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REVIEW PAPER

Neurological Benefits of Omega-3 Fatty Acids

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Abstract The central nervous system is highly enriched in long-chain polyunsaturated fatty acid (PUFA) of the omega-6 and omega-3 series. The presence of these fatty acids as structural components of neuronal membranes influences cellular function both directly, through effects on membrane properties, and also by acting as a precursor pool for lipid-derived messengers. An adequate intake of omega-3 PUFA is essential for optimal visual function and neural development. Furthermore, there is increasing evidence that increased intake of the long-chain omega-3 PUFA, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), may confer benefits in a variety of psychiatric and neurological disorders, and in particular neurodegenerative conditions. However, the mechanisms underlying these beneficial effects are still poorly understood. Recent evidence also indicates that in addition to the positive effects seen in chronic neurodegenerative conditions, omega-3 PUFA may also have significant neuroprotective potential in acute neurological injury. Thus, these compounds offer an intriguing prospect as potentially new therapeutic approaches in both chronic and acute conditions. The purpose of this article is to review the current evidence of the neurological benefits of omega-3 PUFA, looking specifically at neurodegenerative conditions and acute neurological injury.

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Introduction

The essential dietary role of specific polyunsaturated fatty acids (PUFA) was first recognized in the early decades of the 20th century (Burr and Burr 1929, 1930). These PUFA were isolated and identified as linoleic acid (LA) and α-linolenic acid (ALA), and they were consequently defined as essential fatty acids. These fatty acids were subsequently established as the precursors of two distinct series of PUFA, the omega-6 and omega-3 series, respectively.

Hansen followed this work and studied EFA deficiency and eczema in infants, and was the first to suggest an equivalent essential fatty acid requirement in human nutrition (reviewed in Sinclair 1990). Soon after this, Hugh Sinclair was to show tremendous insight by recognising the potential role an imbalance in intake between omega-3 and omega-6 PUFA could have in the aetiology of many diseases (Sinclair 1956). Unfortunately, his work remained largely ignored for many years. Indeed, it was not until epidemiological studies in the Greenland Inuit provided evidence that a high relative intake of omega-3 PUFA compared to omega-6 PUFA was correlated with a decreased prevalence of cardiovascular disease, that their importance began to be more widely recognized (Dyerberg 1993). Since these seminal studies there has been a significant and constant increase in interest in omega-3 PUFA, especially in relation to their roles in the central nervous system.

Metabolism

Essential fatty acid metabolism proceeds through a progressive series of desaturation and elongation steps, with the omega-6 and omega-3 PUFA series sharing the same enzymes, as summarised in Fig. 1. The initial rate-limiting step of omega-3 PUFA metabolism involves desaturation of ALA (18:3$n-3$), which is followed by an elongation. Δ5-desaturase then catalyses a second desaturation to produce EPA (20:5$n-3$). EPA is then further elongated. Traditionally, the pathway was thought to continue with a final desaturation by Δ4-desaturase to produce the terminal PUFA, DHA (22:6$n-3$). However, in vitro microsomal Δ4-desaturase activity has yet to be demonstrated, and an alternative pathway is currently favoured (Voss et al. 1991; Infante and Huszagh 1998). In this pathway 22:5$n-3$ is elongated and then undergoes a second Δ6 desaturation (Voss et al. 1991). Whether this desaturation is catalysed by the same or an alternate Δ6-desaturase isozyme has yet to be determined (Nakamura and Nara 2003). 24:6$n-3$ is then translocated to the peroxisome for a single cycle of β-oxidation to produce DHA (22:6$n-3$), which is then translocated back to the endoplasmic reticulum for subsequent esterification into aminophospholipids (Sprecher 2000). Supporting evidence for the β-oxidative pathway has been provided by patients with Zellweger's syndrome and other peroxisomal disorders, which are associated with low tissue levels of DHA (Petroni et al. 1998; Su et al. 2001). Indeed, supplemental DHA is used as a treatment for Zellweger's syndrome (Martinez et al. 2000). In this disorder, the peroxisomal dysfunction causes an

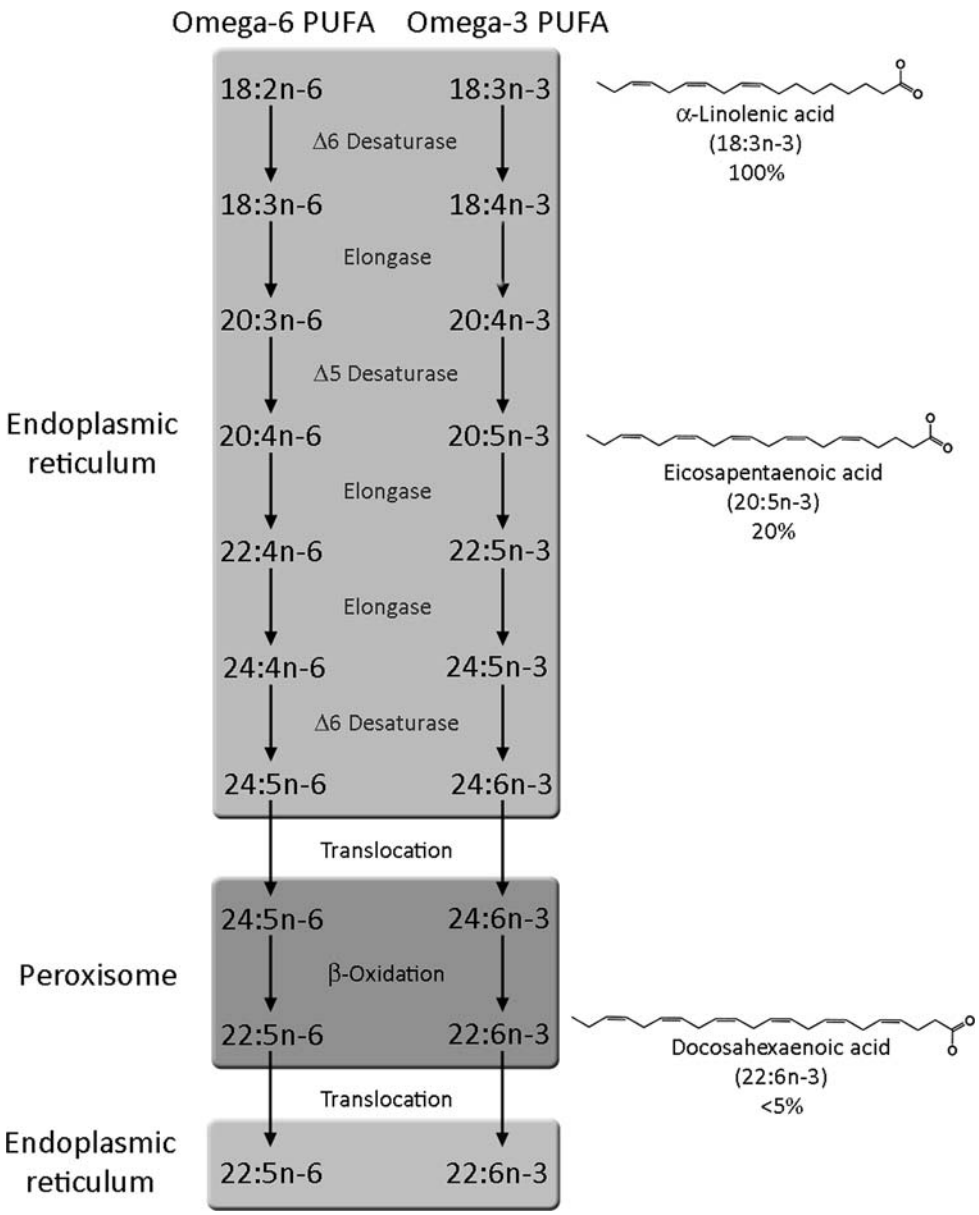

Fig. 1 Summary of omega-3 and omega-6 PUFA biosynthetic pathways. The pathways proceed through a series of desaturation and elongation steps in the endoplasmic reticulum until 24:5$n-6$ and 24:6$n-3$, which are translocated to the peroxisome, where the chains are shorted by C2 by one cycle of the β-oxidation pathway to form 22:5$n-6$ and 22:6$n-3$ (DHA), respectively. These are then translocated back to the endoplasmic reticulum for subsequent esterification into aminophospholipids. The relative efficiencies of the omega-3 PUFA conversion process are shown to the right of the pathways, for further details refer to the text

inability to retroconvert 24 carbon fatty acids to 22 carbon fatty acids, which leads to a decrease in DHA, and an increase in longer chain metabolites.

Human metabolic studies using stable isotopes of ALA show a restricted conversion of ALA to DHA, typically below 5% in adult males (Pawlosky et al. 2001; Brenna 2002; Burdge and Wootton 2002). However, if the background diet is high in omega-6 PUFA, this further reduces conversion by 50% (Gerster 1998). Interestingly, gender differences in the efficiency of conversion have been found in humans, such that women have a greater efficiency of conversion (Burdge 2006). This increased capacity for DHA synthesis may be important for foetal supply during pregnancy. Furthermore, in addition to the limited conversion, there is also an age-related decrease in Δ6-desaturase activity, which is more pronounced in women (Bolton-Smith et al. 1997). Elderly women (>75 years old) have been found to have a significantly decreased phospholipid DHA:EPA ratio compared to younger controls (20–48 years old) (Babin et al. 1999). Overall these studies suggest that a supply of preformed EPA and DHA may be the best way to ensure adequate provision for both sexes, especially in ageing.

The modernisation of food manufacturing and preservation processes has dramatically altered the balance of the EFA in the Western diet (Simopoulos 1999). There has been an increase in the intake of omega-6 PUFA and concomitant decrease in the intake of omega-3 PUFA (Sanders 2000). A deficiency of the long-chain omega-3 PUFA, DHA and EPA, has been linked to a variety of diseases including, but not limited to, cancer (Rose and Connolly 1999), cardiovascular disease (Tapiero et al. 2002), rheumatoid arthritis (Shapiro 2003), asthma (Horrocks and Yeo 1999), depression (Peet et al. 1998), schizophrenia (Peet 2002), attention deficit hyperactivity disorder (Burgess et al. 2000) and Alzheimer's disease (Kyle et al. 1999). Furthermore, there is evidence of beneficial effects of omega-3 PUFA in complex cortical processing in healthy adults (Fontani et al. 2005). However, as will be discussed in the present article, research into the implications of omega-3 PUFA consumption for central nervous system function, and their mechanism of action under pathological conditions is still in its infancy.

Mechanisms of Action

The brain has particularly high levels of omega-3 and omega-6 PUFA, especially DHA and arachidonic acid (AA), and is sensitive to alterations in dietary intake (Marteinsdottir et al. 1998). The fatty acid composition of neuronal membranes influences cellular function through direct effects on membrane biophysical properties, and also via neurotransmission, by providing a precursor pool for signalling molecules and lipid-derived mediators. There is growing evidence that omega-3 PUFA are able to directly and indirectly modulate neurological activity on many different levels, operating through a multitude of overlapping mechanisms. The following section is a brief overview of some of these mechanisms, which have been summarised diagrammatically in Fig. 2. More specific details will be discussed later in the context of different disorders.

Omega-3 PUFA have been shown to influence a number of membrane proteins, such as receptors, ion channels and enzymes. For example, chronic omega-3 PUFA deficiency significantly decreases Na^+/K^+ ATPase activity in rat brain (Bourre et al. 1989). Omega-3 PUFA deficiency can also significantly decreases the efficiency of G protein-coupled signalling, as has been shown in isolated rat retinal rod outer segment membranes (Niu et al. 2004). In this example, deficiency leads to reduced rhodopsin activation, rhodopsin-transducin coupling, cGMP phosphodiesterase activity, and slower formation of the active metarhodopsin II conformation and the metarhodopsin–transducin complex.

Omega-3 PUFA can also modulate dopaminergic, serotoninergic and cholinergic neurotransmission. For example, chronic omega-3 PUFA deficiency significantly decreases dopamine storage vesicle formation (Zimmer et al. 2000), dopamine levels (Delion et al. 1994, 1996) and tyramine-stimulated dopamine release (Zimmer et al. 1998) in the rat frontal cortex. Conversely, omega-3 PUFA supplementation significantly increases dopamine levels in this area (Chalon et al. 1998). Omega-3 PUFA deficiency also reduces the intensity of fenfluramine-stimulated serotonin release in the hippocampus of rats (Kodas et al. 2004). In a recent study the same group investigated the effects of omega-3 PUFA supplementation on serotoninergic neurotransmission in mice exposed to mild stressors (Vancassel et al. 2008). The stressors induced significant reductions in the tissue levels of serotonin in the frontal cortex, striatum and hippocampus, which were reversed by omega-3 PUFA supplementation. Omega-3 PUFA deficiency also alters cholinergic transmission in the rat hippocampus; basal acetylcholine release of deficient rats is significantly higher than controls, whereas KCl-induced release is lower (Aid et al. 2003). The deprivation also causes a 10% reduction in muscarinic acetylcholine receptor binding.

Omega-3 PUFA have also been shown to regulate signal transduction pathways. For example, EPA and DHA inhibit in vitro cAMP-dependent kinase, protein kinase C and Ca^{2+}/calmodulin-dependent protein kinase (Mirnikjoo et al. 2001; Seung Kim et al. 2001). EPA and DHA also inhibit the 5-HT-induced activation of mitogen-activated protein kinase in the hippocampus (Mirnikjoo et al. 2001). Interestingly, both AA and structurally similar fatty acids saturated at the omega-3 position are far less effective at inhibiting mitogen-activated protein kinase activity.

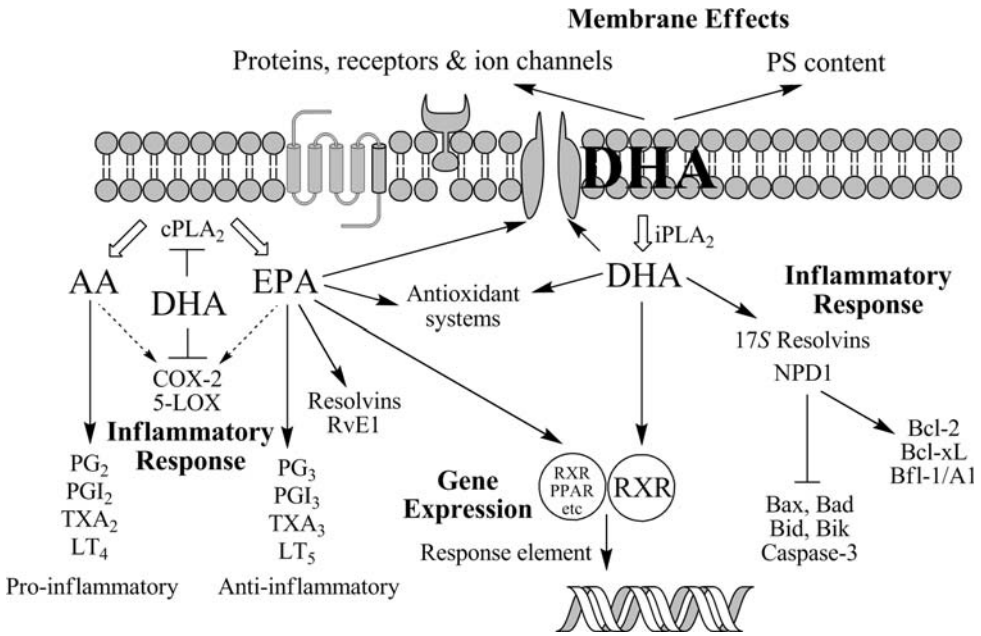

Fig. 2 The neuroprotective effects of EPA and DHA potentially operate through a variety of overlapping mechanisms of action. These are related to direct actions on plasma membranes, altered inflammatory response and control of gene expression, for detailed explanation of mechanisms refer to the text. The membrane effects appear to relate to alterations to the biophysical properties of the cell membrane and modulation of phosphatidylserine synthesis induced by the presence of esterified DHA in aminophospholipids. Alterations in inflammatory response are mediated through competition between AA and EPA for eicosanoid biosynthetic enzymes, with a high EPA content favouring the production of EPA derived anti-inflammatory mediators, such as series 3 prostaglandins, prostacyclins and thromboxanes and series 5 leukotrienes. Non-esterified EPA and DHA are also the precursors of anti-inflammatory resolvins, such as RvE1 and NPD1, respectively. NPD1 has been shown to inhibit pro-apoptotic proteins and enhance apoptotic proteins. Non-esterified EPA and DHA may also regulate gene expression via retinoid and peroxisomal proliferator signalling pathways, influence ion channels and enhance endogenous antioxidant systems. Solid arrows indicate positive effects, flat arrow-heads inhibition, dotted arrows competition and open arrows phospholipase A_2-induced release from the cell membrane. Abbreviations: $cPLA_2$, cytosolic PLA_2; $iPLA_2$, Ca^{2+}-independent PLA_2; LT, leukotriene; PG, prostaglandin; PGI, prostacyclin; PPAR, peroxisomal proliferator-activated receptor; PS, phosphatidylserine; RXR, retinoid X receptor and TXA, thromboxane

Increasing dietary intake of omega-3 PUFA produces widespread effects on gene expression (Jump 2002). Barcelo-Coblijn and coworkers fed rats either a fish oil enriched or control diet for 1 month (Barcelo-Coblijn et al. 2003a). Six genes were up-regulated in the fish oil-supplemented rats, the most notable of which were α-synuclein and transthyretin. Transthyretin (thyroxine binding prealbumin, TBPA) is an amyloid-β peptide scavenger (Link 1995) and α-synuclein is a pre-synaptic protein, with some mutations linked to familial Parkinson's disease. In another study by the same group rats were fed from conception to adulthood on control, high ALA or EPA/DHA diets (Kitajka et al. 2002). Overall 55 genes were overexpressed and 47 were suppressed in the omega-3 PUFA groups. Only one additional gene, coding for a membrane protein of unknown function, was up-regulated in the EPA/DHA group compared to the high ALA group, whereas one additional gene, also of unknown function, was down-regulated in the high ALA group when compared to the EPA/DHA group, indicating a certain equivalence of effect for the different types of omega-3 PUFA, at least under these conditions. The genes affected are involved in a diverse array of functions, in a variety of cellular locations, such as: lipid metabolism (phospholipase D), signal transduction (calmodulin), energy metabolism (ATP synthase subunit d and cytochrome *c* oxidase subunits), receptors (vasopressin V1b receptor), regulatory kinases (protein phosphatase 2A), synaptic proteins (α-synuclein) and membrane proteins (transthyretin).

A putative target involved in the mediation of the omega-3 PUFA control of gene expression is the steroid/thyroid/retinoid receptor superfamily. This superfamily of receptors are nuclear receptors that function as ligand-activated transcription factors, and include the retinoid X receptors (RXRα, -β and -γ) and the peroxisome proliferator-activated receptors (PPARα, -β/δ and -γ) (Duplus and Forest 2002). Retinoid signalling pathways have been implicated in regulating synaptic plasticity and learning and memory in rodents, and also in the pathophysiology of Alzheimer's disease, schizophrenia and depression (reviewed in Lane and Bailey 2005). DHA and EPA have been shown to act as endogenous ligands of RXR (de Urquiza et al. 2000; Lengqvist et al. 2004), and PPAR (Chambrier et al. 2002), and may thus work at a fundamental level of cell regulation.

Membrane-bound phospholipid DHA is also a positive modulator of phosphatidylserine biosynthesis in neuronal tissues (Hamilton et al. 2000). It has been suggested that the observed anti-apoptotic effect of DHA is due at least in part to the DHA-induced phosphatidylserine accumulation (Akbar and Kim 2002). A further potential benefit of DHA-induced phosphatidylserine accumulation may be to prevent the age-related decline in cognitive ability, since phosphatidylserine supplementation has been shown to improve age-related decline in cognitive ability and memory (Corwin et al. 1985; Blokland et al. 1999). This interesting area has been explored in more detail in a recent review (Kim 2007).

A key role for omega-3 PUFA is in the production of eicosanoids and other lipid-derived messengers and mediators involved in the inflammatory response. It is beyond the scope of this article to discuss this area in detail, and there are a number of excellent reviews on these topics (Tapiero et al. 2002; Calder 2006). However, one particular DHA derivative appears especially promising, and deserves special mention. It has been shown that under certain conditions DHA can be metabolised to oxygenated compounds with anti-inflammatory properties, such as 10-17*S*-docosatriene (also called neuroprotectin D-1 or NPD1) (Mukherjee et al. 2004) and 7,17*S*-dihydroperoxy-DHA (Butovich et al. 2006). Non-esterified DHA is the substrate for a 15-lipoxygenase-like (15-LOX-like) enzyme to produce NPD1 and 17*R*-resolvins (Serhan et al. 2002; Hong et al. 2003). These docosanoids were first identified in the retina (Bazan et al. 1984), and NPD1 has been shown to be neuroprotective in ischaemia-reperfusion injury (Marcheselli et al. 2003) and in a model of Alzheimer's disease, where NPD1 repressed the Aβ_{42}-triggered activation of the pro-inflammatory genes, Bad, Bik, Bax and Bid, and up-regulated the anti-apoptotic genes encoding Bcl-2, Bcl-xL and Bfl-1(A1) (Lukiw et al. 2005). NPD1 will be further discussed in relation to disorders such as Alzheimer's disease and spinal cord injury.

Normal Ageing

Epidemiological studies suggest a link between a high omega-3 PUFA intake and a decreased risk of cognitive decline and dementia in middle and old age (Kalmijn et al. 1997, 2004; Johnson and Schaefer 2006). Furthermore, higher omega-3 PUFA erythrocyte (Heude et al. 2003) and plasma (Schaefer et al. 2006) levels are associated with a significantly reduced risk of cognitive decline in ageing. The Zutphen Elderly study found that fish consumption was associated with a significantly decreased cognitive decline, where a difference in DHA and EPA intake of about 380 mg/day was associated with a 1.1 point difference in cognitive decline (van Gelder et al. 2007). The Minneapolis study analysed the association between plasma fatty acids and neuropsychological tests (Beydoun et al. 2007). Cognitive decline was found to be associated with lower plasma EPA and DHA in a subgroup of subjects with hypertension and dyslipidaemia. Overall these studies suggest that omega-3 PUFA may have a neuroprotective effect in ageing or more intriguingly, that they may possess therapeutic potential after the onset of cognitive impairment. In order to explore this further it is important to identify the various cellular and molecular mechanisms that underlie their ability to maintain neurological function in old age.

Normal ageing of the brain is characterised by major biochemical changes, such as increased oxidative stress, increased inflammation and altered energy metabolism (reviewed in Prolla and Mattson 2001). Normal ageing tends to cause metabolic damage to the central nervous system by mechanisms shared with neurodegenerative disorders, which include excitotoxic damage and increased calcium ion influx, leading to cell death by necrosis and apoptosis. Age-related changes also include reduced brain volume and weight, enlargement of the ventricles, a decline in enzyme activity, such as Na^+/K^+ ATPase and decreased membrane fluidity (Viani et al. 1991; Kocak et al. 2000; Anderton 2002). The brain regions most affected by loss of volume are the hippocampus and frontal lobes (Anderton 2002). The ageing brain is especially prone to oxidative stress due to the burden of high metabolic demands and also to the high concentration of PUFA.

Brain ageing is also associated with significant changes in phospholipid fatty acid composition. Studies in rodents consistently show decreases in the levels of PUFA in the central nervous system, and concomitant increases in the levels of monounsaturated fatty acids (Lopez et al. 1995; Favreliere et al. 2000), with DHA and AA showing significant reductions. The situation in humans appears much more complex, with limited alterations in PUFA levels in normal ageing. Although there is a tendency for AA levels to decrease and DHA levels to increase (Soderberg et al. 1991; Carver et al. 2001). However, under conditions of increased oxidative stress, such as in Alzheimer's disease, there are specific decreases in DHA, similar to those seen in rodents (Soderberg et al. 1991). It remains to be determined whether these changes are part of the aetiology of the pathological process of brain ageing, or a result of the process.

The ageing brain is prone to cellular changes that may underlie the loss of memory and learning ability. One such change is a reduction in long term potentiation (LTP) (Yehuda et al. 2002). A number of studies have shown that enriching the diet of old rats with DHA or EPA reverses age-related impairments in LTP (McGahon et al. 1999; Martin et al. 2002). These effects may be mediated through alterations in the glutamate receptor expression. In particular, the

N-methyl-D-aspartate (NMDA) glutamate receptors have an important role in synaptic mechanisms of learning and memory, such as LTP (Lynch 2004). Evidence supports a specific role for the NR2B subunit in learning and memory (Tang et al. 1999; Clayton et al. 2002; Xu et al. 2005a). In both rodents and primates, ageing is accompanied by a decrease in NR2B (Sonntag et al. 2000; Bai et al. 2004), and this deficit is correlated with a decline in learning (Magnusson 1998). Dietary omega-3 PUFA depletion in a murine model of Alzheimer's disease leads to a significant loss in NR2B, which is partially reversed by a DHA-enriched diet (Calon et al. 2005). Moreover, a diet enriched in EPA and DHA reverses age-related decreases in NR2B in old rats (Dyall et al. 2007). Reversal of the age-related NR2B decrease in the hippocampus is associated with improved cognition in rodents (Meshes et al. 2004).

α-Amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors act as the main mediators of fast excitatory neurotransmission by glutamate (Segovia et al. 2001). The permeability of AMPA receptors to Ca^{2+} is determined by the GluR2 subunit (Mishina et al. 1991). GluR2 subunit levels also decrease during ageing (Pagliusi et al. 1994; Hof et al. 2002), which may contribute to alterations in cellular Ca^{2+} homeostasis. It has been suggested that this altered Ca^{2+} flux may contribute to the neuronal losses and damage associated with neurodegenerative conditions of the aged brain, such as Alzheimer's disease (Margulies et al. 1993; Foster and Kumar 2002). Although the exact mechanism whereby increased Ca^{2+} influx contributes to neurodegenerative conditions is not well understood, it is possible it may be related to an overactivation of calcium-dependent enzymes.

The GluR2 subunit is also important for the growth and maintenance of dendritic spines (Passafaro et al. 2003). These are thought to have an important role in information processing (Hering and Sheng 2001). Their structure and number can be modified by neural activity, suggesting they are a substrate for neuroplasticity. Decreased spine density has been reported in aged rats, primates and humans (Jacobs et al. 1997; Hof et al. 2002; Markham and Juraska 2002). DHA significantly increases the density of dendritic spines in hippocampal pyramidal cells and in cerebellar Purkinje cells (Kotchabhakdi et al. 2003), and a diet enriched with EPA and DHA also reverses the age-related decreases in the GluR2 subunit in old rats (Dyall et al. 2007).

Neurodegenerative Disorders

Alzheimer's Disease

Alzheimer's disease is the most common form of dementia in the elderly. It is a progressive neurodegenerative disorder characterised by a decline in cognitive function and also profound alterations in mood and behaviour (Selkoe 2001). The pathology of the disease is characterised by the presence in the brain of extracellular amyloid peptide deposits and intracellular neurofibrillary tangles. The aetiology and pathogenesis of the disease are currently poorly understood, and the present management is to a large extent symptomatic, and focused on ameliorating the cognitive deficits (Murphy et al. 1998). Many hypotheses for the aetiology of the disease have been put forward. Those related to lipid metabolism include mitochondrial defects (Cassarino and Bennet Jr 1999), altered phospholipid metabolism (Horrobin and Bennet 1999) and increased oxidative stress (Markesbery 1997).

Alzheimer's disease is strongly correlated with decreases in omega-3 PUFA levels in the brain and peripheral tissues. Decreases in brain DHA levels have been consistently found in Alzheimer's disease patients compared to age-related controls (Skinner et al. 1989; Soderberg et al. 1991; Corrigan et al. 1998), and a decreased DHA content in serum phosphatidylcholine has been suggested as a significant risk factor for developing Alzheimer's disease (Kyle et al. 1999). Serum cholesteryl ester EPA and DHA have been shown to be significantly lower in Alzheimer's disease patients than in age-matched controls, and furthermore the decrease in DHA levels correlate with the severity of dementia (Tully et al. 2003).

Several groups have investigated the role of DHA-enriched diets in animal models of Alzheimer's disease. Hashimoto and colleagues pre-treated rats with DHA (300 mg/kg per day for 12 weeks) before an infusion of $A\beta_{1-40}$ (Hashimoto et al. 2002). DHA had a significantly protective effect against the decrease in learning ability, and reduced the oxidative stress in the cerebral cortex and hippocampus induced by the amyloid peptide infusion. In a follow-up study this group investigated the protective effects of the DHA pre-treatment before $A\beta_{1-40}$ infusion by analysis of synaptosomal membranes properties (Hashimoto et al. 2006). DHA content significantly increased along with both lateral and rotational membrane fluidity, whereas the cholesterol to phospholipid molar ratio and lipid peroxidation decreased. The authors suggest that these direct modifications to the biophysical properties of synaptosomal membranes contributed to the protective effects in learning ability seen with DHA pre-treatment. As discussed below, it seems likely that DHA operates through several overlapping mechanisms, although a common feature appears to be a surprising decrease in indices of oxidative stress. For example, Tg2576 transgenic mice fed a DHA supplemented diet had a 77% reduction in total $A\beta$ levels compared to DHA deficient mice, and the levels of oxidised proteins were elevated in the DHA deficient group compared to the control group, but were significantly

reduced in the DHA supplemented group (Lim et al. 2005). In the Tg2576 mouse DHA deficiency also leads to significant losses in the postsynaptic markers PSD-95, the actin-regulating protein drebrin, and also in the NR1 and NR2B NMDA glutamate receptors subunits, and DHA treatment partially protects against the NMDA receptor subunit loss (Calon et al. 2004; Calon et al. 2005), which may ultimately positively influence cognitive function.

Recent work by Green and co-workers has shown that DHA reduces the levels of soluble and intraneuronal Aβ and somatodendritic tau protein in the 3xTg Alzheimer's disease mouse model (Green et al. 2007). The reduction was attributed to a decrease in the steady-state levels of presenilin 1. Importantly, when DHA was combined with either arachidonic or docosapentaenoic acids (both omega-6 PUFA) the efficacy of DHA diminished over time, with the effects lost by 9 months. However, the additional presence of docosapentaenoic acid in the diet reduced levels of early-stage phospho-tau epitopes, which correlated the positive outcome of a reduction in phosphorylated (activated) c-Jun N-terminal kinase, a putative tau kinase. It may be that the interrelationship between omega-6 and omega-3 PUFA is an important but as-yet relatively neglected area of research. DHA has also been shown to significantly increase levels of the sorting protein LR11/SorLA in primary rat neurons, aged non-transgenic mice and aged DHA-depleted APPsw Alzheimer's disease mice (Ma et al. 2007). This increase reduces the trafficking of the amyloid precursor protein to secretases involved in the β-amyloidogenic pathway, and reduced LR11/SorLA expression is strongly correlated with Alzheimer's disease neuropathology (Offe et al. 2006).

DHA also attenuates Aβ secretion in cytokine-stressed human neural cells, and this is accompanied by formation of 10-17*S*-docosatriene (NPD1) (Lukiw et al. 2005). DHA and NPD1 were reduced in the hippocampal CA1 region of Alzheimer's disease brains, but not in the thalamus or occipital lobes from the same brains. Furthermore, expression of cytosolic phospholipase A_2 and 15-lipoxygenase, which are key enzymes in NPD1 biosynthesis, were altered in Alzheimer's disease hippocampus. NPD1 also repressed the Aβ_{42}-triggered activation of pro-inflammatory genes and up-regulated the anti-apoptotic genes encoding Bcl-2, Bcl-xl and Bfl-1(A1). The soluble amyloid precursor protein-alpha (APP-α) stimulated the biosynthesis of NPD1 from DHA. These results suggest that the beneficial effects of DHA may in part also be mediated via the production of NPD1, which induces anti-apoptotic and neuroprotective gene expression and consequently suppresses Aβ_{42}-induced neurotoxicity.

Positive effects of DHA treatment have not, however, been universally reported and a recent study by Arendash and co-workers found that a high omega-3 PUFA diet provided no significant benefit in terms of decreasing the levels of soluble/insoluble hippocampal Aβ levels or improving cognitive performance in either amyloid precursor protein (APP)-sw and PS1 double transgenic or wild-type mice (Arendash et al. 2007). The authors did find that higher cortical levels of omega-6 PUFA in both the transgenic and wild-type mice were associated with impaired cognitive function, as measured by the radial arm water maze and Morris water maze tests. It may be that if DHA is acting via a reduction in the steady-state levels of presenilin 1, as suggested by Green et al. (2007), the over-expression of presenilin 1 in the transgenic mouse model used in this study overwhelms the capacity of DHA and therefore this model may not accurately reflect the potential effects in patients, especially those affected by sporadic Alzheimer's disease. Furthermore, the omega-3 PUFA experimental diet contained high levels of EPA, which may have antagonised the effects of DHA (4.7% EPA and 5.7% DHA expressed as % total fat) by, for example, competing for enzymes in the NPD1 biosynthetic pathway.

An additional mechanism leading to a decrease in Aβ levels has been suggested by a study investigating the effect of omega-3 PUFA enrichment on gene expression in aged rats (Barcelo-Coblijn et al. 2003b). In this study there was a 10-fold increase in transthyretin transcription following treatment, and since transthyretin is a Aβ protein scavenger (Link 1995), the authors concluded that the omega-3 PUFA-induced expression could potentially prevent amyloid aggregate formation. Indeed Serot and co-workers found an inverse relationship between transthyretin levels in cerebrospinal fluid and the severity of dementia in Alzheimer's disease patients (Serot et al. 1997).

In addition to the pre-clinical evidence, a number of epidemiological studies have shown strong correlations between lower levels of dietary omega-3 PUFA and the development of Alzheimer's disease. For example, Barberger-Gateau and co-workers found that eating fish at least once a week decreases the likelihood of developing any form of dementia, including Alzheimer's disease (Barberger-Gateau et al. 2002). Furthermore, Morris and co-workers studied subjects aged 65–94 years, who were initially unaffected by Alzheimer's disease (Morris et al. 2003). Consumption of fish once or more per week was associated with a 60% reduction in the risk of developing Alzheimer's disease, compared with rarely or never eating fish. Total intake of omega-3 PUFA was associated with reduced risk of Alzheimer's disease, as was intake of DHA, although interestingly not EPA. The associations remained unchanged with additional adjustment for intake of other dietary fats and of vitamin E, and for cardiovascular conditions.

Although there are strong correlations between low tissue levels of omega-3 PUFA and increased risk of Alzheimer's disease, and low dietary intakes of omega-3 PUFA and

cognitive decline and Alzheimer's disease, the results of dietary intervention studies have so far failed to live up to expectations raised by the preclinical and epidemiological studies. In the first study to look at the effects of omega-3 PUFA in Alzheimer's disease, Yehuda and colleagues conducted a 4-week double-blind trial with 100 Alzheimer's disease patients (Yehuda et al. 1996). The supplemented group showed improvements in mood, cooperativity, short-term memory, appetite, sleep and spatial orientation, whereas no improvements were seen in the placebo group. A subsequent pilot study investigated the effects of 500 mg EPA given twice daily for 12 weeks in patients with Alzheimer's disease (Boston et al. 2004). No differences were found and the authors concluded that EPA had no effects on cognition. A larger study in 174 patients found that administration of 1.7 g of DHA and 0.6 g of EPA per day for 6 months in patients with mild to moderate Alzheimer's disease did not delay the rate of cognitive decline (Freund-Levi et al. 2006). Although, positive effects were observed in a small sub-group of patients with very mild Alzheimer's disease (MMSE $>$ 27 points).

In summary, current evidence appears to indicate that the beneficial effects of omega-3 PUFA are related more to the limitation of the progression of cognitive decline, and that omega-3 PUFA may have limited efficacy after onset of Alzheimer's disease symptoms. However, it should be noted that pre-clinical studies have focused on the effects of DHA, whereas clinical studies have investigated EPA, or may have used insufficient doses of DHA. It is hoped that future clinical studies will help clarify the relative roles and utility of DHA and EPA in the treatment of Alzheimer's disease.

Parkinson's Disease

Parkinson's disease is a neurodegenerative disorder of the basal ganglia. A pathological hallmark of the disease is the loss of dopaminergic neurons in the substantia nigra in the midbrain and also the presence of Lewy bodies, which are intracellular inclusions enriched in the protein α-synuclein. Common symptoms of the disease include resting tremor, rigidity, bradykinesia and postural instability (de Rijk et al. 1997). Parkinson's disease exists in both sporadic and early onset familial forms, the latter representing $<$10% of cases (Thomas and Flint Beal 2007). Although the aetiology is currently unknown, there are a number of putative risk factors such as exposure to environmental toxins. The pathogenic mechanisms include mitochondrial dysfunction (Jenner 2001), neuroinflammation (McGeer et al. 2001) and oxidative stress (Zhang et al. 1999). Parkinson's disease is the second most common neurodegenerative disorder after Alzheimer's disease, and the most consistent risk factor is age, with a prevalence of 1.6% in the elderly (de Rijk et al. 1995).

Symptomatic treatment of Parkinson's disease is currently based on the restoration of dopaminergic signalling, using either the dopamine biosynthetic precursor, levodopa, or dopaminergic agonists. However, the treatment is essentially symptomatic, and a large proportion of patients develop treatment-associated complications, which significantly interfere with the efficacy of the treatment (Marsden 1994). Pre-clinical studies have attempted to mimic Parkinson's disease pathogenesis, for example by using neurotoxins such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which leads to loss of dopaminergic cells (Calon et al. 2000).

Interestingly, levodopa treatment has been shown to alter brain PUFA composition (Julien et al. 2006). Parkinson's disease patients, who experience motor complications associated with levodopa, appear to have higher AA concentrations in the cortex than levodopa-treated Parkinson's disease patients devoid of motor complications. Furthermore, levodopa administration in MPTP-treated monkeys significantly increases AA and decreases DHA concentrations in the cortex. Short-term administration of 100 mg/kg DHA reduces the extent of levodopa-induced dyskinesias without altering the anti-parkinsonian effects in monkeys treated with MPTP (Samadi et al. 2006). This suggests that DHA can reduce the severity or delay the development of levodopa-induced dyskinesia. Indeed, protective effects have been shown in a recent study which exposed mice to either a control or a high omega-3 PUFA diet and then treated them with MPTP (Bousquet et al. 2008). The diet, which provided 7.8 g/kg diet total omega-3 PUFA, and 5.3 g/kg diet DHA, preserved dopamine levels and protected against losses in dopaminergic neurons in the substantia nigra.

To date, there have been two prospective studies investigating the link between fat intake and the incidence of Parkinson's disease. In the first, overall intakes of total fat were not significantly associated with the risk of developing Parkinson's disease, and there was also no significant association between omega-3 PUFA intake and the risk of developing Parkinson's disease (Chen et al. 2003). However, replacement of PUFA with saturated fat was associated with a significant increase in risk of Parkinson's disease in men but not women. In the second study, intake of PUFA was significantly associated with a lower risk of PD (de Lau et al. 2005).

In summary, there is a lack of direct evidence concerning the role of omega-3 PUFA in the treatment of Parkinson's disease, and epidemiological evidence suggests that omega-3 PUFA may offer limited neuroprotection. However, DHA may provide a useful adjunctive treatment in-as-much as it may alleviate the dyskinesias associated with levodopa treatment. It should, however, be noted that alterations in fatty acids can lead to aggregation of α-synuclein, and

possible formation of cytotoxic oligomers (Sharon et al. 2003; Assayag et al. 2007). Therefore, the role of PUFA in Parkinson's disease may be much more complex than what we know so far, and this area warrants further research.

Huntington's Disease

Huntington's disease is an invariably fatal autosomal dominant neurodegenerative disease that is characterised by a progressive development of motor, cognitive and psychiatric abnormalities. The disease is associated with a mutation in the interesting transcript 15 (IT15) gene which encodes the protein huntingtin. The mutation in exon 1 of the gene leads to an expanded trinucleotide (CAG) repeat and to the production of a protein with abnormally long poly-glutamine sequences, in both neurones and glia. The mutation leads to a toxic gain of function. However, the ultimate mechanisms that lead to cell death remain unclear, but very likely involve excitotoxicity, metabolic compromise and oxidative stress. A distinguishing feature of Huntington's disease is the early loss of striatal medium spiny GABAergic neurons which project to the external segment of the globus pallidus. Neuronal loss also can be also observed in the globus pallidus, reticular part of the substantia nigra, ventral anterior nucleus of the thalamus, cerebral cortex, cerebellar dentate nucleus, brainstem and spinal cord (Lauterbach et al. 1998). There are currently treatments to alleviate the symptoms; however, there are as-yet no agents that are able to significantly impact on the progression of the disease.

Animal models of Huntington's disease fall into two main categories: genetic and non-genetic. Genetic models are based on the expression of expanded poly-glutamine repeats. Non-genetic models are based on the induction of cell death through excitotoxic agents (e.g. quinolinic acid and kainic acid, which activate NMDA and kainic acid (KA) receptors, respectively), or through disruption of the mitochondrial activity (using agents such as 3-nitropropionic acid and malonic acid). In animal studies with the R6/1 transgenic mouse model of Huntington's disease (based on expression of a protein with approximately 115 CAG repeats), treatment throughout life with a mixture of EFA and lipoic acid markedly improved the behavioural phenotype and significantly decreased specific motor deficits, such as the decreased stride length, suggesting a potential neuroprotective effect (Clifford et al. 2002). However, it is important to note that the EFA preparation used in this study contained only 3% EPA and 2% DHA. The effects of omega-3 PUFA has also been studied in the genetic YAC128 mouse model of Huntington's disease. In this model, EPA was administered in adult mice from 7 months until sacrifice (Van Raamsdonka et al. 2005). Treatment significantly improved performance on the rotarod and reduced locomotor hypoactivity. However, the mice showed no improvement in striatal volume, striatal neuron counts, striatal neuronal-cross sectional area or striatal DARPP-32 (Dopamine- and cAMP-regulated phosphoprotein with a molecular weight of 32). DARPP-32 expression is critical in dopamine neurotransmission (Svenningsson et al. 2004) and may have a role in the pathogenesis of Huntington's disease as down-regulation has been reported in the RS/1 model (van Dellen et al. 2000).

Preliminary clinical trials have shown early promise in slowing the progression of the disease. An open label study with EPA in Huntington's disease patients showed significant improvements in motor function compared to the placebo group (Vaddadi et al. 2002). A pilot study with EPA was carried out in patients with advanced (stage III) Huntington's disease. After 6 months the patients treated with EPA improved on the Unified Huntington's Disease Rating Scale, while the patients on placebo deteriorated on this scale. Furthermore, 3D magnetic resonance imaging (MRI) brain scans showed progressive cerebral atrophy in the placebo group, whereas there was an apparent reversal in the EPA group (Puri et al. 2003). A more recent larger trial comparing 2 g per day EPA vs. placebo showed that EPA treatment produced no significant benefits in patients with Huntington's disease (Puri et al. 2005). However, the authors noted that a significantly higher number of patients showed stable or improved motor functions in the per protocol cohort. Overall, these studies are not indicative of a strong therapeutic effect, but further studies on the potential efficacy of omega-3 PUFA may be warranted, especially with a view to use of EPA as a symptomatic adjuvant treatment. Furthermore, it may be possible to define a subgroup of patients (low CAG repeats) where EPA may show increased efficacy (Murck and Manku 2007).

Multiple Sclerosis

Multiple sclerosis is thought to be an autoimmune disease, characterized by inflammatory lesions in the brain and spinal cord. It is a chronic neurodegenerative demyelinating disease, reflected in the presence of widespread oligodendrocyte damage and axonal demyelination. The axonopathy and demyelination lead to deficits in impulse conduction, which is expressed in multiple neurological symptoms. The aetiology is currently not well understood although the disease appears to have an immune-mediated basis, and there is strong evidence of genetic susceptibility (Frohman et al. 2005). There have been recent advances in the understanding of the underlying mechanisms of the disease, leading to improved treatments to alleviate the symptoms, mainly targeting the inflammatory component of the disease; however, there is currently no cure (Murray 2006).

The first indication of a beneficial effect of omega-3 PUFA was suggested by Swank et al. (1952). Their

analysis showed a lower incidence of multiple sclerosis among coastal communities with a high consumption of fish, than in areas with a high consumption of animal fat. The evidence for altered fatty acid levels in tissues in MS patients is currently unclear, with decreases in plasma omega-3 PUFA levels shown by some (Cunnane et al. 1989), whereas erythrocyte levels found unaltered by others (Koch et al. 2006).

Recent preclinical evidence has suggested that omega-3 PUFA may be of direct benefit in demyelinating diseases via a direct enhancement of in vivo myelinogenesis (Salvati et al. 2008). In this study, intracerebroventricular injection of either DHA or EPA significantly stimulated the expression of specific myelin proteins in rats, with the effect more pronounced with EPA.

To date, there have been only a limited number of studies investigating the effects of omega-3 PUFA in multiple sclerosis. In a preliminary open label study, 16 newly diagnosed patients were given dietary advice and supplemented with 0.9 g/day of long-chain omega-3 PUFA and vitamins (Nordvik et al. 2000). The patients were followed for 2 years with respect to dietary habits, blood parameters and neurological assessment, including exacerbation rate. There was a significant reduction in the mean annual exacerbation rate and the mean Expanded Disability Status Scale as compared to pre-study values. The plasma total phospholipid omega-3 PUFA increased and omega-6 PUFA decreased significantly. Overall, the study suggested that omega-3 PUFA supplementation given together with vitamins and dietary advice improved clinical outcome in patients with newly diagnosed multiple sclerosis.

Two double-blind placebo-controlled randomised clinical trials have investigated the effects of EPA and DHA. In the first study of 312 patients, patients received either 10 g fish oil or an olive oil placebo (Bates et al. 1989). After 2 years, although not statistically significant, there was an absolute risk reduction of 10% and a relative risk reduction of 18% of progressing one point on the Disability Status Scale. This treatment effect is similar to that reported for standard medical therapies. However, it should be noted that both groups were given dietary advice to increase the intake of omega-6 PUFA, and this may have limited the efficacy of the treatment. The second smaller trial involved 31 relapsing remitting multiple sclerosis patients who had been using disease modifying therapies for at least two months prior to the trial (Weinstock-Guttman et al. 2005). They were given either a very low fat diet (<15% calories from fat) supplemented with omega-3 PUFA (6 capsules per day containing 1.98 g EPA and 1.32 g DHA) or a low fat (<30% calories from fat) and olive oil as a placebo. At the end of 1 year there was a non-significant trend in favour of the omega-3 PUFA-treated group on the Physical Component Scale, and a weaker trend for worsening scores on the Expanded Disability Status Scale scores with the placebo group and improved scores on the omega-3 PUFA group. These studies suggest that supplementation with omega-3 PUFA may have moderate benefits in multiple sclerosis patients; however, further large-scale trials are still required to show significant benefits and determine any potential therapeutic effects.

Acute Neurological Injury

In addition to neurodegenerative conditions, omega-3 PUFA have also been shown to have neuroprotective and neuroregenerative effects following acute neurological injury. Neurodegeneration and acute neurological injury share a number of pathogenic mechanisms. For example, spinal cord injury occurs as a result not only of the initial injury, but also of the degeneration caused by secondary injury in the following minutes, hours and days. The secondary injury results from a multi-factorial cascade of events. The primary injury results in excitotoxicity (Hall and Braughler 1986), which activates cytosolic phospholipase A_2 ($cPLA_2$) releasing AA and leading to the production of pro-inflammatory prostaglandins, and additional inflammation triggered by macrophages and microglia that release inflammatory cytokines (Profyris et al. 2004). Another key early event leading is lipid peroxidation (Azbill et al. 1997). Post-traumatic lipid peroxidation causes direct damage to neuronal and axonal membrane structure and function, and also causes microvascular damage and secondary ischaemia (Hall and Springer 2004). Moreover, lipid peroxidation can initiate further side reactions, potentially leading to protein oxidation (Berlett and Stadtman 1997) and hydroxylation of DNA and RNA (Kasai et al. 1991), leading to subsequent tissue damage and cell death (Xu et al. 2005b).

Evidence of neuroprotective potential has been provided in a variety of models and paradigms of neurological injury, such as ischaemia/reperfusion and kainic acid-induced epileptic seizures. One of the first indications came from feeding rats an omega-3 PUFA-enriched diet for 6 weeks, and then inducing damage by either focal ischaemia or excitotoxicity (Relton et al. 1993). The omega-3 PUFA pre-treatment significantly reduced damage in both cases.

Rats fed a fish oil-supplemented diet prior to middle cerebral artery occlusion have been shown to have a significantly smaller infarct volume compared to the control group (Choi-Kwon et al. 2004). Ischaemia produced by occlusion of the middle cerebral artery is an animal model of brain ischaemia-reperfusion type injury. Interestingly, before ischaemia the fish oil-supplemented groups had higher levels of lipid peroxidation and higher levels of glutathione peroxidase activity, suggesting increased

oxidative stress. However, while the level of lipid peroxidation in the control group increased significantly after ischaemia, the levels in the fish-oil group remained constant throughout. Furthermore, during reperfusion, antioxidant enzyme activity decreased in the control group, but remained at pre-ischaemia levels in the fish-oil group suggesting that the neuroprotection seen with chronic fish-oil treatment may be mediated through induction of antioxidant enzyme activity, and that these adaptive changes enhance antioxidant defences. Enhanced antioxidant capacity has also been shown in another study, in which a single intra-amniotic administration of DHA decreased both Fe^{2+}-stimulated and ischaemia-induced lipid peroxides in foetal rat brain (Glozman et al. 1998).

Administration of moderate to high dose human albumin is neuroprotective in focal ischaemia (Belayev et al. 2001), and middle cerebral artery occlusion selectively stimulates the albumin-mediated mobilization of omega-3 PUFA into the blood stream (Rodriguez de Turco et al. 2002). The presence of DHA and 22:5$n-3$ in systemic rather than jugular venous plasma suggests supply from the liver, rather than local release, indicating a need for replenishment in the neural membranes. DHA-albumin treatment at the onset of reperfusion significantly improved behavioural scores compared to an equivalent dose of albumin, and produced an 86% reduction in infarction compared to 65% for albumin alone (Belayev et al. 2005). Interestingly, the DHA-albumin treatment produced a large accumulation of the NPD1 in the ipsilateral hemisphere. NPD1 has been shown to be neuroprotective in ischaemia-reperfusion injury (Marcheselli et al. 2003). When NPD1 was infused during reperfusion it was found to potently inhibit the infiltration of polymorphonuclear leukocytes, and the increases in NF-κB and COX-2 expression, and there was also a marked reduction in the volume of the stroke. This area of research appears especially promising, and it may be that through dietary interventions endogenous NPD1 biosynthesis is enhanced. NPD1 (or NPD1 analogues) may be used therapeutically in future.

KA is a glutamate analogue which when administered by intraperitoneal injection causes a well-defined seizure syndrome, with excitotoxic neurodegeneration in the CA1 and CA3 subfields of the hippocampus. This paradigm can be compared to human temporal lobe epilepsy (Nadler et al. 1978). Administration of ALA either 30 min before or 30 min after KA treatment led to significant neuroprotection (Lauritzen et al. 2000). Pre-treatment prevented epileptiform activity on EEG recordings, and neuroprotection was confirmed using both measurements of cell survival and apoptotic cell death. Palmitic acid, a saturated fatty acid, failed to prevent the KA-induced neuronal damage. The same group found that ALA was significantly neuroprotective when administered 3 days before the injury induced by KA (Blondeau et al. 2002). ALA pre-treatment induced the heat shock protein HSP70, a molecular chaperone involved in re-folding of denatured proteins, and also prevented expression of the pro-apoptotic protein, Bax. It has been suggested that a key mediator of the neuroprotective effects of omega-3 PUFA is the TREK-1 potassium channel, as the effect is abolished in TREK-1 knock-out mice (Heurteaux et al. 2004).

The first observation that suggested a therapeutic potential of omega-3 PUFA following spinal cord injury was that of the beneficial effects of ALA treatment after spinal cord ischaemia in rats (Lang-Lazdunski et al. 2003). Significant protection was seen, with improved functional outcome, decreased neuronal losses and decreased immunoreactivity for Bax and NF-κB. In a series of studies in our laboratory we have explored the neuroprotective role of omega-3 PUFA following traumatic spinal cord injury (King et al. 2006; Huang et al. 2007). DHA administered intravenously 30 min after spinal cord compression injury or hemisection injury significantly increased neuronal and oligodendrocyte survival and locomotor performance for up to 6 weeks after injury. DHA treatment also significantly decreased a number of indices of oxidative stress. Lipid peroxidation, protein oxidation, RNA/DNA oxidation were all significantly reduced. Furthermore, induction of COX-2 expression and macrophage recruitment were also significantly reduced. Considering the well-documented safety of omega-3 PUFA, there is significant potential for rapid clinical translation of these observations to the neurological trauma clinic.

Conclusions

EPA and DHA have been shown to positively influence a number of aspects of neurological function and dysfunction; however, for many of these effects their mechanism of action remains to be fully elucidated. It is very likely that EPA and DHA operate through a number of different, potentially overlapping mechanisms, involving various cellular targets. These PUFA can act as endogenous agonists for transcription factors such as the retinoid receptors, and the peroxisome-proliferator activated receptors (de Urquiza et al. 2000; Jump 2002). Neuronal excitability can be modulated by PUFA through their effects on sodium and calcium channels (Vreugdenhil et al. 1996; Hong et al. 2004) or the activation of the TREK potassium channels (Franks and Honoré 2004). Furthermore, it cannot be ruled out that their effects may also involve specific fatty acid receptors, such as the recently identified GPR40 receptor (Ma et al. 2007), which has a widespread expression in the central nervous system. Since the neurological conditions reviewed here share common features, such as excitotoxicity, oxidative

stress and inflammation, which appear to be modified by omega-3 PUFA, this may explain the therapeutic potential of EPA and DHA across disease boundaries. However, the relative importance of certain mechanisms and targets may vary depending on the condition considered.

Early studies into the effects of ALA, EPA and DHA have tended not to differentiate between these omega-3 PUFA, with the results broadly attributed to the omega-3 PUFA series as a whole. However, evidence is now accumulating that certain effects may be specific and unique for the different types of omega-3 PUFA. It can no longer be assumed they have a mechanistic equivalence. For example, a recent review into the effects of omega-3 PUFA in mental illness has indicated that EPA may be more beneficial in mood disorders than DHA (Ross et al. 2007). A further important, but as-yet largely unexplored issue concerns the most appropriate dosage of omega-3 PUFA to be used in studies. This area has begun to be explored in relation to cardiovascular disease, where the omega-3 index, or sum of EPA and DHA in erythrocyte membranes, is being used as an index of incorporation (Cao et al. 2006). In this study subjects received supplementation with either fish oil (1.3 g EPA and 0.9 g DHA/day) or flaxseed oil (3.5 g ALA and 0.9 g linoleic acid/day) for 8 weeks. Following fish oil supplementation, erythrocyte membrane EPA and DHA increased 300% and 42%, with the mean erythrocyte omega-3 index reaching a near optimal value of 7.8%. Flaxseed oil supplementation increased erythrocyte membrane EPA to 133% and docosapentaenoic acid (22:5$n-3$) to 120% of baseline, but DHA was unchanged. These observations which are relevant in the context of omega-3 PUFA and cardiovascular benefits also strengthen two points. Firstly, neurological clinical trials must endeavour to treat with PUFA doses which are high enough to produce a therapeutic effect (although the optimum omega-3 index in this case is far from clear). Secondly, there is limited conversion of ALA to DHA; therefore, supplementation must be based on long-chain PUFA. Future studies will no doubt provide a more focused and analytical approach to the type and dose of omega-3 PUFA that is most appropriate for specific neurological conditions.

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