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Synapse formation and cognitive brain development: effect of docosahexaenoic acid and other dietary constituents

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Abstract

The brain is unusual among organs in that the rates of many of its characteristic enzymatic reactions are controlled by the local concentrations of their substrates, which also happen to be nutrients that cross the blood-brain barrier. Thus, for example, brain levels of tryptophan, tyrosine, or choline can control the rates at which neurons synthesize serotonin, dopamine, or acetylcholine, respectively. The rates at which brain cells produce membrane phospholipids such as phosphatidylcholine (PC) are also under such control, both in adult animals and, especially, during early development. If pregnant rats are fed the 3 dietary constituents needed for PC synthesis—docosahexaenoic acid, uridine, and choline—starting 10 days before parturition and continuing for 20 days during nursing, brain levels of PC, and of the other membrane phosphatides (per cell or per mg protein), are increased by 50% or more. In adult animals, this treatment is also known to increase synaptic proteins (eg, synapsin-l, syntaxin-3, GluR-l, PSD-95) but not ubiquitous proteins like β-tubulin and to increase (by 30% or more) the number of dendritic spines on hippocampal neurons. Docosahexaenoic acid currently is widely used, in human infants, to diminish the negative effects of prematurity on cognitive development. Moreover, docosahexaenoic acid, uridine (as uridine monophosphate), and choline are all found in mother's milk, and included in most infant formulas. It is proposed that these substances are part of a regulatory mechanism through which plasma composition influences brain development.

1. Introduction

1.1. ω-3 fatty acids and the brain

The phospholipids in brain membranes contain many different fatty acids (cf, reference [1]). However, one such compound, the ω-3 polyunsaturated fatty acid docosahexaenoic acid (DHA), is both uniquely abundant among them [2] and particularly important in the development and maintenance of brain mechanisms underlying cognitive functions [3]. Thus, cognitive development among breast-fed full-term infants, or in full-term or preterm infants given supplemental DHA, is described as being superior to that in infants consuming formula diets that lack DHA [4]; and the consumption, by term infants of a formula supplemented with DHA (plus the ω-6 fatty acid arachidonic acid [AA]) during the first 17 weeks of life increased test scores on the Mental Development Index, assessed a year or more later [5]. At the other end of life, DHA levels in plasma phosphatidylcholine (PC) are inversely correlated with the risk of developing dementia, as shown in aged participants (average, 76 years) enrolled in the Framingham Heart Study and followed for 9 years [6]; and high intakes of fish or of DHA have been described by most investigators as protective against age-related cognitive decline and the risk of developing Alzheimer disease [7-9]. Docosahexaenoic acid administration has also been found to produce dose-related improvements in cognitive functions in various experimental animals (cf, reference [10]).

A number of hypotheses have been proposed to explain the beneficial effects of DHA consumption on brain functions and, particularly, cognition. These include, among others, changing the "fluidity" of neuronal membranes [11], and thereby alternating the activities of receptors, ion channels, G proteins, and other proteins embedded in the membranes; being transformed to active metabolites [12] such as "neuroprotectin D1" (10,17S-docosatriene), which reportedly suppresses A-β-42 neurotoxicity [13] or to the prostaglandin-like F4-neuroprostanes

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[14]; promoting neurogenesis by causing the differentiation of neuronal stem cells [15]; activating syntaxin-3, a synaptic membrane protein that promotes neurite outgrowth [16]; decreasing the AA content of brain phospholipids [17]; or forming DHA-rich diacylglycerols that are preferentially used for synthesizing membrane phosphatides via the Kennedy cycle [18].

Oral DHA has now also been shown to promote the synthesis of synaptic membranes, elevating the levels, per brain cell, of both the phosphatides and the specific pre- and postsynaptic proteins that characterize these membranes [19]. Docosahexaenoic acid also increases the numbers of dendritic spines [20], and probably synapses, on hippocampal neurons, particularly on excitatory glutamatergic synapses. These effects, described below, can also be produced by eicosapentaenoic acid (EPA), another ω-3 fatty acid, but not by the ω-6 fatty acid AA [21]. They are considerably amplified if animals also receive 2 compounds that, with DHA, are present in mother's milk or infant formulas, that is, uridine [19], a circulating pyrimidine that gives rise in brain to uridine triphosphate (UTP) and cytidine triphosphate (CTP) [22,23], and choline. It is thus possible that DHA affects cognition principally by promoting neurotransmission and that it does so by increasing the numbers of certain synapses.

2. DHA and uridine increase phosphatide and synaptic protein levels in gerbil and rat brains

Three circulating compounds are essential precursors in the synthesis of PC, the major phosphatide in neuronal membranes [1], as well as of phosphatidylethanolamine (PE), and, indirectly, by base exchange, of phosphatidylserine (PS): DHA; a uridine source; and a choline source. Each of these precursors is able to limit the overall rate of PC synthesis because its levels in brain are insufficient to saturate the brain enzymes that catalyze its utilization; moreover, the effects of giving all 3 together tend to be substantially greater than the summed effects of giving each alone. Uridine may also promote membrane synthesis via UTP, which activates P2Y receptors that promote neurite outgrowth [24]; and DHA's effects may, as described above, also involve additional sites of action besides neuronal phosphatide synthesis. Perhaps surprisingly, when the 3 precursors are administered chronically, not only do brain levels of phosphatides—a lipid moiety—rise but also those of various pre- and postsynaptic proteins [19]; moreover, structural changes occur—an increase in the number of dendritic spines, and thus synapses, on hippocampal neurons [20].

The utilization of DHA, uridine, and choline to form phosphatides such as PC and PE is mediated by the enzymes of cytidylyldiphosphate (CDP)-choline cycle or Kennedy cycle [25]. Phosphatidylserine, the other main structural phosphatide, is formed by exchanging a serine molecule for the choline in PC or the ethanolamine in PE. Phosphatidylinositol (PI) synthesis also uses diacylglycerol (DAG) and uridine but different biosynthetic enzymes.

In the CDP-choline cycle, first choline is phosphorylated to phosphocholine by the enzyme choline kinase (CK); then CTP-phosphocholine cytidyl transferase (CT) transfers a cytidylylmonophosphate moiety from CTP to the phosphorus of phosphocholine, yielding cytidylyldiphosphocholine (also known as CDP-choline, or citicoline). Much of the CTP that the human brain uses for this reaction derives from circulating uridine; hence, brain CTP levels vary with plasma uridine concentrations [22]. The third and last reaction, catalyzed by CDP-choline:1,2-diacylglycerol choline phosphotransferase (CPT), bonds the phosphocholine of CDP-choline to the hydroxyl group on the 3-carbon of DAG, yielding PC. There are many types of DAG in the brain, differing in their 2 fatty acid constituents. Diacylglycerol molecules that contain DHA are preferentially used for phosphatide synthesis [18]. Once the new phosphatide molecule has been formed, this DHA can be removed by phospholipase A_2 and replaced by a different fatty acid, which need not be polyunsaturated [1]. Hence, giving DHA can increase total membrane phosphatide levels without necessarily increasing steady-state membrane DHA contents. All 3 of the PC precursors must be obtained by brain entirely or in large part from the circulation; all 3 readily cross the blood-brain barrier [23,26,27] and are metabolized by low-affinity brain enzymes to form PC.

Thus, choline administration increases brain phosphocholine levels in rats [28] and humans [29] because choline kinase's Km for choline (2.6 mmol/L) is much higher than usual brain choline levels (30-60 μmol/L). Generally, the second, CT-catalyzed reaction is most rate-limiting in PC synthesis, either because not all of the CT enzyme is fully activated by being attached to a cellular membrane or because local CTP concentrations are insufficient to saturate the CT [30]. Thus, when brain CTP levels are increased by giving animals uridine [22], CTP's circulating precursor in human blood [31], PC synthesis is accelerated [19]. The activity of CPT, the third enzyme, and the extent to which it is saturated with DAG, can also control the overall rate of PC synthesis, as has been demonstrated in, for example, permeabilized HeLa cells exposed to glycerol-3-phosphate and acyl-CoA [32], or in PC12 cells extending neurites after exposure to the nerve growth factor [24]. In PC-12 cells, nerve growth factor increased DAG levels 5-fold, CPT activity by 70%, and the incorporation of choline into PC by 2-fold [33].

If rodents are given a standard diet supplemented with choline and uridine (as its monophosphate, UMP) and also, by gavage, DHA, brain PC synthesis rapidly increases [22], and absolute levels of PC per cell (DNA) or per milligram of protein increase substantially (eg, by 40%-50% after several weeks of daily treatment [19]). This treatment also increases the levels of each of the other principal membrane phosphatides, as well as of particular proteins [19-21] known to be localized within presynaptic and postsynaptic membranes (eg, synapsin-1, PSD-95, and syntaxin-3, but not