SYNAPSE FORMATION IS ENHANCED BY ORAL ADMINISTRATION OF URIDINE AND DHA, THE CIRCULATING PRECURSORS OF BRAIN PHOSPHATIDES

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Introduction

While the precise pathologic mechanisms that diminish the numbers of brain synapses in patients with Alzheimer’s disease remain unknown, there seems to be a general consensus that these reductions do invariably occur, particularly in the hippocampus, and that they are perhaps the major factor causing patients to develop cognitive disturbances (1). If it were possible to cause the surviving neurons in damaged brain regions to make more or larger synapses, would this restore number of dendritic spines (4-7), it can probably be assumed (if not yet demonstrated) that the treatment also contributes to restoring synaptic number. Although it remains to be determined whether the treatment also affects synapses in brains of normal humans, much less patients with Alzheimer’s Disease, the compounds it uses all occur normally in the blood and in mothers’ milk, and apparently are benign. Hence, it may be useful to determine whether their administration is beneficial to patients with Alzheimer’s disease. An initial clinical trial on 212 patients with mild Alzheimer’s disease, described below, who were treated daily for 12 weeks with a mixture (“Souvenaid”) of these three compounds plus B-vitamins, antioxidants and phospholipids, has in fact demonstrated statistically-significant improvement on a delayed verbal memory task (P. Scheltens, cited in JAMA, September 17, 2008, p. 1289).

The three compounds involved are all essential precursors needed to synthesize phosphatidylcholine (PC), the major phosphatide in neuronal membranes (8), as well as the other principal phosphatides, i.e. the polyunsaturated omega-3 fatty acid docosahexaenoic acid (DHA); a uridine source such as UMP; and a choline source. Each of these three compounds can
be limiting in controlling the overall rate of PC synthesis (because their levels in brain are insufficient to saturate the brain enzymes that catalyze the reactions involved in PC synthesis), and the effects of giving all three together tend to be greater than the summed responses to each alone. Uridine’s phosphorylated nucleotide products also promote synaptic membrane synthesis by activating P2Y receptors (9), and DHA’s effects may also involve alternative sites of action, including for example activation of brain proteins serving as receptors (10). Perhaps surprisingly, when the three precursors are administered chronically not only do brain levels of phosphatides – a lipid moiety – rise, but also those of numerous pre- and post-synaptic proteins (2, 11). And major structural changes also occur – an increase in the number of dendritic spines (3) and increased formation of neurites (2).

This article summarizes available information on the mechanisms that mediate the effects on synaptic membrane of exogenous DHA, uridine, and choline, and on the known consequences of these effects. “Synaptic membrane” is operationally defined as phosphatide-rich cellular membrane that contains pre- and post-synaptic proteins, and that has the capacity to become characteristic synaptic structures (e.g. dendritic spines, postsynaptic densities, synaptic vesicles). The article also provides a rationale for testing these compounds as a treatment for Alzheimer’s disease and other diseases characterized by a major loss of synapses.

Bioynthesis of membrane phosphatides

Mammalian cells utilize DHA and other fatty acids, uridine, and choline to form the phosphatide subunits (e.g. PC) which, when aggregated, constitute the major components of their membranes. PC, the principal such subunit in brain, is synthesized from these precursors by the CDP-choline cycle or “Kennedy Cycle” (12). The phosphatide phosphatidylethanolamine (PE) likewise is synthesized via the Kennedy Cycle, utilizing ethanolamine instead of choline as a precursor, while phosphatidylserine (PS), the third major structural phosphatide, is generated by exchanging a serine molecule for the choline in PC or the ethanolamine in PE (8).

The CDP-choline cycle involves three sequential enzymatic reactions. In the first, catalyzed by choline kinase (CK), a phosphate is transferred from ATP to the hydroxyl oxygen of the choline, yielding phosphocholine. The second, catalyzed by CTP:phosphocholine cytidylyl transferase (CT), transfers cytidylylmonophosphate (CMP) from cytidine-5’-triphosphate (CTP) to the phosphorus of phosphocholine, yielding cytidylylphosphocholine (also known as CDP-choline, or cricoline). As discussed below, much of the CTP that the human brain uses for this reaction derives from circulating uridine (13). 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 diacylglycerol (DAG) (particularly DAG containing DHA), yielding the PC. All three of these PC precursors must be obtained by brain entirely (DHA) or in large part (uridine; choline) from the circulation, and do in fact readily cross the blood-brain barrier (14-17). And because the PC-synthesizing enzymes that act on all three have low affinities for them, treatments that increases blood levels of all three can affect the overall rate of PC synthesis (2, 18).

Thus, choline administration increases brain phosphocholine levels in rats (19) and humans (20), because CK’s Km for choline (2.6 mM (21)) is much higher than usual brain choline levels (30-60 µM) (22-24). Most commonly the second, CTP-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 (25) or because local CTP concentrations are insufficient to saturate the CT (24). Thus, when brain CTP levels are increased by giving animals uridine (18), CTP’s circulating precursor in human blood (14), PC synthesis is accelerated (18). The activity of CPT and the extent to which this enzyme is saturated with DAG can also control the overall rate of PC synthesis (26, 27). DAG species containing DHA or other PUFA on the middle carbon apparently are preferentially utilized for phosphatide synthesis, as opposed to triglyceride synthesis (28). If rodents are given a standard diet supplemented with choline and uridine (as UMP, its monophosphate) and, also by gavage, DHA, brain PC synthesis rapidly increases (2, 18), and absolute levels of PC per cell (DNA) or per mg protein can increase substantially (e.g., by 30-50% after several weeks of daily treatment (2)). Thus this treatment also increases the levels of each of the other principal membrane phosphatides), as well as the levels of particular proteins known to be localized within postsynaptic and postsynaptic membranes (for example synapsin-1 (29), PSD-95 (30), syntaxin-3 [10]) and the GLUR-1 subunit of the AMPA glutamate receptors (3), but not those of a ubiquitously-distributed brain protein, β-tubulin (2, 11).

Enzymes that mediate brain phosphatide synthesis

The ability of each of the three circulating phosphatide precursors to affect the rate of phosphatide synthesis results principally from the low affinities of the enzymes for these nutrients are substrates.

Choline Kinase

CK has a very low affinity for its choline substrate (35, 36); its Km for choline in brain (which, of course, describes the
choline concentrations at which the CK operates at only half-maximal velocity) is reportedly 2.6 mM (21), whereas brain choline levels are only about 30-60 μM (22-24). Hence, the synthesis of phosphocholine is highly responsive to treatments which raise or lower brain choline levels.

**CTP: phosphocholine cytidylyltransferase**

CTP-phosphocholine cytidylyltransferase (CT; EC 2.7.7.15) catalyzes the condensation of CTP and phosphocholine to form CDP-choline. CT is present in both the soluble and particulate fractions of the cell (37); the cytosolic form is reportedly inactive and the membrane-bound form active (25, 38). Increases in the association of CT with membranes reportedly correlate with increases in CT activity and in the net synthesis of PC in vitro (39-41). Some other lipids (e.g. PS) (42) and DAG (39, 43) also stimulate the translocation of CT from the cytosol to membranes in vitro, thereby activating the enzyme (44). The phosphorylation state of CT affects its net activity (45), as does its substrate saturation with CTP and perhaps with phosphocholine. The Km’s of CT for CTP and phosphocholine in brains of laboratory rodents and humans are reportedly 1-1.3 mM and 0.30-0.31 mM (24, 46), respectively, while brain levels of these compounds are only 70-110 μM (18, 47, 48) and 0.32-0.69 mM (19, 23, 49) respectively. Hence, brain CT normally is highly unsaturated with CTP, and only about half-saturated with phosphocholine in vivo, suggesting that its degrees of substrate-saturation, particularly with CTP, exert important limiting roles in PC synthesis. In fact, treatments that increase cellular CTP (e.g. administration of a uridine or cytidine source) have been shown to enhance CDP-choline and PC synthesis in poliovirus-infected HeLa cells (50); undifferentiated PC12 cells (51, 52); slices of rat corpus striatum (54); and gerbil brain in vivo (18).

**CDP-choline:1,2-diacylglycerol cholinephosphotransferase (CPT; EC 2.7.8.2)**

CDP-choline:1,2-diacylglycerol cholinephosphotransferase (CPT; EC 2.7.8.2) catalyzes the final reaction in the Kennedy cycle, transferring the phosphocholine moiety from CDP-choline to DAG, thus yielding PC.

The choline phosphotransferase reaction also is unsaturated with the enzyme’s substrates: Its Km values for CDP-choline and DAG in rat liver are 200 μM and 150 μM (54) respectively, while the concentrations of these compounds in liver are approximately 40 μM (55) and 300 μM (56). (A DAG concentration of at least 1000 μM thus would probably be needed to saturate the enzyme). Brain CDP-choline and DAG levels are even lower, i.e., about 10-30 μM (18, 57) and 75 μM (48), respectively.

**Uptake of uridine into brain and its phosphorylation to UTP and CTP**

Since circulating uridine elevates brain CTP levels, and thereby the substrate saturation of CTP:phosphocholine cytidylyltransferase and, ultimately, PC synthesis and synaptic membrane formation, the enzymes and uptake proteins that mediate blood uridine’s effect on brain UTP and CTP are also discussed here. They also are unsaturated at normal substrate (uridine) levels.

Uridine and cytidine are transported across cell membranes, including the BBB, via two families of transport proteins, i.e. the Na+-dependent, low-affinity, equilibrative transporters (ENT1 and ENT2) (58) and the Na+-dependent, high-affinity, concentrative (CNT1, CNT2, and CNT3) (59) nucleoside transporters (14). The two ENT proteins, which transport uridine and cytidine with similar affinities, have been cloned from rat (60) and mouse (61). Inasmuch as their Km values for the pyrimidines are in the high micromolar range (100-800 μM [62]) they probably mediate BBB pyrimidine uptake only when plasma levels of uridine and cytidine have been elevated experimentally. In contrast, CNT2, which transports both the pyrimidine uridine and such purines as adenosine, probably does mediate uridine transport across the BBB under physiologic conditions. Km values for the binding of uridine and adenosine to this protein (which has been cloned from rat BBB [63]) are in the low micromolar range (9-40 μM in kidney, intestine, spleen, liver, macrophage and monocytes [64]), while plasma uridine levels are subsaturating, i.e., 0.9-3.9 μM in rats (65); 3.1-4.9 μM in humans (65); and around 6.5 μM in gerbils (18). CNT2 can also transport cytidine, however with a much lower affinity than that for uridine (66-68).

It should be noted that, while both uridine and cytidine are present in the blood of laboratory rats, human blood contains unmeasurably low quantities of cytidine (65) even among individuals consuming a cytidine source like oral CDP-choline (13); the cytidine is quantitatively deaminated to uridine in the human liver. Hence, in humans, circulating uridine, and not cytidine, is the precursor of the brain CTP utilized for phosphatidyl synthesis. Gerbil blood contains both of the pyrimidines, but proportionately less cytidine than blood of rats; hence gerbils are often used as a model for studying the effects of uridine sources on the human brain (69).

Like other circulating compounds, pyrimidines may also be taken up into brain via the epithelium of the choroid plexus (CP) and the ENT1, ENT2 and CNT3 transporters (58, 59); all of these proteins have been found in CP epithelial cells of rats (60, 70, 71) and rabbits (72, 73). However the surface area of BBB is probably 1000 times that of the CP epithelium (i.e., 21.6 m² vs 0.021 m² in humans [74]), hence the BBB is the major locus at which circulating uridine enters the brain.

Uridine and cytidine are converted to their respective nucleotides by successive phosphorylations catalyzed by various kinases. Uridine-cytidine kinase (UCK) (ATP:uridine 5’-phosphotransferase, EC 2.7.1.48) phosphorlates uridine and cytidine to form UMP and CMP, respectively (75-77). UCK activity is regulated by cellular UTP and CTP levels: At relatively low UTP and CTP levels, uridine taken up into brain cells is phosphorylated, initially by UCK to form uridine nucleotides; at higher UTP and CTP concentrations UCK’s activity is inhibited, thus suppressing uridine’s phosphorylation...
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EPA can also be acylated to DAG by the Acyl-CoA synthetase (105) or it can be converted to DHA by brain astrocytes (106), allowing its effects on brain phosphatides and synaptic proteins to be mediated by DHA itself. Exogenously administered AA, like DHA, is preferentially incorporated into brain phosphatides (107, 108), as well as into other lipids, e.g. the plasmalogens (109, 110). AA shares with DHA the ability to activate syntaxin-3 (10), however, as described below, its oral administration to laboratory rodents apparently does not promote phosphatide or synaptic membrane synthesis (11); the formation of dendritic spines (3); nor improve rodent cognitive processes (Sarah Holguin, personal communication).

DHA and AA are major components of brain membrane phospholipids (111). While AA is widespread throughout the brain and is abundant in phosphatidylcholine (PC) and PC, DHA is concentrated in synaptic regions of gray matter (112) and is especially abundant in PE and PS (113). EPA is found only in trace amounts in brain phosphatides, mostly in PL (114). No significant differences have been described between the relative proportions of ingested omega-3 and omega-6 PUFAs that actually enter the systemic circulation (115, 116). Moreover, the rates at which radioactively-labeled DHA and AA are taken up into brain and incorporated into phospholipids following systemic injections also are similar (107, 117). On the other hand, the half-lives of the omega-3 PUFAs in the blood (20 ± 5.2 hours for DHA and 67 ± 14 hours for EPA (118)) are substantially higher than that for AA (3.8 seconds (119)). Similarly, the half-life of DHA in brain PC (22.4 ± 2.9 hours), but not in PE or PS, is much longer than that of AA (3.79 ± 0.12 hours) (120). Thus, a considerable proportion of AA may be cleared from plasma or oxidized before it is utilized for PC synthesis, or, once incorporated into phosphatides, may be liberated by hydrolysis (mediated by phospholipase A2 (121), and then oxidized.

The ability of orally-administered DAG, given daily for several weeks, to increase brain phosphatide levels does not necessarily imply that the quantities of DHA in the phosphatides, relative to those of other fatty acids, also are increased. Indeed this has not been demonstrated. Conceivably, DHA-rich DAG is preferentially utilized for PC synthesis, but once the DAG-containing PC is formed it is rapidly hydrolyzed to form lyso-PC lacking DHA, then reacylated to PC by addition of a different fatty acid (c.f. (121)).

Effects of phosphatide precursors on synaptic protein and phosphatide levels in gerbils

Administering UMP, DHA plus choline not only increases brain phosphatide levels but also those of specific proteins (i.e. those known to be concentrated in presynaptic or post-synaptic structures (this perhaps surprising effect is mediated in part by brain P2Y2 receptors, which can be activated by uridine itself or by its nucleotide and/or glycosylated derivatives (UMP, UDP, UTP and UDP-glucose). In vitro each of these compounds increases levels of, for example, neurofilament-70,
neurofilament-Y; synapsin and PSD-95; in vivo 6-
administration with DHA apparently is required to cause
significant elevations. So uridine affects synaptic membrane
production via two pathways: by becoming CTP, required for
the Kennedy Cycle, and as receptor agonists for P2Y2
receptors. This latter mechanism apparently is deficient in
brains of untreated patients with Alzheimer's disease (122).

In experiments designed to compare the effects of
administering each of the three PUFAs, DHA, EPA, or AA, on
brain phosphatide levels, animals received 300 mg/kg daily by
gavage of one of the fatty acids for 4 weeks, and consumed a
choline-containing diet that did or did not contain UMP. Giving
DHA without uridine increased PC, PI, PE and PS
levels significantly, by 18-28%, respectively, throughout the
brain (e.g. in cortex, striatum, hippocampus, brain stem and
cerebellum). EPA given alone also increased brain PE, PS, and
PI levels significantly; by 21-27%. In contrast, AA
administration failed to affect brain levels of any of the
phosphatides (11).

Consuming the UMP-supplemented diet alone increased
brain PS and PC levels significantly (by 15% and 16%,
respectively) compared with those in control gerbils. Among
gerbils receiving both UMP and DHA, brain PC, PE, PS, and PI
levels rose significantly by 12-38%, respectively. Similarly,
among gerbils receiving both UMP and EPA, brain PC, PE, PS,
and PI levels rose significantly by up to 56%. In contrast,
giving UMP with AA failed to increase levels of any brain
phosphatide above those found in gerbils receiving UMP alone.
Essentially similar findings were obtained whether data were
expressed per µg DNA (i.e. per cell) or per mg protein.

Giving the gerbils, as above, DHA or EPA alone
significantly increased brain levels of the postsynaptic density
protein PSD-95, by 24-28%. When this treatment was
combined with dietary UMP the observed increases in PSD-95
were 29-33% greater than those observed after UMP
supplementation alone. AA failed to affect brain PSD-95 levels,
either when given alone or in combination with the UMP
supplemented diet. Levels of Synapsin-1, a presynaptic
vesicular protein like those of PSD-95, were significantly
increased by DHA or EPA treatment when given alone or when
combined with UMP. Again, AA failed to affect brain
Synapsin-1 levels when given alone or concurrent with a UMP
supplemented diet.

Also similarly to those of PSD-95 and Synapsin-1, brain
levels of Syntaxin-3, a plasma membrane SNARE protein,
which reportedly mediates the stimulation by PUFAs of neurite
outgrowth (10) and exocytosis (123) in cultured cells, were
significantly increased in animals receiving DHA or EPA
whether or not they also received UMP, but AA was without
any effect if given alone or in combination with UMP. None of
the PUFA, given alone or with UMP, changed brain levels of
the structural protein β-tubulin, perhaps reflecting its ubiquity in
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The mechanism that allows the omega-3 fatty acids DHA
and EPA, but not the omega-6 fatty acid AA to increase brain
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(107,108), as well as into other brain lipids (e.g. the
plasmalogens; (109, 110)) and AA shares with DHA the ability
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Effects of DHA and other PUFA on dendritic spine
formation and synaptogenesis

Dendritic spines are small membranous protrusions
extending from post-synaptic dendrites in neurons, most of
which eventually form synapses with presynaptic axon
terminals. The dendritic spines compartmentalize post-synaptic
responses, and their numbers are thought to reflect the density
of excitatory synapses (i.e. glutamatergic) within regions of the
central nervous system (126-128). Oral supplementation with
DHA to adult gerbils increases the number of dendritic spines
in the hippocampus, particularly if the animals are also
supplemented with UMP (3). As described above, this
treatment also increases the levels of membrane phosphatides
and of various pre- and post-synaptic proteins (2). Oral DHA,
particularly when co-administered with UMP, may thus
increase the number of brain synapses.

Gerbils that received daily doses of DHA for 4 weeks (100
or 300 mg/kg, by gavage) exhibited increased dendritic spine
density (i.e. the number of spines per length of dendrite) in
CA1 pyramidal neurons; the increases were 12 percent (p = .04)
with the 100 mg/kg/day dose, and 18 percent (p < .001) with
the 300 mg/kg/day dose (3). These effects were amplified if
gerbils also received both DHA and UMP (0.5%, via the
standard choline-containing diet) for 4 weeks, DHA
supplementation alone increasing spine density by 19 percent
(p < .004) and co-administration of both precursors doing so by
36%, or approximately double the increase produced by DHA
alone (p = .008). (Giving UMP alone did not affect dendritic
spine density significantly, however, it did increase spine
density when all dendritic protrusions were included for
statistical analysis, including the filopodia, which are precursor
forms of dendritic spines). The effect on dendritic spine density
of giving both DHA and UMP was already apparent after 1
week of treatment (p = .02), and continued for as long as
animals were treated (4 weeks). Giving the phosphatide
precursors failed to affect the length or width of individual

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dendritic spines, only their number.

In the above experiments hippocampal phosphatide levels, as before, also increased as did pre- and post-synaptic proteins examined in the hippocampus of the same animals. Expression levels of PSD-95 (129) and Glur1 (130, 131) are known to be highly associated with the growth of dendritic spines, and also with the intensity of the physiological responses of the post-synaptic neurons. Synapsin-1, on the other hand, is expressed in pre-synaptic terminals, and apparently anchors synaptic vesicles to the actin cytoskeleton for exocytosis or synaptogenesis (132, 133). The increases in PSD-95, Synapsin-1, and Glur1 subunit of glutamatergic AMPA receptor after treatment with DHA alone were 38-42% (all p ≤ .05), and were further increased by treatment with UMP. Treatment with DHA or with DHA plus UMP also elevated brain levels of actin, a cytoskeletal protein which can directly regulate the morphology of dendritic spines and which is implicated in such manifestations of synaptic plasticity as long-term potentiation (LTP) and depression (LTD) (126-128, 131, 134). Actin levels rose by 60 percent after DHA, and by 88 percent in animals receiving DHA plus UMP (3). In contrast, levels of β-tubulin, a cytoskeletal protein that is not specifically localized within synaptic structures, are unaffected by the treatments (2).

Oral supplementation with AA failed to affect dendritic spine density in the CA1 region of the adult gerbil hippocampus even though, like DHA, AA does affect synaptic plasticity in cultured neurons (135-137). As described above, AA also failed to affect hippocampal levels of phosphatides or of synaptic proteins (3).

The mechanisms through which DHA, with or without uridine, increases dendritic spine formation may also involve presynaptic processes. Results from various model systems indicate that both DHA (10, 138, 139) and uridine (9, 33, 34) can promote axonal growth and exocytosis in cultured cells. As mentioned previously, DHA can activate the SNARE protein Syntaxin-3 (10) while uridine, through UTP, can activate P2Y receptors (9), which are expressed in hippocampal neurons (140) and are implicated in pre-synaptic induction of LTP (141). Formation of dendritic spines and synaptogenesis in mammalian brains can be induced or initiated by pre-synaptic neurons, and this process may involve calcium (126-128, 142). The increases in spine density with DHA and UMP treatment may thus result from potentiation of presynaptic or postsynaptic mechnisms.

Effects of uridine on neurotransmitter release, and of UMP plus DHA on behavior

Consumption by rats of a diet containing uridine (as UMP) and choline can increase dopamine (DA) and ACh levels in, and – as assessed using in vivo microdialysis – their release from, corpus striatum neurons (33, 34). Apparently no data are available on the effects on neurotransmitter production or release of giving DHA alone or with the other two phosphatide precursors. Dietary supplementation of aged male Fischer 344 rats with 2.5% UMP for 6 weeks, ad libitum, increased the release of striatal DA evoked by potassium-induced depolarization receiving the UMP (P<0.05) (33). In general, each animal’s DA release correlated with its striatal DA content, measured postmortem. In a similar microdialysis study, ACh release, basally as well as after administration of atropine (a muscarinic antagonist which blocks inhibitory presynaptic cholinergic receptors), was found to be enhanced following UMP consumption. Among aged animals consuming a UMP-containing diet (2.5%, w/w) for 1 or 6 weeks, baseline ACh levels in striatal microdialysates doubled after 1 week of treatment (p<0.05) and further increased after 6 weeks (p≤0.05) (34). Dietary UMP also amplified the increase in ACh release caused by giving young rats atropine (10 μM, via the artificial CSF); giving a uridine source may enhance some cholinergic functions, perhaps by increasing the amount of synaptic membrane, or the quantities of ACh stored in synaptic vesicles.

Additional evidence that treatment with UMP alone or with UMP plus DHA can affect brain neurotransmission comes from behavioral studies (31, 143). Among socially-impoverished rats giving DHA or DHA plus dietary UMP treatment for 4 weeks reversed the deficits in hippocampal-dependent learning and memory performance (31). Chronic dietary administration of UMP (0.1%) alone for 3 months also ameliorated this impairment among the impoverished rats (143). UMP plus DHA and choline also significantly enhanced cognitive function in normal adult gerbils (32).

Human studies

One study has examined effects on humans of daily consumption of a liquid mixture (“Souvenaid”) containing DHA, UMP, choline and additional nutrients that promote endogenous choline synthesis, suppress auto-oxidation; or enhance the solubility of other ingredients. This randomized, controlled, double-blind, parallel group, multi-centre, multi-country clinical trial, involving 212 drug-naive subjects with mild Alzheimer’s disease and directed by Prof. Phillip Scheltens examined the treatment’s effects on a delayed verbal memory task (derived from the Wechsler Memory Scale-revised) and the 13-item modified ADAS-cog at 12 weeks. The trial was pre-registered with the Dutch Trial Registry (No. ISRCTN 72254645).

In the group receiving Souvenaid a significant benefit was found in mild and very mild Alzheimer’s disease patients on the verbal memory task. The unadjusted analyses showed no significant effect on the modified ADAS-cog. However, the baseline modified ADAS-cog score was a predictor for the intervention effect, i.e., patients with a higher baseline score showed a greater effect on Souvenaid. Intervention with Souvenaid was well tolerated (compliance was 94%) and safe. This proof-of-concept study was interpreted as demonstrating that Souvenaid, a drink that contains DHA, uridine, choline and other nutrients for 12 weeks improves memory in mild and very
mild Alzheimer’s disease; further studies are justified.

Conclusions

The three Kennedy Cycle enzymes that catalyze the formation of brain phosphatides from uridine, DHA, and choline, and the proteins that take up uridine into the brain and convert it to UTP and CTP, all have low affinities for these substances and are thus saturated. Hence administering these substrates can accelerate the biosynthesis, and elevate brain levels of membrane phosphatides. Moreover UTP or uridine can activate brain P2Y2 receptors, which increases brain levels of pre- and post-synaptic proteins and, ultimately, the quantity of synaptic membrane and the formation of additional neuritis, dendritic spines, and synapses. A mixture containing these compounds has been found to increase test scores in a Phase 2 clinical trial on 212 subjects with mild Alzheimer’s Disease.

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