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Review

Folic acid and polyunsaturated fatty acids improve cognitive function and prevent depression, dementia, and Alzheimer's disease—But how and why?

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Abstract

Low blood folate and raised homocysteine concentrations are associated with poor cognitive function. Folic acid supplementation improves cognitive function. Folic acid enhances the plasma concentrations of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). EPA, DHA, and arachidonic acid (AA) are of benefit in dementia and Alzheimer's disease by up-regulating gene expression concerned with neurogenesis, neurotransmission and connectivity, improving endothelial nitric oxide (eNO) generation, enhancing brain acetylcholine levels, and suppressing the production of pro-inflammatory cytokines. EPA, DHA, and AA also form precursors to anti-inflammatory compounds such as lipoxins, resolvins, and neuroprotectin D1 (NPD1) that protect neurons from the cytotoxic action of various noxious stimuli. Furthermore, various neurotrophins and statins enhance the formation of NPD1 and thus, protect neurons from oxidative stress and prevent neuronal apoptosis Folic acid improves eNO generation, enhances plasma levels of EPA/DHA and thus, could augment the formation of NPD1. These results suggest that a combination of EPA, DHA, AA and folic acid could be of significant benefit in dementia, depression, and Alzheimer's disease and improve cognitive function.

1. Introduction

Risk of dementia or cognitive impairment is high in those with elevated homocysteine levels [1]. A randomized, double blind, placebo controlled study [2] showed that daily supplementation of 800 μg of oral folic acid for 3 years increased serum folate concentrations, reduced plasma total homocysteine levels, and improved cognitive function. These studies suggest that a close association exists between folic acid, homocysteine and cognitive function.

2. Homocysteine and nitric oxide

Homocysteine is readily oxidized as a consequence of auto-oxidation leading to superoxide anion and hydrogen peroxide generation that are toxic to endothelium [3]. These free radicals initiate lipid peroxidation and oxidize low-density lipoprotein, events that convert antithrombotic endothelium to a more prothrombotic phenotype by increasing factor V and factor XVII activity, decreasing protein C activation, inhibiting tissue factor expression, suppressing heparan sulfate expression, reducing the binding of tissue-type plasminogen activator to its endothelial receptor annexin II, and reducing the production of nitric oxide (NO) and prostacyclin (PGI_2) (see Fig. 1 for the metabolism of essential fatty acids), events that lead to the generation of thrombin and facilitates thrombotic tendency [4]. Normal endothelium detoxifies homocysteine by releasing NO or related *S*-nitroso thiol that attenuate sulfhydryl-dependent generation of H_2O_2. Thus, when homocysteine levels are reduced by vitamin B_{12} and folic acid supplementation it leads to enhanced production of NO and PGI_2 by endothelial cells that have potent

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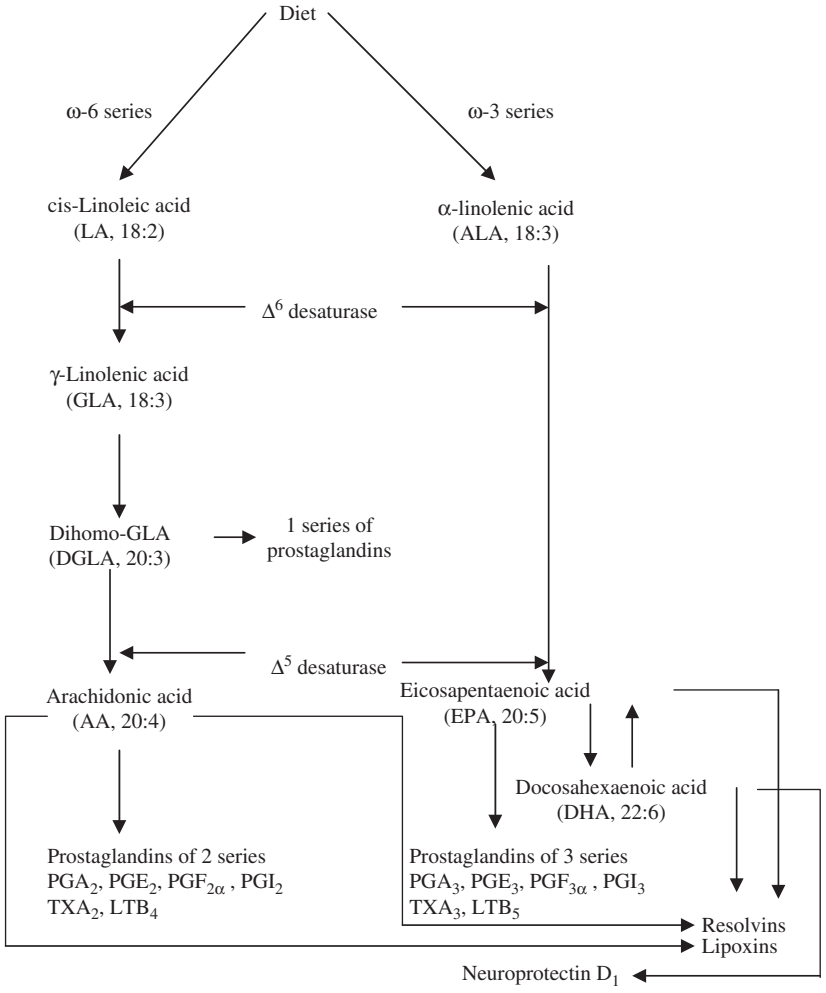

Fig. 1. Metabolism of essential fatty acids. Prostaglandins of 3 series are less pro-inflammatory compared to prostaglandins of 2 series. Resolvins are formed from both EPA and DHA and are known to have anti-inflammatory actions and participate in the resolution of inflammation. EPA can be converted to DHA. DHA can be retroconverted to EPA. It is estimated that about 30–40% of DHA can be retroconverted to EPA.

vasodilator and platelet anti-aggregatory actions, though folic acid can also improve endothelial function by mechanisms independent of homocysteine. NO is also a neurotransmitter.

3. Folic acid and ω-3 fatty acids enhance NO generation and brain acetylcholine levels

Oral folic acid supplementation to healthy human volunteers not only restored NO synthesis but also prevented nitrate tolerance to continuous treatment with nitroglycerine by restoring and/or stimulating endogenous generation of tetrahydrobiopterin (H_4B), an essential co-factor for NO synthesis [4]. In addition, folic acid increases concentrations of ω-3 polyunsaturated fatty acids (PUFAs) such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [5] that are useful in the prevention of dementia and Alzheimer's disease [6,7], which, in part, could be attributed to their ability to enhance NO generation [8], suppress production of pro-inflammatory cytokines [9,10], and enhance brain acetylcholine levels [11,12], a neurotransmitter whose levels are decreased in Alzheimer's disease [13] (see Fig. 2). Furthermore, folic acid may enhance the formation of neuroprotectin D1 (NPD1), an anti-inflammatory and cytoprotective molecule from DHA and lipoxins and resolvins from EPA, DHA, and arachidonic acid (AA) by virtue of its ability to enhance plasma levels of these PUFAs.

Folates are involved in the cerebral metabolism of cobalamine, methionine, L-tyrosine and acetylcholine. In general, cerebrospinal fluid (CSF)-folate levels are 3–4 times higher than blood-folate levels. To reach the brain, folates are actively transported by choroid plexus (CP) as well as vitamins B_6, B_{12}, C and E. Under normal conditions, CSF-folate concentrations do not vary with age (10.47 ± 1.93 ng/ml between 20 and 60 years; 9.96 ± 2.01 ng/ml in elderly control patients older than 60 years of age, $p > 0.05$) while late-onset Alzheimer's

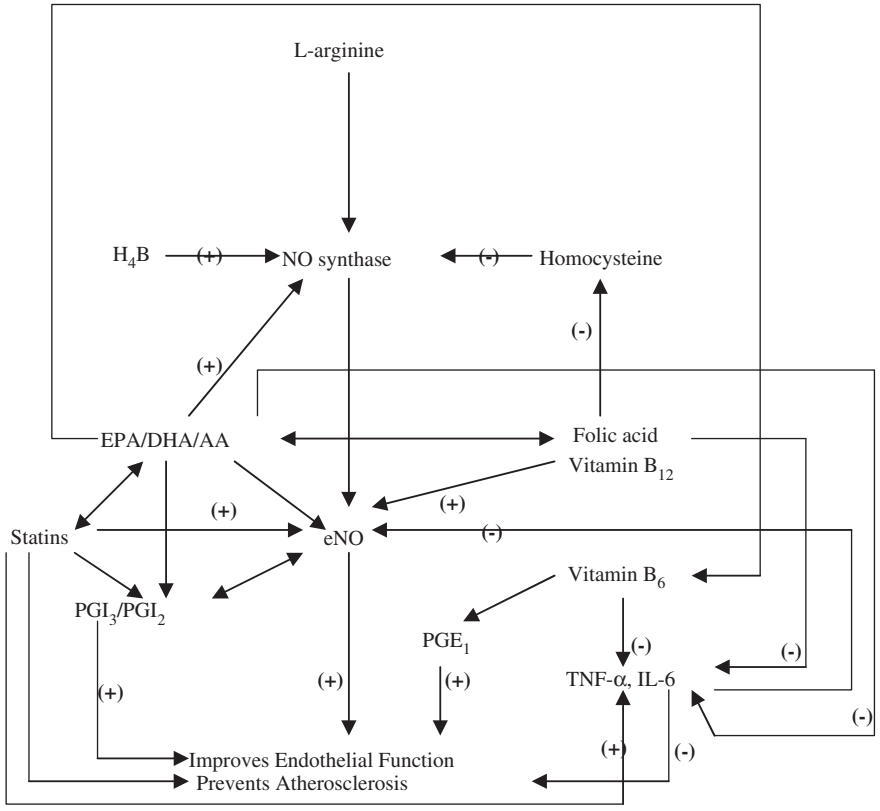

Fig. 2. Scheme showing the relationship between homocysteine, folic acid, NO metabolism, H_4B, cytokines, endothelial function, and atherosclerosis. (−) Indicates inhibition of synthesis, action or negative feed back control. (+) Indicates increase in synthesis, action or positive feed back control. For details see the text.

disease patients had significantly lower CSF-folate levels (8.26 ± 1.82 ng/ml, $p < 0.001$), supporting the concept that a specific alteration of CP transport occurs in AD patients [14]. In addition, vitamin B_{12} was significantly reduced in AD patients [15].

4. Depression is a low-grade systemic inflammatory condition

Pro-inflammatory cytokines might cause depressive illness. This is based on the observations that: (a) activation of the immune system, and administration of endotoxin (LPS) or interleukin-1 (IL-1) induces sickness behavior, which resembles depression in experimental animals [16]; (b) activation of the immune system is observed in many depressed patients [17]; (c) subjects with immune dysfunction are more frequently affected by depression [18]; (d) treatment of patients with cytokines can produce symptoms of depression [19]; (e) chronic treatment with anti-depressants inhibits sickness behavior induced by LPS [20]; (f) activation of the hypothalamo-pituitary-adrenocortical axis (HPAA) is seen in depressed patients and those treated with pro-inflammatory cytokines [16]; (g) cytokines activate cerebral noradrenergic systems that is known to occur in depressed patients [19]; and (h) several pro-inflammatory cytokines activate brain serotonergic systems, which have been implicated in major depressive illness and its treatment [21,22]. These data suggest that depression is a low-grade systemic inflammatory condition [23].

Central nervous system regulates the production of pro-inflammatory cytokines: TNF, IL-1, HMGB1, IL-6, and MIF through the efferent vagus nerve [24,25]. Acetylcholine, the principal vagus neurotransmitter, inhibits the production of pro-inflammatory cytokines through a mechanism dependent on the α7 nicotinic acetylcholine receptor subunit. Since vagal nerve stimulation (VNS) is of benefit in depression, previously I proposed that the beneficial effect of VNS in depression is due to its (VNS) inhibitory action on the production of pro-inflammatory cytokines [26].

5. Depression and ω-3 fatty acids

It is known that there is a significant decrease of ω-3 fatty acids in plasma and/or in the membranes of red blood cells in subjects with depression [27–29]. ω-3 fatty acids suppress the production of IL-1β, IL-2, IL-6 and TNF-α. This suggests that ω-3 fatty acids could play a

major role in major depression, through their roles in maintaining membrane fluidity that influences neurotransmission and by modulating the production of pro-inflammatory cytokines [30]. Furthermore, anti-depressants exhibit an immunoregulating effect by reducing the release of pro-inflammatory cytokines, by increasing the release of endogenous antagonists of pro-inflammatory cytokines like IL-10 and, by acting like inhibitors of cyclo-oxygenase [31]. Double-blind placebo-controlled and other studies [32–34] showed that addition of ω-3 fatty acids EPA and DHA was associated with a longer period of remission among depressed patients. Thus, epidemiological, experimental and clinical data favour the idea that PUFAs play a major role in the pathogenesis and hence, are of significant benefit in the treatment of depression.

6. Alzheimer's is an inflammatory condition

Cultured human neuronal cells synthesize α-2 macroglobulin, a potent human proteinase inhibitor, upon stimulation with the inflammatory mediator IL-6. Alzheimer's disease cortical senile plaques displayed strong α-2 macroglobulin and IL-6 immunoreactivity while age-matched controls did not show such immunoreactivity [35]. In addition, strong perinuclear α-2 macroglobulin immunoreactivity in hippocampal CA1 neurons of Alzheimer's disease brains with no elevated IL-6 or α-2 macroglobulin levels in the CSF of Alzheimer's disease patients indicates that inflammatory events are restricted to the local cortical areas where Alzheimer's pathology is present. These studies led to the suggestion that βA4 peptide; a major constituent of Alzheimer's disease senile plaques is formed due to the proteolytic cleavage of amyloid precursor protein (APP) inside its βA4 sequence due to the action of α-2 macroglobulin, emphasizing the occurrence of acute-phase state in Alzheimer's disease cortices. Some studies did report an increase of circulating IL-6 in Alzheimer's [36,37] though other studies did not support this observation [38,39]. But, it is now generally believed that Alzheimer's disease is an inflammatory condition and this is supported by the demonstration of the (i) presence of IL-6 in cortices of these patients; (ii) non-steroidal anti-inflammatory drugs, inhibitors of prostaglandin (PG) synthesis, have been shown to be beneficial in Alzheimer's; (iii) PGs induce IL-6 synthesis in human astrocytoma cells in vitro, and PGE_1 and PGE_2 induced a rapid and transient induction of astrocytic IL-6 m RNA, followed by IL-6 protein synthesis; (iv) PGE_2 potentiated IL-1β-induced IL-6 mRNA synthesis, evidences that link PGs and IL-6 events; and (v) the fact that microglia are the source of PGE_2 indicated that these cells could be the origin of the pathogenic cascade [40]. These data coupled with the observation that (i) elevated levels of cytokines occurs in brains of Alzheimer's disease patients; (ii) altered peripheral levels of IL-1β, TNF-α and IL-6 is detectable in them; and (iii) the fact acetylcholinesterase treatment down-regulates IL-1, IL-6 and TNF, and up-regulates the expression and production of IL-4 in PBMC in Alzheimer's disease patients, suggests that cytokine network and cholinergic system play a significant role in its pathogenesis [41]. Acetylcholine inhibits the production of pro-inflammatory cytokines through a mechanism dependent on the α7 nicotinic acetylcholine receptor subunit [24,25], and enhances NO, whereas acetylcholinesterase enhances acetylcholine levels, lending support to the close association between inflammation, cholinergic system, and Alzheimer's disease.

7. Alzheimer's disease and beneficial actions of ω-3 and ω-6 fatty acids

A large prospective cohort study reported that fish, a direct source of ω-3 fatty acids, EPA and DHA; intake was associated with a slower rate of cognitive decline [42]. Increased consumption of EPA/DHA has been associated with lower risk of Alzheimer's disease [43] and cognitive decline [44]. EPA and DHA are essential for neurocognitive development and normal brain functioning [45,46]. DHA improved memory performance in aged mice [47]. A reduction in dietary DHA in an Alzheimer's mouse model showed loss of postsynaptic proteins associated with increased oxidation, increased caspase-cleaved actin, which was localized in dendrites, whereas DHA-restricted mice when given DHA protected them against dendritic pathology and behavioral deficits and increased anti-apoptotic BAD phosphorylation, implying that DHA could be useful in preventing Alzheimer's disease in which synaptic loss is critical [48]. DHA attenuated amyloid-β secretion accompanied by the formation of NPD1, a DHA-derived 10,17S-docosatriene. In Alzheimer's hippocampal cornu ammonis region DHA and NPD1 were reduced including the expression of enzymes involved in NPD1 synthesis, cytosolic phospholipase A_2 and 15-lipoxygenase [49]. NPD1 repressed amyloid-β-induced activation of pro-inflammatory genes and up-regulated the anti-apoptotic genes encoding Bcl-2, Bcl-xl, and Bfl-1 (A1) indicating its (NPD1) anti-inflammatory nature. Soluble APP-α stimulated NPD1 synthesis from DHA [49].

In this context, it is important to note that when subjects who had cognitive dysfunction (21 mild cognitive dysfunction, 10 organic brain lesions, and 8 Alzheimer's disease) were supplemented with 240 mg/day AA and DHA showed a significant improvement in their cognitive function, though no significant improvement

was seen in the Alzheimer's and the placebo groups. These results suggest that AA and DHA supplementation can improve the cognitive dysfunction due to organic brain damages or aging [50].

Statins mediate many of their actions by modulating the metabolism of PUFAs, and increase the production of lipoxins and resolvins that suppress inflammation [51] that may explain their beneficial action in Alzheimer's. Presenilin, a major component of γ-secretase, generates amyloid-β. Overexpression of phospholipase D1 decreases the catalytic activity of γ-secretase [52], and releases PUFAs as evidenced by increased formation of PG E_2 [53]. This suggests that PUFAs could suppress the activity of γ-secretase. PUFAs (especially AA and DHA) enhance acetylcholine release in the brain [54,55] accounting for some of their beneficial effects in Alzheimer's. This is similar to the beneficial effects reported with choline esterase inhibitors in Alzheimer's. All these evidences suggest that PUFAs are of benefit in the prevention and treatment of Alzheimer's disease, though some studies did not support these conclusions [56,57]. These negative results could be due to inadequate supplementation of EPA/DHA, the duration of the studies were not long enough to document improvement in cognitive function, differences in the study protocol, and/or due to inadequate provision of AA during supplementation.

8. Polyunsaturated fatty acids and cognitive function

PUFAs have important effects on membrane and cellular properties of neural tissue and are preferentially accumulated by the brain during the last trimester of pregnancy and the first months of life [58,59]. The breast-fed babies have a better IQ compared to formula fed. The concentrations of PUFAs in plasma, red blood cell, and cerebral cortex are lower in formula-fed infants than they are in infants who were breast-fed or formula supplemented with PUFAs [60,61]. When infant cognitive behavior was assessed at 10 months of age following the supplementation of infant feed formula containing PUFAs containing mainly AA and DHA from birth to age 4 months, they showed significantly more intentional solutions than infants who received formula with no PUFAs [62]. These results suggest that supplementation with PUFAs are important for the development of childhood intelligence, cognitive function, and to prevent dementia in later life. This is supported by the observation that low serum levels of DHA could be a risk factor for Alzheimer's disease [63], PUFAs protect neurons directly by preventing neuronal apoptosis and suppressing the production of neurotoxic TNF (reviewed in [64]). Thus, PUFAs might be beneficial in Alzheimer's disease and other dementias.

9. Conclusion and therapeutic implications

It is evident from the preceding discussion that optimal amounts of folic acid and vitamin B_{12} enhance NO generation, stimulate endogenous H_4B regeneration, inhibits intracellular superoxide production, and prolong half-life of NO; increase ω-3 PUFAs, and brain acetylcholine levels, and indirectly show anti-inflammatory actions since NO, ω-3 PUFAs and acetylcholine suppress inflammation by inhibiting tumor necrosis factor-α production [4,9,10,15]. These evidences suggest that dietary factors vitamin B_{12}, folic acid, and ω-3 PUFAs influence plasma and neuronal levels of NO, cellular content of H_4B, and regulate concentrations of pro-inflammatory cytokines, and superoxide anion that may ultimately determine the susceptibility of an individual to develop dementia and Alzheimer's disease. Hence, the beneficial action of folic acid, vitamin B_{12}, and ω-3 PUFAs observed in some of these studies reported [1,2,15,27–29] is not only due to a decrease in homocysteine levels but also could be as a result of increased generation of NO, and the ability of ω-3 PUFAs to modulate neural function, including neurotransmission, membrane fluidity, ion channel and enzyme regulation and gene expression, and prevent inflammation (Fig. 3). These evidences are further supported by the recent observation that AA and DHA are implicated in neurite outgrowth [65–71] by activating syntaxin 3 that is specifically involved in fast calcium-triggered exocytosis of neurotransmitters. Furthermore, synaptosomal-associated protein of 25 kDa (SNAP25), a syntaxin partner implicated in neurite outgrowth, interacted with syntaxin 3 only in the presence of AA that allowed the formation of the binary syntaxin 3-SNAP 25 complex. AA stimulated syntaxin 3 to form the ternary SNARE complex (soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor), which is needed for the fusion of plasmalemmal precursor vesicles into the cell surface membrane that leads to membrane fusion that facilitates neurite outgrowth. These results imply that a combination of folic acid, vitamin B_{12}, and ω-3 PUFAs: EPA and DHA (including appropriate amounts of AA) when given in optimal combination could be of significant benefit in the prevention and treatment of depression and Alzheimer's disease, and improve cognitive function. Cognitive impairment that occurs due to vascular causes could also be improved by supplementation of adequate amounts of AA/EPA/DHA and folic acid, vitamin B_6, and other co-factors involved in the metabolism of various PUFAs. Such a beneficial action of PUFAs, folic acid and vitamin B_6 in vascular causes of cognitive impairment could, in part, be attributed to their ability to prevent atherosclerosis as discussed in detail elsewhere [72,73], and protect neuronal cells from apoptosis induced by ischemia,

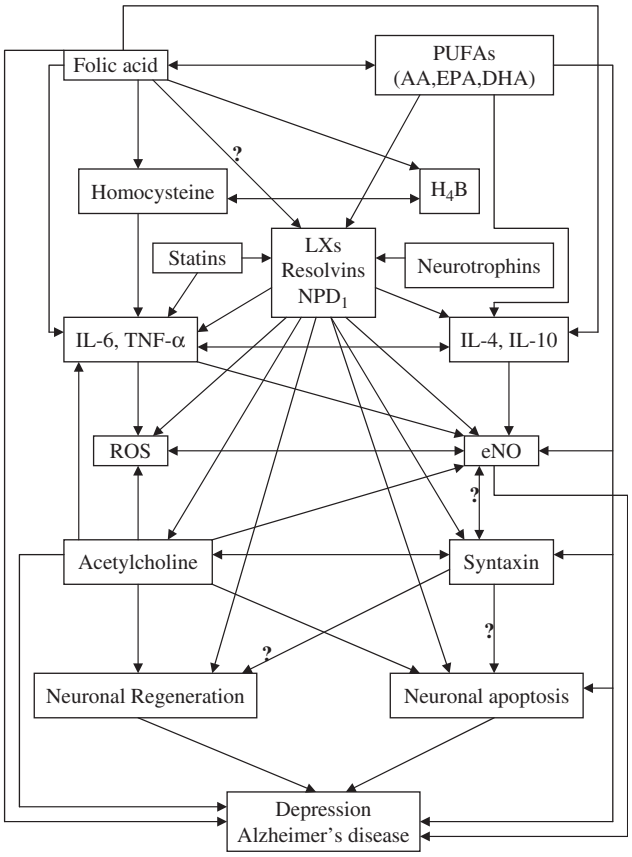

Fig. 3. Scheme showing relationship and interaction(s) between folic acid, PUFAs, reactive oxygen species, eNO, acetylcholine, and depression and Alzheimer's disease. ? Indicates that this interaction needs to be established. ROS = reactive oxygen species, H_4B = tetrahydrobiopterin.

pro-inflammatory cytokines, and other neurotoxic factors [74,75].

In this context, it is important to note that nerve growth factor (NGF), a protein that promotes survival, differentiation, and process extension of selected neuronal populations during development and in the mature organism, prevents degenerative changes in adult primate basal forebrain cholinergic neurons, the loss of which is common in Alzheimer's disease [76]. Furthermore, several different neurotrophic factors prevent death of cortical and hippocampal neurons induced by excitotoxic and oxidative insults in cell culture and in vivo by suppressing oxidative stress and mitochondrial dysfunction, enhancing basal glucose and glutamate transport, and attenuating oxidative impairment of glucose and glutamate transport induced by amyloid beta-peptide and Fe^{2+} in neocortical synaptosomes [77]. Since cognitive impairment is common in major depression and Alzheimer's disease, it was suggested that decreased brain-derived neurotrophic factor (BDNF), a member of the neurotrophic factor family, plays a significant role in both Alzheimer's disease and depression [78]. These results coupled with the observation that the amount of pro-BDNF decreased in subjects with mild cognitive impairment and Alzheimer's disease as compared with those with no cognitive impairment and that the decrease in mature BDNF and pro-BDNF precedes the decline in choline acetyltransferase activity that occurs later in Alzheimer's disease suggests that neurotrophins play a role in synaptic loss and cellular dysfunction underlying cognitive impairment [79].

Furthermore, lipopolysaccharide (LPS) activated microglia produced increased amounts of IL-1α and TNF-α in the hippocampus that led to learning and memory deficits in animals without histochemical evidence of neuronal cell death. The genetic expression of BDNF and its receptor, TrkB, decreased during the course of LPS treatment and glutamatergic transmission was attenuated in the LPS-treated rats. These results suggest that activation of microglia induced by LPS leads to an increase in the production of pro-inflammatory cytokines that lead to a decrease of glutamatergic transmission and consequent learning and memory deficits without neuronal cell death [80]. On the other hand, EPA/DHA suppresses the production of pro-inflammatory cytokines [26,30]. In addition, neurotrophins, especially pigment epithelium-derived factor, induce NPD1 synthesis from DHA, in particular, when challenged with oxidative stress, activate anti-apoptotic proteins and decrease pro-apoptotic proteins, and attenuate caspase 3 activation. These results suggest that neurotrophins regulate NPD1 synthesis and thus, bring about their neuroprotective actions [81]. Thus, it is likely that EPA/DHA/AA and other co-factors involved in the metabolism of PUFAs not only improve cognitive function, but also are beneficial in the prevention of cognitive decline that occurs due to ageing, stroke, Alzheimer's disease, and depression.

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