats and other laboratory rodents do have cytidine as well as uridine in their blood, more so in rats and less in gerbils, thus gerbils are sometimes used for studying uridine's effects (because its metabolism of pyrimidines is closest, among laboratory rodents, to that of humans).

Like the nutrients tyrosine and choline, circulating uridine can derive from both endogenous syntheses in the liver and from dietary sources. When infants consume mothers' milk or infant formulas they ingest uridine in a bioavailable form, i.e., as uridine monphosphate (UMP), and consumption of this source by adults has been shown to produce dose-related increases in plasma uridine levels. In contrast, most of the uridine in the adult's diet is apparently in poorly-bioavailable forms, and is virtually completely destroyed in passage through the gut and liver (Gasser et al., 1981). Thus no normal adult food has been compellingly shown to raise plasma uridine levels.

4. Conclusions

Some nutrients have dual functions: Consumed in foods within a low dosage range, they are essential for sustaining normal metabolism or growth; and if given at higher doses or in pure form they can also exert pharmacologic effects, particularly on the syntheses of neurotransmitters, synaptic membranes, and other brain constituents. Thus giving the essential amino acid tryptophan, or consuming carbohydrates – which also raise brain tryptophan levels – promotes the synthesis and release of serotonin, as well as serotonin-dependent behaviors. Or giving the circulating pyrimidine uridine – obtained from hepatic synthesis or by consuming uridine monophosphate (UMP) in mothers' milk or synthetic mixtures – raises brain levels of UTP (which activates P2Y receptors) and CTP (which activates the Kennedy Cycle of phosphatide synthesis), thereby promoting synaptogenesis. Nutrients with such dual functions may serve as a novel type of new drug.

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