The Rate of Synaptogenesis Can be Enhanced by Co-Administering Three Specific Nutrients

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Abstract: The memory impairments of early Alzheimer ’s disease are thought to result from a deficiency in synapses within the hypothalamus and related brain regions. This deficiency could result from an acceleration in synapse turnover – perhaps caused by an endogenous neurotoxin like A-beta oligomers – or from a decrease in the production of new synapses. A decrease in synapse synthesis almost certainly does occur, since major decreases are also observed in the numbers of hippocampal dendritic spines, the immediate and essential cytologic precursor of glutamatergic synapses. Although the formation of new dendritic spines and synapses is triggered by neuronal depolarization, the number of synapses that actually form can be modulated by jointly administering three circulating nutrients – uridine, DHA, and choline - which are precursors for the phosphatides that are the major component of synaptic membranes. Uridine also increases the production of the other major membrane constituent, synaptic proteins, and the outgrowth of neurites. These actions are mediated by UTP, which, after release as a neurotransmitter from presynaptic terminals, activates P2Y2 receptors causing the formation of diacylglycerol, inositol phosphates, and other chemical signals.

Keywords: hippocampus, synapses, dendritic spines, choline, DHA, uridine, synaptic proteins, memory

The memory disturbances of early Alzheimer's Disease are thought to result from a deficiency in synapses within the hippocampus and related brain regions. (Terry et al 1991; Selkoe 2002). . This deficiency could be the result of a pathologic increase in synapse turnover, perhaps reflecting a neurotoxic effect of an A-beta oligomer, or could arise from the failure of neurons to synthesize adequate numbers of synapses to replace those that have turned over. That the synthesis of synapses is indeed depressed in Alzheimer 's disease and other dementias is affirmed by the concurrent major decline in the number of dendritic spines (Catala et al 1988), the immediate and essential precursor of glutamatergic and other synapses.

As described below, dendritic spines are increased in hippocampus of normal laboratory animals (Sakamoto et al 2007) if the animals receive orally, for several weeks, a mixture that contains three compounds – uridine as UMP; choline; and DHA or EPA – that are normally present in the blood. These compounds are rate-limiting in the enzymatic reactions that produce brain phosphatides, the major constituent of synaptic membranes (Wurtman et al 2006; Wurtman et al 2009). The uridine can also be converted in presynaptic terminals to UTP, for release into synapses as a neurotransmitter (Cansev 2015) which activates post-synaptic P2Y2 receptors. This receptor activation then accelerates the formation of synaptic proteins - thus completing the formation of additional synaptic membrane (Wurtman et al 2006; Wurtman et al, 2009) - and enhances neurite outgrowth (Pooler 2005). Administering the mixture to laboratory animals also improves their capacities to learn and to remember (Holguin 2008). Like choline and DHA/EPA uridine is present in many foods, principally as a constituent of RNA; however in this form very little of the uridine is bioavailable, so adult foods cannot substitute for the uridine in the UMP/choline/DHA mixtures.

Recognition of these effects has raised the possibility that a similar mixture might be useful in combatting the synaptic deficiency and thus memory loss of early Alzheimer ’s disease. Two clinical trials have been performed on such patients (Scheltens et al 2012); both yielded positive effects, and in an ongoing not-yet-published 2-year study (the “LipiDiDiet Study”) on patients with prodromal Alzheimer’s Disease the mixture also diminished the rate of progression to full disease ( ). That the clinical effects were mediated by enhanced synaptogenesis is suggested by the observation that the characteristic impairment of connectivity between regions of AD brain was also ameliorated (DeWaal et al 2014). The mixture probably would not be effective in patients in whom late-stage disease had already caused significant loss of the neurons that would be needed for making the additional synapses, and indeed no benefit was observed in a clinical trial on such patients (Shah et al 2013).

Circulating choline, DHA, and uridine are all obtained both from endogenous hepatic synthesis (starting with, respectively, the methylation of phosphatidylethanolamine; the metabolism of linolenic acid; and amino acids) and, for choline and DHA, from dietary sources as well (egg yolk; fish). Though uridine is present in many foods as a component of RNA, it is poorly bioavailable in that form (Gasser et al 1981), and no adult food has ever been clearly demonstrated to raise plasma uridine levels. In infants, dietary uridine is largely provided as the UMP in mothers’ milk or is added to virtually all infant formulas, and the uridine in UMP is indeed bioavailable. Uridine, as UMP, began to be supplemented to infant formulae about twenty years ago, based on its demonstrated ability to promote the development of immune tissue in the gastrointestinal tract (Carver 1999, Carver and Walker 1999, Uauy 1989); uridine’s special role in synapse formation was discovered years later (Wurtman et al 2006). USP’s need by infants caused it to be considered a “conditionally essential nutrient”.

Could one or all of the three components of the mixture that promotes synaptogenesis be replaced by a drug, for example one that activates P2Y receptors? Conceivably, but that drug still wouldn't replace the authentic uridine needed, along with choline and DHA, for phosphatidylcholine synthesis. Moreover the drug would also have to share the mixture's remarkable safety profile: No side effects have been observed in any of the mixture's clinical trials (Scheltens 2012), perhaps because the components are all normally present in the blood stream. The mixtures utilized in the existing clinical trials all contained additional nutrients besides UMP, choline, and DHA, - for example particular B-vitamins (B6, B12, folic acid) – added in doses that enhance choline biosynthesis in the liver (VanWijk 2012), and thus supplement the exogenous choline in the mixture. This is necessary because when humans consume large doses of choline much of the amine is metabolized in the gut to form trimethylamine, the "rotten-fish" odor of which is unpleasant and could compromise subject compliance. So hepatic choline production is promoted by including the B-vitamins, thus enabling a decrease in the mixture's free choline content.

Numerous additional neurologic diseases besides Alzheimer's are characterized by deficiencies in synapses (e.g., strokes; Parkinson's disease). Perhaps a treatment that enhances synapse formation might be useful in those diseases as well.

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