



## Full length article

## Synapse formation in the brain can be enhanced by co-administering three specific nutrients



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## ARTICLE INFO

## Keywords:

Hippocampus  
Synapses  
Dendritic spines  
Choline  
DHA  
Uridine  
Synaptic proteins  
Memory

## ABSTRACT

The memory impairments of early Alzheimer's disease [AD] are thought to result from a deficiency in synapses within the hippocampus 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 the synaptic membrane needed to form new synapses. An AD-associated decrease in synaptogenesis almost certainly does occur, inasmuch as major decreases are also observed in the numbers of hippocampal dendritic spines, the immediate cytologic precursor of glutamatergic synapses. The syntheses of new dendritic spines and synapses can, however, be increased by concurrently raising brain levels of three circulating nutrients – uridine, omega-3 fatty acids docosahexaenoic acid (DHA) or eicosapentaenoic acid (EPA), and choline. This could provide an additional strategy for restoring synapses and thereby memory. The three nutrients are rate-limiting precursors in the Kennedy Cycle, the pathway which forms the phosphatides that are the major component of synaptic membranes. Uridine also increases the production of synaptic proteins, the other major membrane constituent, and the outgrowth of neurites. Hence administering the three nutrients accelerates synapse formation.

These actions of uridine are largely mediated by uridine triphosphate (UTP), which can be released as a neurotransmitter from presynaptic terminals and can then activate P2Y2 receptors. The UTP in neurons can also be converted to cytidylyl triphosphate, CTP, the intermediate utilized in the Kennedy Cycle.

The memory disturbances of early AD 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 acceleration of synapse turnover, perhaps reflecting a neurotoxic effect of an A-beta oligomer, or it could arise from the failure of neurons to synthesize adequate numbers of new synapses to replace those that have been lost. That the synthesis of synapses is indeed depressed in AD and other dementias is affirmed by the concurrent major decline in the numbers 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 Kennedy Cycle (Kennedy and Weiss, 1956) the enzymatic pathway that produces brain phosphatides, the major constituent of synaptic membranes (Wurtman et al., 2006, 2009). The uridine can also be converted in presynaptic terminals to UTP, for release into synapses as a

neurotransmitter (Cansev et al., 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, 2009) - and enhances neurite outgrowth (Pooler et al., 2005) and synapse formation (de Waal et al., 2014). Administering the mixture to laboratory animals also improves their capacities to learn and to remember (Holguin et al., 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 resulting memory loss of early AD - a condition also known to be associated with deficiencies in brain levels of the two principal membrane phosphatides (phosphatidylcholine [PC] and phosphatidylethanolamine [PE]) and their precursors choline and ethanolamine (Nitsch et al., 1992). Two clinical trials have been performed on patients with early AD receiving the three compounds (Scheltens et al., 2010, 2012); both yielded positive findings. That the clinical effects were mediated

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Received 25 November 2016; Received in revised form 27 June 2017; Accepted 26 September 2017

Available online 12 October 2017

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by enhanced synaptogenesis is compatible with the observation that the characteristic impairment of connectivity between various regions of AD brain was also ameliorated (de Waal et al., 2014). The mixture was ineffective in patients in whom late-stage disease had already caused significant loss of the neurons that would be needed for making the additional synapses (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 the metabolism of precursor amino acids) and, for choline and DHA, from dietary sources as well (e.g., 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 clearly been demonstrated to raise plasma uridine levels. In infants, dietary uridine is largely provided in a bioavailable form as the UMP naturally present in mothers' milk or added to virtually all infant formulas. Uridine, as UMP began to be included in 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). UMP's need in infancy caused it to be identified as a "conditionally essential nutrient" during periods of maximal synaptogenesis (Carver and Walker, 1999).

Numerous studies have been described in which the ability of supplemental DHA to promote or restore memory was tested; some have shown positive results but at least as many have failed to do so. This divergence could be explained if the DHA acted principally – with uridine and choline – to promote synaptogenesis; in patients whose brain levels of DHA but not uridine and choline happened to be low, a DHA deficiency would slow traffic through the Kennedy Cycle.

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 significant 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 nutrient 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 (van Wijk et al., 2012) thus supplementing 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. Including the B-vitamins enables a decrease in the mixture's free choline content, thereby enhancing compliances.

Other common neurologic diseases in addition to AD also are characterized by deficiencies in synapses (e.g., strokes; Parkinson's disease). Perhaps a treatment that enhances synapse formation might

be useful in managing those diseases as well. A major long-term study, the "Lipididiet Study", now in its third year, is designed to determine whether taking Souvenaid, a preparation that includes the three nutrients, can protect patients with prodromal AD from progressing to clinical AD.

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