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REVIEW

Modulation of inflammation in brain: a matter of fat

Akhlaq A. Farooqui,* Lloyd A. Horrocks* and Tahira Farooqui†

**Departments of Molecular and Cellular Biochemistry, and †Entomology, The Ohio State University, Columbus, Ohio, USA*

Abstract

Neuroinflammation is a host defense mechanism associated with neutralization of an insult and restoration of normal structure and function of brain. Neuroinflammation is a hallmark of all major CNS diseases. The main mediators of neuroinflammation are microglial cells. These cells are activated during a CNS injury. Microglial cells initiate a rapid response that involves cell migration, proliferation, release of cytokines/chemokines and trophic and/or toxic effects. Cytokines/chemokines stimulate phospholipases A_2 and cyclooxygenases. This results in breakdown of membrane glycerophospholipids with the release of arachidonic acid (AA) and docosahexaenoic acid (DHA). Oxidation of AA produces pro-inflammatory prostaglandins, leukotrienes, and thromboxanes. One of the lyso-glycerophospholipids, the other products of reactions catalyzed by phospholipase A_2, is used for the synthesis of pro-inflammatory platelet-activating factor. These pro-inflammatory mediators intensify neuroinflammation. Lipoxin, an oxidized product of AA through 5-lipoxygenase, is involved in the resolution of inflammation and is anti-inflammatory. Docosahexaenoic acid is metabolized to resolvins and neuroprotectins. These lipid mediators inhibit the generation of prostaglandins, leukotrienes, and thromboxanes. Levels of prostaglandins, leukotrienes, and thromboxanes are markedly increased in acute neural trauma and neurodegenerative diseases. Docosahexaenoic acid and its lipid mediators prevent neuroinflammation by inhibiting transcription factor NFκB, preventing cytokine secretion, blocking the synthesis of prostaglandins, leukotrienes, and thromboxanes, and modulating leukocyte trafficking. Depending on its timing and magnitude in brain tissue, inflammation serves multiple purposes. It is involved in the protection of uninjured neurons and removal of degenerating neuronal debris and also in assisting repair and recovery processes. The dietary ratio of AA to DHA may affect neurodegeneration associated with acute neural trauma and neurodegenerative diseases. The dietary intake of docosahexaenoic acid offers the possibility of counter-balancing the harmful effects of high levels of AA-derived pro-inflammatory lipid mediators.

Keywords: Arachidonic acid, cytokines, docosahexaenoic acid, docosanoids, eicosanoids, neurodegenerative diseases.
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Brain is an immunologically active organ. It is in direct communication with the immune and endocrine systems. The immune system is an excellent example of the integrated connections between the brain and the body. Thus, systemic inflammatory reactions and responses can influence brain function (Wilson *et al.* 2002). Neuroinflammation is a protective mechanism that isolates the damaged brain tissue from uninjured area, destroys affected cells, and repairs the extracellular matrix (Correale and Villa 2004). Without a strong inflammatory response, brain tissue would be a sitting

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Address correspondence and reprint requests to Lloyd A Horrocks, Department of Molecular and Cellular Biochemistry, The Ohio State University, 1645 Neil Avenue, Columbus, OH 43210, USA.
E-mail: horrocks.2@osu.edu

Abbreviations used: PMN, Polymorphonuclear leukocytes; IL-1α, interleukin-1 alpha; IL-1β, interleukin-1-beta; IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha; TGF- α and β, tumor growth factors; IFN-γ, interferon-γ; NFκB, transcription factor nuclear factor kappa B; PLA_2, phospholipase A_2; PLC, phospholipase C; PLD, phospholipase D; COX-1, cyclooxygenase-1; COX-2, cyclooxygenase-2; LOX, lipoxygenases; PAF, platelet-activating factor; PtdEtn, phosphatidylethanolamine; PlsEtn, plasmenylethanolamine; PtdCho, phosphatidylcholine; lyso-PtdCho, lysophosphatidylcholine; PtdIns, phosphatidylinositol; PtdSer, phosphatidylserine; PtdH, phosphatidic acid; lyso-PtdH, lysophosphatidic acid; AA, arachidonic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; PGH_2, prostaglandin H_2; TXA_2, thromboxanes; LXA_4, lipoxin A_4; LXB_4, lipoxin B_4; IsoPs, Isoprostanes; NP, neuroprostanes; NK, neuroketals; RvE1, resolvin E1; AEA, arachidonoylethanolamide; 2-AG, 2-arachidonoylglycerol; NSAIDs, non-steroid anti-inflammatory drugs; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; PPARs, peroxisome proliferator-activated receptors; TLRs, toll-like receptors; VCAM-1, vascular adhesion molecule-1; AD, Alzheimer disease; PD, Parkinson disease; DS, Down syndrome; HD, Huntington disease; MS, multiple sclerosis.

duck for acute neural trauma, neurodegenerative diseases, and microbial, viral, and prion infections. All neural cells, including microglia, astrocytes, neurons, and oligodendrocytes, participate in inflammatory responses.

The main mediators of neuroinflammation are microglial cells. In the normal healthy brain, microglial cells are characterized by a ramified morphology and are called resting microglia. The resting microglia are activated during CNS injury and transformed into an activated form characterized by amoeboid morphology. Microglial cells initiate a rapid response that involves cell migration and proliferation. Activated microglia migrate rapidly to the injury site; phagocytose dead cells, and clear cellular debris. The signals and mechanisms of microglial activation following CNS injury are just beginning to be understood.

Inflammatory responses resulting from brain injury or infection generally result in a beneficial, self-limiting, healing process. Histologically, the neuroinflammatory response requires the activation of microglia and recruitment of polymorphonuclear leukocytes (PMN) from the blood stream into brain tissue. This PMN migration is a co-ordinated multistep process involving chemotaxis, adhesion of PMN to endothelial cells in the area of inflammation, and diapedesis, the penetration of tight junctions and migration through the endothelial monolayer and into the interstitium (Diamond *et al.* 1999). These PMN eliminate invading antigens by phagocytosis and release free radicals and lytic enzymes into phagolysosomes. This is followed by a process called resolution, a turning off mechanism by neural cells to limit tissue injury. Acute inflammation normally resolves spontaneously, but the mechanism associated with this process remains elusive (Serhan and Savill 2005).

An active, co-ordinated program of inflammatory resolution is initiated in the first few hours after an inflammatory response begins. After entering tissues, granulocytes promote the switch of arachidonic acid-derived prostaglandins and leukotrienes to lipoxins, which initiate the termination sequence (Serhan and Savill 2005). Neutrophil recruitment thus ceases. The onset of cellular apoptosis occurs. These events coincide with the biosynthesis of resolvins and protectins, which critically shorten the period of neutrophil infiltration by initiating apoptosis (see below). Consequently, apoptotic neutrophils undergo phagocytosis by macrophages, leading to neutrophil clearance and release of anti-inflammatory and reparative cytokines such as transforming growth factor-β_1 (Serhan and Savill 2005). The anti-inflammatory program ends with the departure of macrophages through the lymphatics.

Acute neuroinflammation develops rapidly with the experience of pain, whereas chronic inflammation develops slowly. Chronic neuroinflammation differs from acute inflammation in that it is below the threshold of pain perception. As a result, the immune system continues to attack at the cellular level. Chronic inflammation lingers for years causing continued insult to the brain tissue, ultimately reaching the threshold of detection (Wood 1998). Morphologically, in brain tissue, major hallmarks of neuroinflammation are phenotypic changes of glial cells, mainly activation and transformation of microglial cells into phagocytic cells, and to a lesser extent, reactive astrocytosis. The molecular mechanisms and internal and external factors that modulate the dynamic aspects of acute and chronic neuroinflammation remain unclear. Furthermore, it remains unclear to what extent neuroinflammation is beneficial for the injured or infected brain tissue, and how it contributes to secondary brain injury and progressive neuronal loss. The purpose of this commentary is to discuss the contribution and role of neural membrane fatty acids in the inflammatory process. We hope that this discussion will initiate more studies on the molecular mechanisms of neuroinflammation and on the control of neuroinflammation by dietary factors.

Participation of glial cells in neuroinflammation

Glial cells, the microglia, astrocytes, and oligodendrocytes, constitute more than 70% of the total cell population in the brain tissue. Once thought of as merely a supportive system for neurons, glial cells are now regarded as key modulatory, trophic, and immune elements in the brain tissue. Oligodendrocytes are responsible for myelination, astrocytes participate in a wide variety of physiological and pathophysiological processes, and microglial cells in collaboration with astrocytes monitor and maintain the physiological homeostasis and microenvironment for the survival of neurons (Kempermann and Neumann 2003). Residential microglia, which represent 20% of the total glial cell population (Kreutzberg 1996; Kettenmann and Ransom 2005), also sense changes in the periphery and respond quickly to pathogenic stimuli in order to protect the brain. A variety of immune system modulators including complement proteins, adhesion molecules, inflammatory cytokines such as interleukin-1 alpha (IL-1α), interleukin-1 beta (IL-1β), interleukin-3 (IL-3), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), colony-stimulating factor-1, and tumor and growth factors (TGF- α and β), are made and secreted by both microglia and astrocytes (Hays 1998; Wu *et al.* 1998; Kim *et al.* 2001; Sun *et al.* 2004a; Drew *et al.* 2005; Minghetti *et al.* 2005; Noda *et al.* 2006). These factors propagate and maintain neuroinflammation by a number of mechanisms, including the activation of multiple forms of PLA_2, cyclooxygenases (COX), and lipoxygenases (LOX), causing the release of non-esterified AA from neural membrane phospholipids and generating lyso- glycerophospholipids, platelet-activating factor (PAF), pro-inflammatory prostaglandins, and reactive oxygen species (ROS) (Lin *et al.* 2004; Moses *et al.* 2006; Phillis *et al.* 2006). Furthermore, microglia, astrocytes, neurons, endothelial cells, and oligodendrocytes also produce complement proteins (Hosokawa *et al.* 2003).

Cytokines are major effectors of the neuroinflammatory cascade. They play an important role in neural cell response to infection and brain injury (Allan and Rothwell 2003; Lucas *et al.* 2006). Normally, they are beneficial for neural cell survival, but when they are secreted in an imbalanced fashion they become detrimental to neurons (Rothwell 1999). TNF-α and IL-1β are usually the first cytokines to be up-regulated after neural trauma and infection. These cytokines also induce the synthesis of IL-6, an anti-inflammatory cytokine involved in the recovery process. This process creates an autoregulatory feedback loop associated with cytokine action (Xing *et al.* 1998). In injured brain, astrocyte and microglial cells also secrete neurotrophic factors such as neurotrophin-3 and brain-derived neurotrophic factor which promote neuronal survival (Correale and Villa 2004). Furthermore, TNF-α, IL-1, and IFN-γ, the pro-inflammatory cytokines, are also associated with immunosuppressive functions. Their subsequent expression following neuroinflammation assists in repair and recovery processes in brain tissue (Correale and Villa 2004). Collectively, these studies suggest that actions of cytokines require a complex network that often involves feedback loops and cascades. The overall cytokine response may be dependent on the synergistic or antagonistic activities of various cytokines (Xing *et al.* 1998; Rothwell 1999).

The expression of genes involved in the inflammatory response is controlled transcriptionally and post-transcriptionally. The released cytokines act through their receptors causing activation of cascades of protein kinases and the pathway leading to activation of the transcription factor nuclear factor kappa B, NFκB. In microglial cells NFκB is present in the cytoplasm in an inhibitory form attached to its inhibitory protein, IκB. NFκB activity is tightly controlled by the IκB kinase complex, consisting of IκB kinases IκKα, IκKβ, and IκKγ. IκKβ is essential for the inflammatory cytokine-mediated activation of NFκB (Yamamoto and Gaynor 2004). Upon stimulation IκB is rapidly phosphorylated, ubiquinated, and then degraded by proteasomes resulting in the release and subsequent nuclear translocation of active NFκB.

In the nucleus NFκB mediates the transcription of many genes implicated in inflammatory and immune responses (Fig. 1). These genes include COX-2, intracellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1 (VCAM-1), E-selectin, TNF-α, IL-1β, IL-6, $sPLA_2$, inducible nitric oxide synthase (iNOS), and matrix metalloproteinases (MMPs). Its activation also leads to the local generation of more cytokines, which in turn promulgate inflammatory signals. NFκB is also stimulated by polyunsaturated fatty acids, products of reactions catalyzed by $cPLA_2$, $iPLA_2$, and $sPLA_2$. This induction of NFκB is blocked by N-acetylcysteine as well as vitamin E (Mazière *et al.* 1999), suggesting the involvement of ROS during NFκB-mediated processes. NFκB activation mediated by ROS involves NADPH oxidase. It is an important component of the innate immune response against toxic agents, metabolic as well as microbial, and is involved in shaping the cellular response to a variety of physiological and pathological signals (Rubin *et al.* 2005; Zhang *et al.* 2005; Anrather *et al.* 2006; Frey *et al.* 2006; Miller *et al.* 2006). NFκB controls the expression of a large array of genes involved in immune function and cell survival (Fig. 1). Upon stimulation of $cPLA_2$, NFκB is recruited to the plasma membranes where it interacts with NADPH oxidase (Shmelzer *et al.* 2003). The interaction between NFκB and $cPLA_2$ provides the molecular basis for AA release by $cPLA_2$ and generation of reactive species to activate the NADPH oxidase (Shmelzer *et al.* 2003). The ability of $cPLA_2$ to modulate superoxide production and generation of eicosanoids (see below) indicates its importance in inflammatory processes. Meanwhile, endothelial cells lining the local cerebral blood vessels are stimulated to produce adhesion molecules, causing the migration of peripheral circulating leukocytes into the compromised brain tissue, an event that amplifies inflammatory signaling cascades.

A second group of transcription factors called peroxisome proliferator-activated receptors (PPARs), has also been implicated in neuroinflammation. PPARs are members of the nuclear hormone receptor family. Several forms, PPAR-α, PPAR-γ, and PPAR-δ, are known to occur in neural tissues (Drew *et al.* 2005). Activation of PPAR isoforms elicits both anti-neoplastic and anti-inflammatory activities in neural cells. Although the molecular mechanism involved in the anti-inflammatory process is not fully understood, 15-deoxy-$\Delta^{12,\ 14}$-prostaglandin J_2 (15d-PGJ) reduces the phosphorylation of STAT1 and STAT3 as well as Janus kinase 1 (JAK1) and JAK2 in activated astrocytes and microglia (Park *et al.* 2003).

Endogenous ligands for PPAR-γ include long-chain polyunsaturated fatty acids (products of PLA_2 catalyzed reactions), eicosanoid derivatives (products of COX catalyzed reactions), and oxidized phospholipids (products of non-enzymic oxidation). In the presence of the peroxisome proliferator-activated receptor response element (PPAR-RE), PPAR heteromerizes with retinoid X-receptors (RXR), recruits the co-activator containing histone acetylase activity, and subsequently facilitates gene expression (Farooqui *et al.* 2004a). Mice deficient in PPAR have a prolonged response to inflammatory stimuli. PPAR ligands, in particular those of PPARα and PPARγ, inhibit the activation of inflammatory gene expression and can negatively interfere with pro-inflammatory transcription factor signaling pathways in vascular and inflammatory cells (Moraes *et al.* 2006).

Toll-like receptors (TLRs) play a key role in the recognition of products from virtually all classes of pathogenic organisms. Production of these cytokines also initiates signaling through TLRs that recognize host-derived mole-

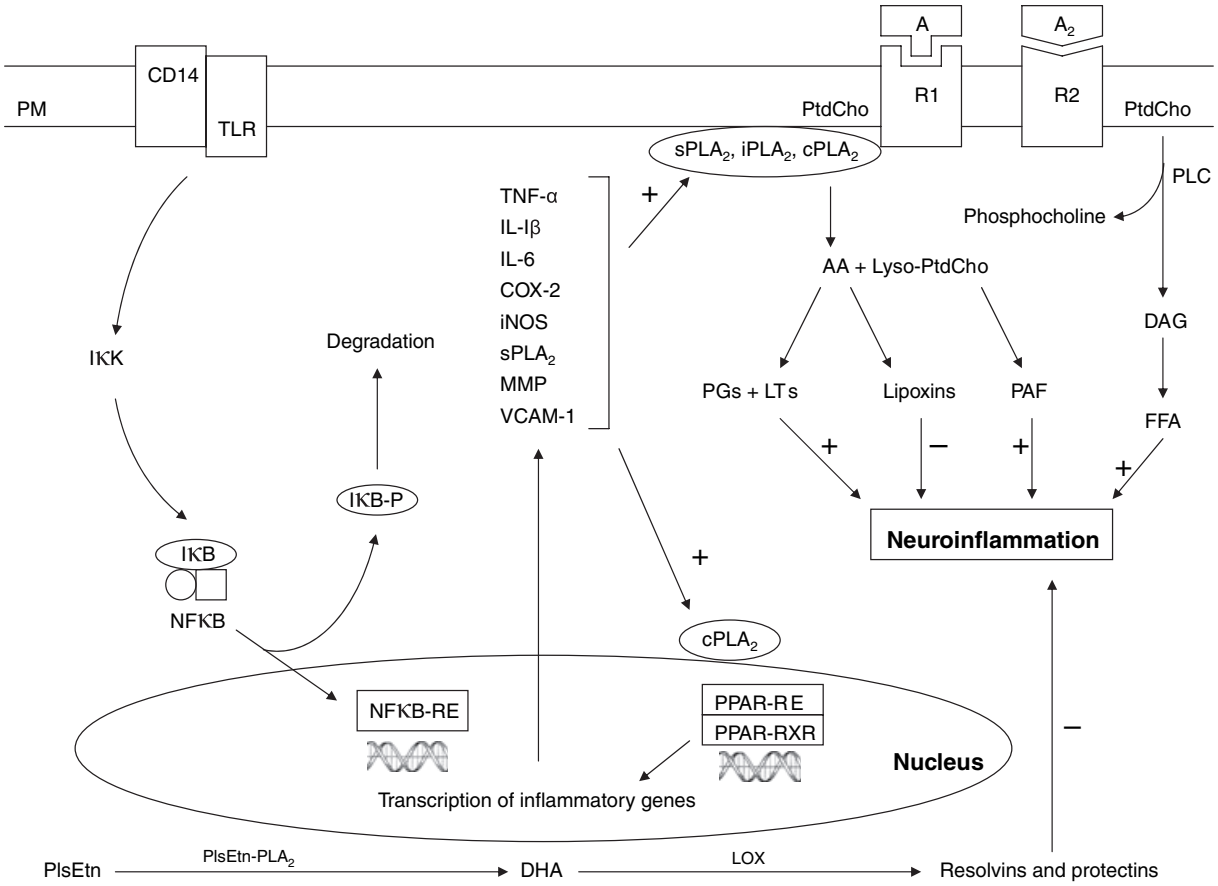

Fig. 1 Up-regulation of inflammatory gene expression by NFκB-mediated stimulation of $cPLA_2$ and its association with eicosanoid and PAF-mediated neuroinflammation. PM, plasma membrane; TLR, toll--like receptor; CD14 (LPS receptor), a 55 kDa glycosylphosphatidylinositol-anchored surface myeloid glycoprotein expressed on microglial cells for phagocytosis; NFκB, nuclear factor κB; NFκB-RE, nuclear factor κB-response element; IκB, inhibitory subunit of NFκB; IκK, IκB kinase; TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; IL-6, interleukin-6; COX-2, cyclooxygenase-2; iNOS, inducible nitric oxide synthase; MMPs, matrix metalloproteinases; VCAM-1, vascular adhesion molecule-1; $cPLA_2$, cytosolic phospholipase A_2; $sPLA_2$, secretory phospholipase A_2; $iPLA_2$, calcium-independent phospholipase A_2; PLC, PtdCho-specific phospholipase C; PtdCho, phosphatidylcholine; A1, agonist; lyso-PtdCho, lysophosphatidylcholine; A_2, agonist; R1, receptor includes NMDA, AMPA, P2X, acetylcholine, TNF-α, IL-1β, and metabotropic glutamate receptors; R2, TNF-α receptor coupled to PtdCho-PLC; DAG, diacylglycerol; AA, arachidonic acid; lyso-PtdCho, lyso-phosphatidylcholine; PGs, prostaglandins; LTs, leukotrienes; PAF, platelet activating factor; PlsEtn, ethanolamine plasmalogen; DHA, docosahexaenoic acid; LOX, 15-lipoxygenase like enzyme; PPAR, peroxisome proliferator-activated receptor; PPAR-RE, peroxisome proliferator-activated receptor response element; and RXR, retinoic acid receptor. DAG is utilized by diacylglycerol kinase or diacylglycerol lipase. Positive sign (+) indicates stimulation (proinflammatory) and negative sign (-) indicates inhibition (anti-inflammatory).

cules released from injured tissues and cells (Fig. 1). Recently, great strides have been made in understanding the regulation of the innate immune system, particularly the signaling mechanisms of TLRs. Negative feedback inhibitors of TLRs and inflammatory cytokines have now been identified and characterized. TLRs may be associated with neuroinflammation-mediated signaling in brain (Lee *et al.* 2003). Neural membrane lipid rafts (Farooqui *et al.* 2006a) may also facilitate receptor-mediated inflammatory signaling events (Kariko *et al.* 2004).

Astrocytes also express cell-adhesion molecules, receptors for cytokines and chemokines, and nitric oxide synthase. The reaction between superoxide anion and nitric oxide results in the production of peroxynitrite. This metabolite may be a major cytotoxic agent during neuroinflammation-mediated neural cell death (Kim *et al.* 2005). Cytokines and chemokines are proteins that participate in the interaction among neuro-glio-vascular cells and play an important role in the induction and maintenance of inflammation in brain (Minami *et al.* 2006). They bind to their receptors that are coupled to 'effector' enzymes such as PLA_2 and PLC. Cytokines not only provoke the neuroinflammatory signaling cascade, but also stimulate hexose transport through PLA_2-mediated processes. This process may be involved in the homeostasis

of the nervous system, in particular, by contributing to the regulation of local energy metabolism (Yu *et al.* 1995). Furthermore, TNF-α, IL-1β, and chemokines also alter blood flow and increase vascular permeability. This may lead to secondary brain damage and accumulation of immune cells in the brain.

The hydrolysis of PtdCho in neural and non-neural tissue mediated by TNF-α also involves the stimulation of the PLC that hydrolyzes PtdCho and the sphingomyelinase (SMase) that hydrolyzes sphingomyelin (Machleidt *et al.* 1996). The hydrolysis of PtdCho by PLC generates diacylglycerol (DAG) and phosphocholine whereas the degradation of sphingomyelin by SMase liberates ceramide (Fig. 1). Although both enzymes are stimulated by TNF-α, the SMase activation is secondary to the generation of DAG. DAG production may be coupled to the synthesis of ceramide, which eventually triggers the rapid induction of nuclear NFκB activity (Schütze *et al.* 1992). In murine $P388D_1$ macrophages, ceramide and DAG stimulate $sPLA_2$ suggesting the modulation of AA and eicosanoid levels by metabolites of sphingolipid metabolism (Balsinde *et al.* 1997). The xanthogenate tricyclodecan-9-yl (D609), a potent inhibitor of PtdCho-PLC, retards the cytotoxic action of TNF-α. *In vivo*, D609 blocks adhesion molecule expression in the vasculature and the accompanying leukocyte infiltration in TNF-α-treated mice. D609 also inhibits sphingomyelin synthase (Luberto and Hannun 1998), indicating that this inhibitor may limit the synthesis of sphingomyelin. More importantly, D609 protects BALB/c mice from the lethal shock induced by TNF-α, lipopolysaccharide, or staphylococcal enterotoxin B. Together, these findings suggest that PtdCho-PLC is not only an important mediator of the pathogenic action of TNF-α, but it also potentiates the generation of ceramide through SMase stimulation. This may intensify inflammation and apoptotic cell death in brain tissue. PtdCho-PLC may also serve as a novel target for anti-inflammatory TNF-α antagonists (Machleidt *et al.* 1996).

Activated microglia have been observed around degenerative neurons in Alzheimer disease (AD), Parkinson disease (PD), Down syndrome (DS), Huntington disease (HD), multiple sclerosis (MS), and AIDS-dementia. They act as effector cells in the degeneration of neural cells in the central nervous system (Takeuchi *et al.* 2005). Two types of inflammatory processes, namely chronic and acute, are known to occur in brain tissue. Chronic neuroinflammation is associated with slow progressive neurodegenerative diseases such as AD, PD, DS, HD, MS, and AIDS-dementia. Acute neuroinflammation is involved in ischemia, head injury, and spinal cord trauma. Acute neuroinflammation is a short-lived process characterized by a neutrophilic infiltration and complete resolution; by contrast, chronic inflammation presents as a long-lasting phenomenon associated with mononuclear infiltration, tissue hyperplasia, progressive cavitation, and glial scarring in the brain tissue (Fitch *et al.* 1999). Time-lapse video analyses of inflammation-induced cavitation show astrocyte abandonment of neuronal processes and neurite stretching. These processes are associated with secondary injury (Fitch *et al.* 1999).

Polyunsaturated fatty acids as precursors for neuroinflammatory mediators

The proportions of arachidonic acid (AA) and docosahexaenoic acid (DHA) in neural membrane glycerophospholipids vary considerably in the various subclasses of glycerophospholipids. AA is distributed rather evenly in gray and white matter and among the different cell types in brain. In contrast, DHA is highly enriched in neuronal membranes including synaptic membranes. Among the glycerophospholipids, phosphatidylethanolamine (PtdEtn), plasmenylethanolamine (PlsEtn), and phosphatidylserine (PtdSer) contain high levels of docosahexaenoyl groups (22:6n-3) at the *sn*-2 position of the glycerol moiety, whereas phosphatidylcholine (PtdCho), phosphatidylinositol (PtdIns), and phosphatidic acid (PtdH) contain high levels of arachidonoyl groups (20:4n-6) (Farooqui *et al.* 2000b; Tillman and Cascio 2003). In neural membranes, glycerophospholipid homeostasis is based on a balance between glycerophospholipid catabolism via multiple forms of phospholipases A_2 (PLA_2) and resynthesis by the reacylation/deacylation cycle and *de novo* synthesis pathways (Farooqui *et al.* 2000a,b).

Two major mechanisms are associated with the release of polyunsaturated fatty acids from neural membrane glycerophospholipids. A direct mechanism involves multiple forms of PLA_2 and release of AA and DHA. The other mechanism of AA release involves the phospholipase C (PLC)/diacylglycerol lipase pathway (Farooqui *et al.* 1989). According to Bazan and Flower (Bazan and Flower 2002), neural membranes are a Pandora's box of lipid mediators, many of which have powerful neurochemical effects, some beneficial and others harmful. Multiple forms of PLA_2 play the role of Pandora and release AA, DHA, and lyso-glycerophospholipids. These products serve as intracellular second messengers themselves (Farooqui and Horrocks 2006b). AA is metabolized into the potent inflammatory mediators such as prostaglandins (PG), leukotrienes (LT), and hydroxyeicosatetraenoic acids (HETE). DHA is metabolized to the anti-inflammatory mediators, resolvins, and protectins. 1-Alkyl-2-lyso-*sn*-glycero-3-phosphocholine (lyso-PakCho) is a precursor of the pro-inflammatory mediator, platelet-activating factor (PAF) (Farooqui *et al.* 1997; Farooqui and Horrocks 2006b). Thus, neural membrane glycerophospholipids and polyunsaturated fatty acids are precursors for the above lipid mediators that modulate many cellular functions including neuroinflammation, neural cell proliferation, differentiation, and apoptosis (Farooqui and Horrocks 2006a).

Oxidative modification of neural membrane glycerophospholipids also occurs during inflammatory processes. This

leads to the formation and accumulation of biologically active lipid oxidation products that induce specific cellular reactions (Bochkov and Leitinger 2003). These reactions modulate the inflammatory process. This may determine the fate and outcome of the body's reaction to acute inflammation during host defense. Oxidized glycerophospholipids may play an important role in the resolution of inflammation and adaptive immune responses (Bochkov and Leitinger 2003). Defense strategies may include (a) induction of signaling pathways leading to the upregulation of anti-inflammatory genes, (b) inhibition of signaling pathways coupled to the expression of proinflammatory genes, and (c) prevention of the interaction of proinflammatory bacterial products with host cells (Bochkov and Leitinger 2003).

Enzymically derived arachidonic acid metabolites and neuroinflammation

The production of prostaglandins and leukotrienes from neural membrane glycerophospholipids is regulated by multiple forms of PLA_2, cyclooxygenases (COX-1 and COX-2) and lipoxygenases (LOX). All these enzymes are stimulated during neuroinflammation (Murakami and Kudo 2006). Stimulated $cPLA_2$ and $sPLA_2$ release AA from membrane glycerophospholipids with a marked increase of AA metabolism during inflammation caused by the infusion of bacterial lipopolysaccharide (Morioka *et al.* 2002; Lee *et al.* 2004; Rosenberger *et al.* 2004). In neurons $cPLA_2$ is coupled to many G protein-dependent and independent receptors. These receptors include NMDA, AMPA, P2X, acetylcholine, TNF-α, IL-1β, and metabotropic glutamate receptors (Lazarewicz *et al.* 1990; Kim *et al.* 1995; Farooqui *et al.* 2006b).

In contrast, $sPLA_2$ is a secreted enzyme and has its own receptors. It binds to N-type receptors on neurons and M-type receptors found on skeletal muscle cell surfaces (DeCoster *et al.* 2002; Kolko *et al.* 2002). Thus $sPLA_2$ either acts extracellularly through its receptors, or it can be internalized to reach its intracellular targets (Sun *et al.* 2004b). At low concentrations, $sPLA_2$ IIA enhances glutamate toxicity that leads to cell swelling and apoptotic cell death (Rodriguez de Turco *et al.* 2002; Yagami *et al.* 2002). $sPLA_2$ IIA activity is markedly increased in the acute phase of LPS-mediated inflammation and is the major contributor to the excessive production of AA under pathological conditions. It is designated as the inflammatory PLA_2 (Murakami *et al.* 1998; Lin *et al.* 2004; Moses *et al.* 2006). In non-neural cells during the inflammatory process, $sPLA_2$-IIA expression mediates its effect through PPARα activation and TNF-α stimulates its own expression via an autocrine loop involving $cPLA_2$ and PPARα. This suggests that $cPLA_2$ and $sPLA_2$ interact and modulate the intensity of inflammation (Beck *et al.* 2003). $cPLA_2$ and $sPLA_2$ are functionally linked with both COX-1 and COX-2 during immediate and delayed eicosanoid synthesis, whereas $iPLA_2$ is preferentially linked with COX-1 for housekeeping activities such as membrane remodeling, maintenance of homoeostatic lyso-glycerophospholipid levels, and destruction of neural membrane glycerophospholipids subsequent to cells entering apoptotic cell death (Farooqui *et al.* 2004b). Furthermore, in macrophages $iPLA_2$ also participates in the transcriptional regulation and expression of iNOS during viral infections (Moran *et al.* 2005). Collective evidence suggests that a coordinated up-regulation of $sPLA_2$, $cPLA_2$, and $iPLA_2$ along with COX-2 and iNOS activities may occur in inflammatory lesions during neuroinflammation (Farooqui *et al.* 1999; Murakami *et al.* 1999; Phillis *et al.* 2006).

All isoforms of PLA_2, $cPLA_2$, $iPLA_2$, and $sPLA_2$, together with COX and LOX enzymes, are stimulated in inflammatory processes in brain tissue through the involvement of the NFκB-mediated induction of TNF-α, IL-β, and chemokines (Hayakawa *et al.* 1993; Kronke and Adam-Klages 2002; Lin *et al.* 2004; Farooqui and Horrocks 2005). This stimulation of $cPLA_2$, $sPLA_2$, COX, and LOX activities can be blocked by inhibitors of $sPLA_2$, $cPLA_2$, and 5-lipoxygenase (Anthonsen *et al.* 2001). These inhibitors also attenuate TNF-α- and IL-1β-stimulated NFκB activation. Exogenous addition of leukotriene B_4 (LTB_4) restores NFκB activation that is reduced by 5-lipoxygenase inhibitors or an LTB_4 receptor antagonist, thus identifying LTB_4 as a mediator in signaling to NFκB. AA release from cellular membranes induced by TNF-α- and IL-1β is accompanied by phosphorylation of $cPLA_2$. Inhibitors of $sPLA_2$ and of 5-lipoxygenase/LTB_4 functionality markedly reduce AA release and nearly completely abolish $cPLA_2$ phosphorylation. This not only suggests that $sPLA_2$, through 5-lipoxygenase metabolites, is an essential upstream regulator of $cPLA_2$ and AA release, but also indicates the existence of a functional link between $sPLA_2$ and cytosolic PLA_2 in cytokine-activated non-neural cells (cross-talk) and provides a molecular explanation for the participation of both $sPLA_2$ and $cPLA_2$ in AA signaling and NFκB activation in response to proinflammatory cytokines (Wu *et al.* 1998; Woo *et al.* 2000; Anthonsen *et al.* 2001).

Lyso-PtdCho, the other product generated by $sPLA_2$, $iPLA_2$, and $cPLA_2$ reactions, is a chemo-attractant that induces the expression of growth factors and adhesion molecules in endothelial cells. It also activates white blood cells. This activation increases their ability to permeate the endothelium. Lyso-PtdSer triggers the secretion of histamine by mast cells (Lloret and Moreno 1995). All these processes contribute to induction and maintenance of inflammatory reaction and apoptotic cell death.

COX enzymes oxidize AA to prostaglandin H_2 (PGH_2). PGH_2 is a precursor to several prostaglandins, thromboxanes (TXA_2), and prostacyclins (PGI_2). These metabolites are collectively known as eicosanoids (Table 1). Some eicosa-

noids make nerve endings hypersensitive and others lead to inflammation. During inflammatory reactions, eicosanoids not only initiate inflammatory responses, but also mediate resolution. There are two phases in inflammatory responses: one at the onset for the generation of pro-inflammatory eicosanoids and the other at resolution for the synthesis of pro-resolving eicosanoids (Gilroy *et al.* 2004). The first phase of arachidonic acid formation involves the expression and stimulation of $iPLA_2$ with the generation of PGE_2, LTB_4, and PAF through COX-2, LOX, and acetyl-CoA acetyltransferase reactions, respectively. The second phase of arachidonic acid release utilizes $sPLA_2$ as well as $cPLA_2$ and is associated with the generation of PAF, lipoxins, and the pro-resolving prostaglandin, PGD_2 (Gilroy *et al.* 2004). Thus, eicosanoids (prostaglandins) not only serve as autocrine factors regulating platelet aggregation, vascular tone, and edema, but are also involved in the resolution of inflammation by lipoxins (Fig. 1). PLA_2, COX-2, and LOX inhibitors have been used to treat acute inflammation in various animal models of pain mediated by inflammation (de Gaetano *et al.* 2003; Yeo *et al.* 2004; Farooqui *et al.* 2006b).

The roles of isoforms of PLA_2, COX, and LOX enzymes in chronic inflammation are controlled by their environment, levels of available glycerophospholipid substrates, the expression of multiple forms of PLA_2, COX, and LOX enzymes, and the expression of cellular targets of eicosanoid receptors that mediate their actions. This suggests that isoforms of PLA_2, COX, and LOX have multiple roles depending on their localization and environment. During a chronic inflammatory reaction, the environment in the brain may change with expression of isoforms of PLA_2, COX, and LOX at high levels that may lead to the generation of deleteriously large amounts of PGE_2 (Phillis *et al.* 2006).

In vivo, prostaglandins are also involved in the regulation of cytokines and maintenance of the inflammatory cascade. For example, when released from activated microglial cells, PGE_1 and PGE_2 stimulate the expression of interleukin-6 in astrocytes (Fiebich *et al.* 1997). This process in turn, initiates the synthesis of additional prostaglandins. At the injury site PGE_2 is involved in modulating the immune response while its pro-inflammatory signaling is associated with vascular and microglial cell activation (Zhang and Rivest 2001). Some prostaglandins, PGE_1, PGE_2, and PGD_2 are inflammatory (Mohri *et al.* 2006), whereas others are anti-inflammatory, for example PGD_2 and 15-deoxy-$\Delta^{12,\ 14}$-prostaglandin J_2 (Itoh and Yamamoto 2005). Not only activated neutrophils and macrophages, but also astrocytes and oligodendrocytes produce leukotriene B_4, which induces its neurochemical effects by interacting with specific G protein-coupled receptors. Thus, high levels of eicosanoids and other AA-related metabolites contribute to the development of cytotoxicity, vasogenic brain edema, and neuronal damage mediated by inflammation (Phillis *et al.* 2006).

Furthermore, the action of lipoxygenases on HPETE and HETE also leads to the formation of lipoxins (LXA_4 and LXB_4), a group of trihydroxytetraene eicosanoids involved in the resolution of acute inflammation by modulating key steps in leukocyte trafficking and preventing neutrophil-

Table 1 Arachidonic acid and docosahexaenoic acid-derived biomarkers with inflammatory and anti-inflammatory activities in brain

Biomarker	Levels	Nature	Reference
$cPLA_2$, $iPLA_2$, and $sPLA_2$	Increased	Pro-inflammatory	(Farooqui and Horrocks 2006b)
COX-2	Increased	Pro-inflammatory	(Phillis *et al.* 2006)
NOS	Increased	Pro-inflammatory	(De Caterina and Massaro 2005)
MMP	Increased	Pro-inflammatory	(De Caterina and Massaro 2005)
NFκB	Increased	Pro-inflammatory	(De Caterina and Massaro 2005)
Cytokines (TNF-α and IL-1β)	Increased	Pro-inflammatory	(Minghetti *et al.* 2005; Noda *et al.* 2006)
Chemokines	Increased	Pro-inflammatory	(Drew *et al.* 2005; Minghetti *et al.* 2005)
ICAM-1		Pro-inflammatory	(Drew *et al.* 2005; Noda *et al.* 2006)
VCAM-1		Pro-inflammatory	(Drew *et al.* 2005; Minghetti *et al.* 2005)
Prostaglandins	Increased	Pro-inflammatory	(Phillis *et al.* 2006)
Leukotrienes	Increased	Pro-inflammatory	(Phillis *et al.* 2006)
PAF	Increased	Pro-inflammatory	(Bazan *et al.* 1994; Tokuoka *et al.* 2003)
Lipoxins	Increased	Anti-inflammatory	(Norel and Brink 2004; Chiang *et al.* 2005)
Resolvins	Increased	Anti-inflammatory	(Serhan 2005b)
Neuroprotectins	Increased	Anti-inflammatory	(Bazan 2005a,c)
2-AG	Increased	Anti-inflammatory	(Rockwell *et al.* 2006)

$cPLA_2$, cytosolic phospholipase A_2; $iPLA_2$, calcium-independent phospholipase A_2; $sPLA_2$, secretory phospholipase A_2; COX-2, cyclooxygenase-2; NOS, nitric oxide synthase; MPP, matrix metalloproteinase; NFκB, nuclear factor κB; ICAM-1, intracellular adhesion molecule-1; VCAM-1, vascular adhesion molecule-1; PAF, platelet-activating factor; and 2-AG, 2-arachidonylglycerol.

mediated acute tissue injury (Serhan 1994; Kantarci and Van Dyke 2003; Serhan and Levy 2003). Although the occurrence of lipoxins in brain tissue has been established, detailed investigations on their neurochemical effects and involvement in signal transduction processes are not available (Serhan and Levy 2003). However, recent work from Serhan's laboratory indicates that aspirin mediates the generation of lipoxins.

These lipoxins are potent anti-inflammatory and pro-resolving molecules that act through specific G protein-coupled receptors, ALX and LXA receptors (Norel and Brink 2004; Chiang *et al.* 2005). The activation of these receptors triggers the expression of a suppressor of cytokine signaling (SOCS-2). SOCS-2-deficient mice show uncontrolled synthesis of pro-inflammatory cytokines, aberrant leukocyte infiltration, and increased mortality (Machado *et al.* 2006). In the absence of biosynthetic pathways for LXA_4, the resulting uncontrolled inflammation can become lethal, despite pathogen clearance (Machado *et al.* 2006). Collectively, these studies suggest that lipoxins regulate cellular activities associated with inflammation and resolution (Chiang *et al.* 2005; Serhan 2005a). In mouse cornea, LXA_4 limits inflammation and promotes wound healing (Gronert 2005). LXA_4 also serves as a 'stop signal' that regulates key steps in leukocyte trafficking and prevents neutrophil-mediated tissue injury (Kantarci and Van Dyke 2003). In periodontal disease, lipoxin generation provides protection against neutrophil-mediated injury (Kantarci and Van Dyke 2005).

The lipoxin pathway also provides a new explanation for the anti-inflammatory action of aspirin. Acetylation of COX-2 enables it to behave like lipoxygenase (LOX), producing the lipoxin precursor 15-hydroxyeicosatetraenoic acid from AA, which is then transformed by leukocyte 5-LOX to 15-epi-LXA_4 or 15-epi-LXB_4. These aspirin-triggered lipoxins are more potent anti-inflammatory metabolites than their conventional counterpart LXA_4 (Serhan 2005a; Weylandt and Kang 2005). Aspirin in low doses also facilitates the generation of anti-inflammatory mediators from EPA. Detailed investigations are needed on the anti-inflammatory effects of AA and EPA-derived lipid mediators in neurological disorders.

Non-enzymically derived metabolites of AA and neuroinflammation

Isoprostanes (IsoPs) are PG-like mediators formed non-enzymically by free radical-catalyzed peroxidation of esterified AA *in vivo* (Basu 2004; Greco and Minghetti 2004). They differ from PGs. In IsoPs the side chains are *cis* to the cyclopentane ring, whereas in PGs they have the *trans* orientation. The mechanism by which IsoPs are formed is analogous to the formation of PGs by COX enzymes (Morrow *et al.* 1999; Morrow 2006). Unlike PGs, the formation of IsoPs *in situ* initially takes place at the esterified AA on the glycerophospholipid molecule (Fam and Morrow 2003). IsoPs are subsequently released in free form by the action of PLA_2 (Morrow *et al.* 1992; Fam and Morrow 2003).

IsoPs are very potent vasoconstrictors in brain microvasculature. F_2-IsoP exerts its action in vascular beds by facilitating binding between endothelial cells and monocytes (Lahaie *et al.* 1998; Fam and Morrow 2003). Binding between endothelial cells and monocytes is the key initial event in atherogenesis-related inflammation. Isoprostane-mediated monocyte adhesion is VCAM-1 independent but involves protein kinase A and mitogen-activated protein kinase kinase 1. F_2-IsoP also modulates the p38 MAPK pathway during monocyte adhesion (Cracowski 2004). All these processes relate to inflammation and atherosclerosis. Collectively, these studies suggest that IsoPs are not only feedback regulators related to neuroinflammation, but also to vasoconstriction, mitogenesis, and monocyte adhesion (Cracowski 2004).

Lyso-glycerophospholipids and neuroinflammation

Lyso-phosphatidylcholine (lyso-PtdCho), another product of PLA_2-catalyzed reactions, is known to induce rapid breakdown and removal of myelin from the adult brain (Lovas *et al.* 2000; Ousman and David 2000; Birgbauer *et al.* 2004). Lyso-PtdCho promotes the activation of microglia and other immune cells and induces the de-ramification of murine microglia (Schilling *et al.* 2004). De-ramification, i.e., transformation from ramified into amoeboid morphology, is one of the earliest manifestations of microglial activation and neuroinflammation. It results in complete retraction of cell extensions and increased size of cell bodies with amoeboid morphology. Lyso-PtdCho is a potent chemotactic factor. It stimulates phosphorylation of CREB with concomitant up-regulation of COX-2 expression. In non-neural cells, it suppresses the release of nitric oxide and up-regulates CD40 ligand expression. Its generation plays a positive role in the initiation and maintenance of inflammatory processes in brain tissue.

Time-lapse video microscopic studies have shown that another lyso-glycerophospholipid, lyso-phosphatidic acid (lyso-PtdH), enhances chemokinetic migration of murine microglial cells in brain tissue. This migration is modulated by Ca^{2+}-activated K^+ channels (Schilling *et al.* 2004). Lyso-PtdH plays an important role in the inflammatory response by brain tissue. Lyso-PtdH also modulates IL-13 gene expression in human T cells by enhancing the transcriptional activation of the IL-13 promoter via regulatory elements associated with the proximal 312 bp. This effect of lyso-PtdH on IL-13 promoter activation is distinct from that mediated by GATA-3. Collective evidence suggests that

modulation of IL-13 gene expression mediated by lyso-PtdH may aid neuroinflammatory processes in brain tissue (Rubenfeld *et al.* 2006).

Platelet-activating factor and neuroinflammation

PAF (1-*O*-alkyl-2-acetyl-*sn*-glycerophosphocholine) is a potent pro-inflammatory agent in infectious and inflammatory diseases (Snyder 1995). PAF is released by a wide variety of cells including macrophages, platelets, endothelial cells, mast cells, neutrophils, and neural cells (Ishii *et al.* 2002; Tokuoka *et al.* 2003). It exerts its biological effects by activating the PAF receptors that consequently activate leukocytes, stimulate platelet aggregation, and induce the release of cytokines and expression of cell adhesion molecules (Snyder 1995; Maclennan *et al.* 1996; Honda *et al.* 2002; Ishii *et al.* 2002). During the inflammatory process, PAF activates leukocytes tethered to the blood vessel wall via specific adhesion molecules expressed by endothelial cells. The physiological activity of PAF is not limited to its pro-inflammatory function. PAF is also involved in a variety of other settings including allergic reactions, brain function, and circulatory system disturbances such as atherosclerosis (Honda *et al.* 2002).

The binding of PAF to intracellular sites elicits gene expression in neuronal and glial cell lines (Bazan *et al.* 1994; Tokuoka *et al.* 2003). PAF also stimulates the inducible isoform of PLA_2 and cyclooxygenase-2 (COX-2). COX-2 is encoded by an immediate early gene and is responsible for prostaglandin synthesis in neuropathological processes. PAF receptors are also involved in the release of PGE_2 from astrocytes. This release of prostaglandin E_2 is closely associated with pathophysiology of inflammatory pain (Watkins *et al.* 2001). PAF is also an essential component of the intricate mechanisms by which immune cells such as leukocytes are recruited to their targets (Zimmerman *et al.* 1996). Collective evidence suggests that PAF-mediated neuroinflammation is closely associated with short-and long-term responses of cells to stimulation or neural trauma (Bazan *et al.* 1997). PAF has an acetyl group at the *sn*-2 position of its glycerol moiety. This acetyl group is essential for its pro-inflammatory activity. PAF acetylhydrolase blocks the pro-inflammatory effects of PAF by hydrolyzing the acetyl group (Neto *et al.* 2005). The anti-inflammatory effect of PAF acetylhydrolase is accompanied by inhibition of PAF-induced chemotaxis and changes in intracellular Ca^{2+} (Kuijpers *et al.* 2001). All these processes are associated with neuroinflammation in brain tissue.

Enzymically derived EPA and DHA metabolites and neuroinflammation

EPA and DHA belong to the same family of fatty acids, n-3. EPA is a substrate for both cyclooxygenases and 5-lipoxygenase giving rise to 3-series prostaglandins, thromboxanes, and 5-series leukotrienes. EPA-derived eicosanoids are much less active than AA-derived eicosanoids. In contrast, DHA is not a substrate for cyclooxygenase. Actions of a 15-lipoxygenase-like enzyme on DHA produce 17S-resolvins, 10-,17S-docosatrienes, and protectins (Hong *et al.* 2003; Marcheselli *et al.* 2003; Serhan *et al.* 2004; Serhan and Savill 2005). These second messengers have the collective name of docosanoids. They are potent endogenous anti-inflammatory and pro-resolving chemical lipid mediators (Serhan 2006). They antagonize the effects of eicosanoids, modulate leukocyte trafficking, and down-regulate the expression of cytokines in glial cells (Hong *et al.* 2003; Marcheselli *et al.* 2003; Serhan *et al.* 2004). The specific receptors for these bioactive lipid metabolites occur in neural and non-neural tissues. These receptors include resolvin D receptors (resoDR1), resolvin E receptors (resoER1), and neuroprotectin D receptors (NPDR). Characterization of these receptors in brain tissue is in progress (Hong *et al.* 2003; Marcheselli *et al.* 2003; Mukherjee *et al.* 2004; Serhan *et al.* 2004).

Microglial cells release cytokines in brain. The D class resolvins block tumor necrosis factor α-induced interleukin (IL)-1β transcripts and are potent regulators of PMN infiltration in brain (Serhan *et al.* 2004). Resolvin E1 (RvE1) is a novel bioactive oxygenated product of eicosapentaenoic acid (EPA). At nanomolar levels, RvE1 dramatically reduced dermal inflammation, peritonitis, dendritic cell migration, and interleukin IL-12 production. Its action is mediated by the ChemR23 receptor. Specific binding of RvE1 to this receptor was confirmed using synthetic ^3H-labeled RvE1. Treatment of dendritic cells with small interference RNA specific for ChemR23 sharply reduces RvE1 regulation of IL-12 (Arita *et al.* 2005a). These results demonstrate novel counter-regulatory responses in inflammation initiated via RvE1 receptor activation that provide the first evidence for EPA-derived potent endogenous agonists of anti-inflammation (Arita *et al.* 2005a,b). Another possible mechanism of RvE1 may be that this metabolite prevents the binding of LTB4 to its receptor and therefore blocks the propagation of a pro-inflammatory signal.

DHA is a precursor of (10,17S)-docosatriene/neuroprotectin also known as protectin D1 (PD1) (Marcheselli *et al.* 2003; Mukherjee *et al.* 2004). It is generated in neural cells and also in T helper type 2-skewed peripheral mononuclear cells by a 15-lipoxygenase-like enzyme (Ariel *et al.* 2005). This metabolite potently blocks the generation of both TNF-α and IFN-γ by T cells stimulated by anti-CD3 + anti-CD28 (Ariel *et al.* 2005). Based on these observations, PD1-mediated T cell clearance during neuroinflammation may be related to apoptotic cell death and inducing resolution of inflammation. Interactions of PD1 with lipid rafts, structures enriched in sphingolipid and cholesterol located on cell plasma membranes, are also involved in the suppressive

action of TH2 cells in neuroinflammation (Ariel *et al.* 2005). Thus, growing evidence suggests that the generation of n-3 fatty acid metabolites may be an internal anti-inflammatory protective mechanism for preventing brain damage in neural trauma and neurodegenerative diseases (Hong *et al.* 2003; Marcheselli *et al.* 2003; Mukherjee *et al.* 2004; Bazan 2005b; Serhan 2005b).

Resolvins and neuroprotectins (Table 1) slow down the inflammatory cycle induced and maintained by the action of cytokines on astrocytes. In fact, these lipid mediators along with lipoxins control the duration and magnitude of inflammation in brain tissue. The infusion of neuroprotectin D1 (NPD1), following ischemic reperfusion injury or during oxidative stress in cell culture, down-regulates oxidative stress and apoptotic DNA damage. NPD1 also up-regulates the anti-apoptotic Bcl-2 proteins, Bcl-2 and bclxL, and decreases the expression of the pro-apoptotic proteins, Bax and Bad (Mukherjee *et al.* 2004; Bazan 2005c). Furthermore, this metabolite inhibits caspase-3 activity and blocks IL-1-mediated expression of cyclooxygenase-2. Similarly, in injured mouse corneas, treatment with NPD1 increases the rate of re-epithelialization and attenuates the sequence and effect of thermal injury (Gronert *et al.* 2005). The cellular mechanism by which NPD1 exerts its effect on wound healing remains unknown. However, NPD1 may have a receptor-mediated effect on epithelial cell proliferation (Gronert *et al.* 2005). In contrast, the pro-inflammatory eicosanoids have no impact on corneal re-epithelialization.

Non-enzymic metabolites of EPA and DHA and neuroinflammation

DHA undergoes non-enzymic oxidation. Compounds generated by this process are neuroprostanes (NP) (Roberts *et al.* 1998,; Nourooz-Zadeh *et al.* 1999; Greco and Minghetti 2004; Roberts and Fessel 2004; Yin *et al.* 2005). Similarly, non-enzymic oxidation of eicosapentaenoic acid (EPA) results in formation of F_3 isoprostane (Nourooz-Zadeh *et al.* 1997). Non-enzymic oxidation of DHA also produces neuroketals (NK) (Bernoud-Hubac *et al.* 2001). Like IsoK, NK are very reactive. They form not only lactam and Schiff base adducts, but also generate lysine adducts suggesting that these metabolites may be involved in protein–protein cross-linking in brain tissue under oxidative stress. These metabolites may have neurochemical effects that intensify both neuroinflammation and oxidative stress in acute neural trauma and neurodegenerative diseases (Roberts and Fessel 2004; Roberts *et al.* 2005; Farooqui and Horrocks 2006b).

Endocannabinoids and neuroinflammation

The discovery of cannabinoid receptors and identification of the endogenous cannabinoid (endocannabinoid) agonists, arachidonoylethanolamide (AEA) or anandamide, and 2-arachidonoylglycerol (2-AG), has generated considerable interest in these substances (Schmid *et al.* 2002). AEA is synthesized from the cleavage of its precursor *N*-arachidonoyl-PtdEtn by phospholipase D (PLD), whereas 2-AG is generated through the action of diacylglycerol lipase on diacylglycerol (Piomelli 2003). Both mediators are degraded into AA by fatty acid amide hydrolase and monoacylglycerol lipase, respectively (Saario *et al.* 2004; Walter and Stella 2004). Cultured microglial and astroglial cells are known to produce 2-AG as well as anandamide in smaller quantities. In primary cultures of microglia, 2-AG causes cell migration and this process is blocked by SR144528, a CB2 antagonist. Furthermore, the secretion of TNF-α in LPS-stimulated microglial cell cultures is inhibited by anandamide and 2-AG, indicating that cannabinoid agonists decrease neurotoxicity and secretion of pro-inflammatory cytokines in microglial cells (Walter and Stella 2004).

2-AG activation of CB_2 receptors may contribute to the proliferative response in microglial cells, a process that occurs in neurodegenerative diseases associated with neuroinflammation (Carrier *et al.* 2004). Addition of 2-AG to RTMGL1 microglia cell cultures increases their proliferation. This increased proliferation can be blocked by an antagonist of the CB_2 receptor N-[(1S)endo-1,3,3-trimethyl bicyclo heptan-2-yl]-5-(4-chloro-3-methylphenyl)-1-(4-methylbenzyl)-pyrazole-3-carboxamide (SR144528) and mimicked by the CB_2 receptor-specific agonist 1,1-dimethylbutyl-1-deoxy-Δ^9-tetrahydrocannabinol (JWH133). AEA cellular uptake improves motor function and reduces inflammation responses in microglia/macrophages supporting the concept that potentiation of endocannabinoid receptors lowers the severity of inflammation and MS-like symptoms in chronic relapsing remitting experimental allergic encephalomyelitis (CREAE) (Baker *et al.* 2001).

2-AG also suppresses IL-2 expression independently of CB1 and CB2. This process may be associated with the modulation of neuroinflammation (Rockwell *et al.* 2006). Endocannabinoids also have a vasodilatory action on the cerebral microcirculation (Chen *et al.* 2005). They increase the expression of COX-2 protein, which is associated with eicosanoid production in brain. It is stated that endogenous cannabinoid system components are also involved in modulating immune cells (Berdyshev 2000). During neuroinflammation, activated microglia migrate towards degenerating neurons. Very little is known about the signaling mechanism that triggers microglial cell migration. Based on neuropharmacological studies, 2-AG may trigger microglial cell migration through CB2 receptors (Walter *et al.* 2003). Thus, there is growing evidence that the cannabinoid signaling system participates in the modulation of neuroinflammation and immune responses (Walter and Stella 2004; Maresz *et al.* 2005).

Modulation of neuroinflammation by dietary fatty acids

Brain tissue is enriched in AA and DHA. Despite their abundance in the nervous system, AA and DHA cannot be synthesized *de novo* by mammals; they, or their precursors, must be ingested from dietary sources and transported to the brain (Horrocks and Farooqui 2004; Marszalek and Lodish 2005). The present day western diet has a ratio of AA to DHA of about 15:1. The Paleolithic diet on which human beings have evolved, and lived for most of their existence, has a ratio of AA to DHA of 1 : 1. Changes in eating habits and agriculture development within the past 100 to 200 years caused these changes in the AA to DHA ratio. The decreased consumption of DHA-enriched foods and increased consumption of n-6 enriched vegetable oils is responsible for the 15 : 1 AA : DHA ratio (Weylandt and Kang 2005). The richest source of DHA is fish oil. The consumption of DHA has numerous beneficial effects on the health of the human brain (Horrocks and Yeo 1999; Horrocks and Farooqui 2004). The beneficial effects of DHA may be due not only because of its effect on the physicochemical properties of neural membranes, but also of its modulation of neurotransmission (Chalon *et al.* 1998; Itokazu *et al.* 2000; Zimmer *et al.* 2000; Högyes *et al.* 2003), gene expression (Farkas *et al.* 2000; Kitajka *et al.* 2002; Barceló-Coblijn *et al.* 2003; Puskás *et al.* 2003; De Caterina and Massaro 2005), enzyme, ion channel, receptor activities, and immunity (Tsutsumi *et al.* 1995; Yehuda *et al.* 2002, 2005) (Table 2).

EPA and DHA resemble each other in many biochemical effects including the decrease in production of the key immunoregulatory cytokines, IL-10, TNF-α and IFNγ, and in prevention of lipopolysaccharide (LPS) toxicity (Lonergan *et al.* 2004; Verlengia *et al.* 2004; Zhao *et al.* 2004). They differ from each other in expression of specific genes and in many biochemical and physicochemical effects (Verlengia *et al.* 2004; De Caterina and Massaro 2005). For example, EPA is hypotriglyceridemic and hypocholesterolemic, and DHA has no effect on plasma triglycerides (Hashimoto *et al.* 1999). DHA is less effective than EPA in inhibiting vascular smooth muscle proliferation. DHA is a more potent inhibitor than EPA of lymphocyte adhesion to endothelial cells (Hashimoto *et al.* 1999).

Furthermore, EPA and DHA differ from each other in their effect on neural membrane capacitance. Thus, EPA increases PC12 cells membrane capacitance whereas DHA has not effect (Ong *et al.* 2006). The reason for the stimulatory effect of EPA on membrane capacitance is not understood. However, it is likely that EPA interacts with the external ion channel domain of PC12 membranes differently than DHA. DHA blocks voltage-activated sodium channels whilst EPA has no effect on membrane excitability and sodium channels in hippocampal neurons (Xiao and Li 1999). Similarly, DHA modulates certain voltage-gated K^+ channels in Chinese hamster ovary cells whereas EPA has no effect on K^+ channels.

EPA modulates DHA synthesis in SH-SY5Y neuroblastoma cell cultures. EPA has anti-depressant and anti-psychotic activity while DHA does not. Quantification of the mRNA levels of genes encoding for several key enzymes of both the endoplasmic reticulum and peroxisomal steps of fatty acid metabolism indicates that EPA down-regulates the enzymes involved in DHA synthesis and decreases DHA synthesis from its precursor, α-linolenic acid (Poumès-Ballihaut *et al.* 2001; Langelier *et al.* 2005). Collectively, these studies suggest that EPA and DHA differ in their effects on plasma lipid profiles, gene expression, and neural membrane structure.

DHA and EPA reduce chronic inflammation by attenuating NFκB, in turn modulating the expression of pro-inflammatory cytokines including TNF-α and IL-1α and β (Fig. 1). The intake of DHA and EPA reduces the synthesis of eicosanoids derived from AA (Mills *et al.* 2005). How DHA and EPA decrease the activation of NFκB is not clear at present. However, these fatty acids may decrease the phosphorylation of IκB, thereby modulating the availability of NFκB. This process can modulate the expression of the pro-inflammatory genes for COX-2, intracellular adhesion

Table 2 Roles of docosahexaenoic acid in brain tissue

Role of DHA	Reference
Modulation of neurotransmitter release	(Chalon *et al.* 1998; Itokazu *et al.* 2000)
Modulation of gene expression	(Farkas *et al.* 2000; Kitajka *et al.* 2002; Barceló-Coblijn *et al.* 2003)
Modulation of membrane enzymes, ion channels, and receptors	(Fernstrom 1999; Lee *et al.* 2003)
Modulation of learning and memory processes	(Fujimoto *et al.* 1989; Fujita *et al.* 2001; Hashimoto *et al.* 2002)
Modulation of immunity and inflammation	(Wu and Meydani 1998; Calder and Grimble 2002;)
Modulation of blood-brain barrier	(Yehuda *et al.* 2002)
Modulation of apoptosis	(Kim *et al.* 2000)

molecule-1 (ICAM-1), vascular adehesion molecule-1 (VCAM-1), E-selectin, TNF-α, IL-β, IL-6, nitric oxide synthase, and matrix metalloproteinases (MMP) (De Caterina and Massaro 2005). These genes control the availability of lipid mediators such as PGs, LTs, and TXs, which not only modulate the intensity and duration of immune responses, but are also involved in neuroinflammation and pain.

Neurochemically, enrichment of DHA and EPA in the diet competitively inhibits the oxygenation of AA by cyclooxygenase thus suppressing the production of pro-inflammatory eicosanoids and pro-inflammatory cytokines (Calder 2005). The action of cyclooxygenases on EPA generates the 3-series prostaglandins and thromboxanes and the 5-series leukotrienes. These metabolites have different biological properties than the corresponding analogs produced by the metabolism of AA. For example, TXA_3 is less active than TXA_2 in aggregating platelets and constricting blood vessels (James *et al.* 2000; Calder and Grimble 2002). In contrast, the metabolism of EPA and DHA produces resolvins and neuroprotectins (Hong *et al.* 2003; Marcheselli *et al.* 2003). These metabolites not only antagonize the effects of AA-generated metabolites, but also display potent actions on leukocyte trafficking as well as on glial cell functions by down-regulating expression of cytokines. Thus, resolvins and neuroprotectins inhibit both interleukin 1-β-mediated NFκB activation and cyclooxygenase activation, indicating that resolvins and neuroprotectins not only counteract leukocyte-mediated injury but also down-regulate pro-inflammatory gene induction (Hong *et al.* 2003; Marcheselli *et al.* 2003). Collective evidence suggests that feeding EPA and DHA produces numerous immune responses including a decrease in lymphocyte proliferation, suppression of pro-inflammatory cytokines production, reduced gene expression of COX-2, and reduction in natural killer cell activity. These observations suggest that interactions among EPA, DHA, cytokines, eicosanoids, resolvins and neuroprotectins are quite complex and may be associated with beneficial effects of fish oil ingestion on inflammation and immune function (Song 2003). DHA also targets TLR (Lee *et al.* 2003), cannabinoid receptors (Watanabe *et al.* 2003), and PPARγ-mediated signaling (Calder 2005; Shiraki *et al.* 2005). Modulation of these receptors by different dietary fatty acids may contribute to the regulation of acute and chronic inflammatory processes. Thus, a moderate intake of AA and its precursors and the appropriate ratio between AA and DHA may play an important role in physiologic functioning of the immune system and in modulation of inflammation in brain tissue. Very little is known about the optimal AA to DHA ratio for the immunologic response against pathogens that can be effective in treating neuroinflammation. Studies on this topic are complicated by interactions between fatty acids and other nutrients such as vitamin E that are needed for normal immune function and response in mammalian tissues. The consumption of increased amounts of EPA and DHA results in a partial replacement of the AA in cell membranes by EPA and DHA. This can lead to decreased production of AA-derived mediators. This alone is a potentially beneficial anti-inflammatory effect of EPA and DHA (Calder 2005).

In addition, diets enriched in EPA and DHA increase membrane fluidity, affect signal transduction, and modulate gene expression and antigen presenting capacity (Horrocks and Farooqui 2004). Incorporation of EPA and DHA into membranes changes the composition of lipid rafts and alters the signal transduction process by affecting the distribution of cytokine receptors (Li *et al.* 2006a,b). DHA also acts as an antioxidant (Kalmijn *et al.* 1997; Hossain *et al.* 1998, 1999). To explain the role of DHA in protecting the brain from lipid peroxidation, the levels of reactive oxygen species, glutathione, and activities of catalase and glutathione peroxidase have been determined in brains of aged and hypercholesterolemic rats. DHA induces antioxidant defense mechanisms by enhancing cerebral activities of catalase and glutathione peroxidase and increasing levels of glutathione (Hossain *et al.* 1999). DHA also modulates physiological processes such as long-term potentiation and memory processes and pathological events such as oxidative stress in which arachidonic acid and its metabolites participate directly or indirectly (McGahon *et al.* 1999; Fujita *et al.* 2001).

Phospholipid degradation and neuroinflammation in neurological disorders

In chronic neurodegenerative diseases, microglial activation is an early event that often precedes brain damage and neuronal death. In these diseases, activated microglia sustain a local inflammatory response (Minghetti *et al.* 2005). Nonetheless, the potential detrimental or protective role of this response remains to be understood, mainly because of the lack of direct evidence of the functional properties acquired by microglia in the course of chronic diseases. Neural trauma, ischemia, spinal cord trauma, and head injury, and neurodegenerative disease such as AD, PD, and HD are characterized by activation of microglia, overexpression of cytokines, and stimulation of multiple forms of PLA_2 and COX-2 and induction of inflammatory events because of the formation of PGs and PAF (Farooqui *et al.* 2006b; Phillis *et al.* 2006). At present, it is unknown whether neuroinflammation is the cause or consequence of chronic oxidative stress involved in acute neural trauma and neurodegenerative diseases. Cytokine-stimulated microglial cells generate copious amounts of reactive oxygen and nitrogen species, creating a stress upon ambient neurons. Conversely, oxidants can stimulate pro-inflammatory gene transcription in glia, leading to various inflammatory reactions (Mhatre *et al.* 2004).

Levels of glycerophospholipids, such as PtdCho, PlsEtn, and PtdIns, are markedly decreased in neural membranes from different regions of human brain of patients with acute neural trauma, ischemia, spinal cord injury, and head injury

(Edgar *et al.* 1982; Taylor 1988; Shohami *et al.* 1989; Rordorf *et al.* 1991; Clemens *et al.* 1996), and neurodegenerative diseases, such as AD and PD (Stokes and Hawthorne 1987; Söderberg *et al.* 1990; Wells *et al.* 1995; Guan *et al.* 1999; Han *et al.* 2001; Pettegrew *et al.* 2001). Ischemic injury only up-regulates the levels of $sPLA_2$-IIA mRNA and protein, PtdCho-PLC activity, and PLD2 protein expression following ischemia/reperfusion injury (Adibhatla *et al.* 2006), CDP-choline treatment attenuates $sPLA_2$-IIA mRNA and its protein levels, and PtdCho-PLC activity, but has no effect on PLD2 protein expression. No changes have been reported in $cPLA_2$ or $iPLA_2$ following ischemic injury (Adibhatla *et al.* 2006). This contrasts with earlier investigations that support the view that $cPLA_2$ and PlsEtn-PLA_2 are stimulated along with $sPLA_2$ activity during ischemic injury and may be responsible for the decrease in levels of PtdCho and PlsEtn in ischemic brain (Farooqui and Horrocks 2006b; Farooqui *et al.* 2006b; Phillis *et al.* 2006). Furthermore, it is not possible to account for the release of arachidonic acid on the basis of increased $sPLA_2$-IIA activity. This isoform of PLA_2 is not specific for arachidonic acid. It acts on any fatty acid located at the *sn*-2 position of glycerol moiety. It is likely that different isoforms of PLA_2 are upregulated in different ischemic injury models under different experimental conditions. Thus, detailed investigations are needed to understand the involvement of multiple forms of PLA_2 in ischemic/reperfusion injury.

The stimulation of multiple forms of PLA_2 and decreased levels of neural membrane glycerophospholipids is also accompanied by an elevation in metabolites of glycerophospholipid degradation products, such as phosphodiesters, phosphomonoesters, fatty acids, prostaglandins, isoprostanes, 4-hydroxynonenals, and other lipid mediators generated by lipid peroxidation (Farooqui and Horrocks 2006b). Many of these lipid mediators are pro-inflammatory. Their effects are accompanied by the activation of astrocytes and microglia and the release of inflammatory cytokines. These cytokines in turn propagate and intensify neuroinflammation by a number of mechanisms including further up-regulation of PLA_2 isoforms, generation of PAF, stimulation of nitric oxide synthase, and calpain activation (Farooqui and Horrocks 1991, 2006b; Farooqui *et al.* 2000c, 2002; Ray *et al.* 2003). Similarly, the degradation of sphingomyelin through the stimulation of SMase increases the levels of ceramide and its metabolic products including the generation of psychosine (galactosylsphingosine). The levels of psychosine are markedly increased in twitcher mice, a murine model of Krabbe disease (Khan *et al.* 2005; Giri *et al.* 2006). This demyelinating disease is characterized by neuroinflammation, oxidative stress, and oligodendrocyte degeneration. It is recently suggested that psychosine mediated down-regulation of PPAR-α causes a decrease in peroxisomal proteins resulting in oligodendroglial cell death (Haq *et al.* 2006). The psychosine-induced down-regulation of PPARα activity and cell death can be attenuated by a $sPLA_2$ inhibitor. This suggests that PLA_2 isoforms may play an important role in the pathogenesis of Krabbe disease. Collectively, these studies suggest that increased glycerophospholipid and sphingolipid degradation through the activation of PLA_2 and COX-2 and SMase isoforms can lead to neuroinflammation (Farooqui and Horrocks 1994, 2006a,b; Farooqui *et al.* 2000b).

Brain tissue is enriched in DHA. Its enrichment in the diet can reduce the production of prostaglandins not only by direct inhibition of cyclooxygenases but also by reduction of expression of inducible COX-2 (Strokin *et al.* 2004). Additionally, DHA may also influence intracellular Ca^{2+} signaling, which results in changes of activity of Ca^{2+}-dependent PLA_2, hence reducing the amount of arachidonic acid available for prostaglandin production. Astrocytes, the main supporter of neurons in the brain tissue, control the release of AA, DHA, and the formation of prostaglandins. The release of AA and DHA in astrocytes is controlled by different isoforms of PLA_2, i.e., $cPLA_2$ and $iPLA_2$, respectively (Strokin *et al.* 2004). Moreover, the release of AA and DHA is differently regulated through Ca^{2+}- and cAMP-dependent signal transduction pathways (Kruger and Schollum 2005).

Based on these findings, $cPLA_2$ and COX-2 are promising targets. Their inhibitors can be used for the treatment of neuroinflammation in brain tissue (Farooqui *et al.* 2006b; Phillis *et al.* 2006).

Therapeutic value of DHA for neuroinflammation associated with neurological disorders

The increased appreciation of the involvement of microglial cell-mediated neuroinflammation in neurological disorders, such as AD, PD, stroke, traumatic brain and spinal cord injuries, and multiple sclerosis, has attracted considerable interest in treatment with anti-inflammatory drugs such as glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs), COX inhibitors, and PLA_2 inhibitors (Kempermann and Neumann 2003; Consilvio *et al.* 2004; Farooqui *et al.* 2006b). The therapeutic effects of glucocorticoids are mediated through the induction of annexins, a group of PLA_2 inhibitory proteins. The effects of NSAIDs, COX and LOX inhibitors are mediated by the inhibition of COX and LOX enzymes (Kuhn and O'Donnell 2006; Phillis *et al.* 2006). PLA_2 inhibitors block PLA_2 activity (Farooqui *et al.* 2006b). The treatment of neurological disorders suffers from side effects of glucocorticoids, NSAIDs, COX, LOX, and PLA_2 inhibitors and also from the lack of beneficial effects (Serhan 2004; Craft *et al.* 2005; Farooqui *et al.* 2006b). Therefore, for the treatment of neuroinflammation, one has to look beyond therapy with glucocorticoids, NSAIDs, COX, LOX, and PLA_2 inhibitors.

A substantial body of biochemical and clinical data supports the use of n-3 fatty acids as anti-inflammatory

agents (Mori and Beilin 2004). The future appears to be bright for the dietary use of n-3 fatty acids for reducing neuroinflammation and providing neuroprotection in neurological disorders (Table 3). The most important dietary supplement that can reduce neuroinflammation is fish oil because it is rich in EPA and DHA. Fish oil reduces neuroinflammation in several ways. First; it decreases the formation of AA by blocking the activity of Δ5-desaturase; second, it inhibits the synthesis of eicosanoids (Calder 2005); and at last, it induces the synthesis of resolvins and neuroprotectins (Bazan 2005a,c; Serhan 2005b, 2006). Collective evidence suggests that the ratio of AA to n-3 fatty acid is an important dietary factor in reducing inflammation in brain tissue.

DHA plays an important role in normal neurological and cognitive function (Horrocks and Farooqui 2004). Levels of DHA are markedly decreased in neural membranes obtained from brains of aged healthy elderly people and also from patients with neurological disorders (Bechoua *et al.* 2003; Horrocks and Farooqui 2004). Numerous epidemiological studies indicate that increased fatty fish consumption and high DHA intake are associated with reduced risk of AD (Kalmijn *et al.* 2004). Reduction of dietary DHA in the TG2576 AD mouse model results in a loss of post-synaptic proteins and behavioral deficits and a DHA-enriched diet can prevent these effects (Calon *et al.* 2004; Olivo and Hilakivi-Clarke 2005). Dietary DHA incorporates into neuronal membranes and restores neuronal functions (Rapoport 1999). Chronic pre-administration of DHA prevents β-amyloid-induced impairment of an avoidance ability-related memory function in a rat model of AD (Hashimoto *et al.* 2005) and protects mice from synaptic loss and dendritic pathology in another model of AD (Calon *et al.* 2004). DHA prevents β-amyloid secretion from aging brain cells accompanied by neuroprotectin D1 synthesis (Lukiw *et al.* 2005). Neuroprotectin D1 may block apoptotic cell death induced by β-amyloid. Thus, DHA is beneficial in preventing the learning deficiencies in animal AD models.

DHA also affects amyloid precursor protein processing by inhibiting α- and β-secretase activities (de Wilde *et al.* 2003; Walsh and Selkoe 2004; Olivo and Hilakivi-Clarke 2005). DHA reverses the age-related impairment in LTP. DHA acts as an antioxidant (Hossain *et al.* 1998). It induces antioxidant defenses by enhancing cerebral activities of catalase, glutathione peroxidase, and levels of glutathione (Hossain *et al.* 1999). Thus, DHA exerts neuroprotective effects by modulating the secretion of cytokines and inhibiting neuroinflammation and oxidative stress. Furthermore, in brain tissue, DHA-derived metabolites promote resolution and protect neural cells from neurodegeneration (Bazan 2005c; Lukiw *et al.* 2005; Serhan 2005b). Collectively, these studies suggest that the generation of resolvins and docosatrienes may be an internal neuroprotective mechanism for preventing brain damage (Bazan 2005b; Lukiw *et al.* 2005; Serhan 2005b). Thus, DHA supplementation may restore signal transduction processes by protecting neurons from harmful effects of neuroinflammation. Therefore, DHA may have a protective effect against dementia (Lim *et al.* 2006).

During ischemic injury, deprivation of oxygen induces activation, proliferation, and hypertrophy in microglial cells and astrocytes (Perry and Gordon 1991). Activated glial cells secrete more cytokines that further stimulate glial cells and induce gliosis. Ischemic injury not only damages parenchymal cells, but also involves infiltration and accumulation of polymorphonuclear leukocytes, monocytes/macrophages, and serum proteins due to breakdown of the blood–brain barrier (Sharkey *et al.* 1997). DHA protects the brain against ischemic and excitotoxic damage in rat brain and hippocampal slice cultures (Strokin *et al.* 2006). The antioxidant action of DHA is of considerable interest because of the intrinsic potential of brain tissue for free radical generation (Hossain *et al.* 1998).

Studies on the uptake and distribution of DHA into different glycerophospholipid classes indicate that the maximum incorporation of DHA occurs in ethanolamine plas-

Table 3 Beneficial effects of docosahexaenoic acid in neurological disorders

Neurological disorders	Inflammatory Biomarkers	Changes in DHA levels	DHA treatment	Reference
Ischemia	Cytokines and eicosanoids ↑	Decreased	Beneficial	(Högyes *et al.* 2003)
Alzheimer disease	Cytokines and eicosanoids ↑	Decreased	Beneficial	(Puskás *et al.* 2003; Cole *et al.* 2005; Hashimoto *et al.* 2005; Olivo and Hilakivi-Clarke 2005)
Parkinson disease	Cytokines and eicosanoids ↑	-	Beneficial	(Samadi *et al.* 2006)
Huntington disease	Cytokines and eicosanoids ↑	-	Beneficial	(Das and Vaddadi 2004; Puri 2005)
Epilepsy	Cytokines and eicosanoids ↑	Decreased	Beneficial	(Yuen *et al.* 2005)
Spinal cord injury	Cytokines and eicosanoids ↑	-	Beneficial	(King *et al.* 2006)
Multiple sclerosis	Cytokines and eicosanoids ↑	Decreased	Beneficial	(Nordvik *et al.* 2000)
Peroxisomal disorders	Cytokines and eicosanoids ↑	Decreased	Beneficial	(Martínez *et al.* 2000)

Upward arrow (↑) indicates increase in cytokines and eicosanoids.

malogens, PlsEtn (Rapoport 1999), which are unique glycerophospholipids with a vinyl ether group at the *sn*-1 position and AA or DHA at the *sn*-2 position of the glycerol moiety. Myelin possesses the highest proportion of PlsEtn (Lee 1998; Farooqui and Horrocks 2001; Brites *et al.* 2004). PlsEtn protect biomembranes against free radical attack (Zoeller *et al.* 1999; Engelmann 2004; Maeba and Ueta 2004; Kuczynski and Reo 2006).

In biomembranes, transition metal ions (copper and iron) initiate lipid peroxidation by generating peroxyl and alkoxyl radicals from the decomposition of lipid hydroperoxides (Murphy 2001). Plasmalogen-containing liposomes have a strong ability to chelate transition metal ions and thereby prevent the formation of peroxyl and alkoxyl radicals (Sindelar *et al.* 1999). In contrast to the above view, studies based on the effect of menadione, an intracellular reactive oxygen species generator, on plasmalogen-deficient fibroblasts (Jansen and Wanders 1997), and lactic acid on astrocytic cultures, suggest that plasmalogens do not play a major role in the protection of cells against superoxide anion radicals and lactic acid-induced oxidative stress (Fauconneau *et al.* 2001). Thus, more studies are required on this controversial topic.

The incorporation of DHA into ethanolamine plasmalogens may stabilize neural membranes. These PlsEtn may replace lost molecules. The losses may be due to neuroinflammatory stimulation of PlsEtn-selective PLA_2 or to oxidation of the vinyl ether group after exhaustion of other antioxidants. DHA also stimulates the synthesis of the peroxisomal enzymes needed for the synthesis of PlsEtn.

DHA administration reduces L-DOPA induced dyskinesias in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated monkeys (Samadi *et al.* 2006) suggesting that that DHA can reduce the severity or delay the development of L-DOPA induced dyskinesias in a nonhuman primate model of Parkinson disease. A DHA-enriched diet may represent a new approach to improve the quality of life of Parkinson disease patients.

EPA and DHA have also been used for the treatment of HD (Puri 2005). HD is caused by a mutation in exon 1 of the Huntingtin gene that encodes a stretch of polyglutamine (polyQ) residues close to the N-terminus of the huntingtin protein. Randomized, placebo-controlled, double-blind studies indicate that highly unsaturated fatty acids are beneficial to HD patients (Das and Vaddadi 2004), suggesting that either unsaturated fatty acids may prevent or arrest polyQ aggregation, inhibit histone deacetylation, or activate the ubiquitin-proteasome system (Das and Vaddadi 2004). It is tempting to suggest that unsaturated fatty acids may be useful for the treatment of HD and more trials on human subjects are needed.

Treatment with α-linolenic acid and DHA of rats with injured spinal cords at 30 min after injury significantly improves locomotor performance and neuroprotection, including decreased lesion size and apoptosis, and increased neuronal and oligodendrocyte survival (King *et al.* 2006). Evidence showing a decrease in RNA/DNA oxidation suggests that the neuroprotective effect of n-3 PUFAs involved a significant antioxidant function. In contrast, animals treated with arachidonic acid have a significantly worse outcome than controls. This suggests that DHA treatment after spinal cord compression greatly increases the survival of neurons and results in significantly better locomotor performance for up to 6 weeks after injury. Given the proven clinical safety of DHA and other n-3 fatty acids, these PUFAs have significant therapeutic potential for spinal cord injury (King *et al.* 2006).

Neuropharmacological studies in humans indicate that DHA increases seizure thresholds and lowers the inflammatory mediators that are increased in patients with epilepsy (Yuen *et al.* 2005). Although the seizure frequency is reduced over the first 6 weeks of treatment in the supplement group, this effect is not sustained, suggesting that further studies are required to examine different DHA preparations, different doses, longer treatment duration, and larger sample size. DHA improves spatial memory in rats following pentylenetetrazole-induced seizures (Chen *et al.* 2006). The molecular mechanism of DHA action is unknown, but it is likely that DHA and DHA-derived metabolites (resolvins and neuroprotectins) can be beneficial for the treatment of neuroinflammation associated with epilepsy.

Although the above studies on the use of dietary DHA and other n-3 fatty acids in neurological disorders provide encouraging results, the specificity, quantity, duration of clinical trials, and sample size remain controversial. Development of Omacor™, a preparation of n-3 fatty acids approved by the FDA, is an important development. This preparation has been used for the treatment of IgA nephropathy (Donadio and Grande 2004). It is proposed that n-3 PUFA prevents renal disease progression by interfering with a number of effector pathways triggered by mesangial immune-complex deposition. Omacor also decreases cardiovascular deaths and mainly fatal arrhythmias after myocardial infarction (Pater *et al.* 2003; Ducobu 2005). At present, attempts are being made to develop novel DHA-derived lipid mediator-based compounds that can selectively down-regulate neuroinflammatory responses.

The use of drugs targeting anti-inflammatory and pro-resolving properties of lipoxins, resolvins, docosatrienes, and neuroprotectins and their aspirin-triggered counterparts would be of great importance in treating inflammation in brain tissue. Treatment of neurological disorders with existing synthetic anti-inflammatory drugs to target neuroinflammation has largely met with failure due to a lack of definition of the dose-window, length of treatment, lack of efficacy, and side-effects (Yamazaki *et al.* 2002; Gasparini *et al.* 2004; Imbimbo 2004; Craft *et al.* 2005). However, the

de novo development of new classes of therapeutics based on targeting selective aspects of glia activation pathways and studies on the generation of lipid mediators derived from EPA and DHA, versus targeting pathways of quantitative importance in non-CNS inflammatory responses, may provide promising results in animal models of neurodegenerative diseases associated with neuroinflammation (Serhan 2004; Craft *et al.* 2005). Development of drugs based on this concept may be an important step in controlling the duration and magnitude of neuroinflammation in brain tissue.

A balanced ratio of n-6 to n-3 fatty acid also plays an important role in prevention of cancer (Xia *et al.* 2006). Implantation of mouse melanoma B16 in fat-1 transgenic mice, which have a balanced ratio of n-6 to n-3 fatty acids in their tissues and can convert n-6 fatty acids to n-3 fatty acids, produces a dramatic reduction of melanoma formation and growth compared to WT littermates. The levels of n-3 fatty acids and their metabolite PGE_3 were higher in the tumor and surrounding tissues of fat-1 mice than in WT mice, suggesting that n-3 fatty acids inhibit the growth of melanoma caused by the implanted B16 cell line. Collectively these studies indicate that n-3 fatty acids have anticancer properties and can be used as therapeutic agents to treat this cancer in mice (Xia *et al.* 2006).

Conclusion

Neuroinflammation is an active defensive process against diverse insults, metabolic and traumatic injuries, neurodegenerative diseases, and infection. Neuroinflammation removes toxic agents and blocks their detrimental effects. Although neuroinflammation serves as a neuroprotective mechanism associated with repair and recovery, it can also cause brain damage. Most of the inflammatory reactions are initiated, maintained, and modulated by cytokines/chemokines and eicosanoids from microglial cells, astrocytes, macrophages, and endothelial cells in response to insult. Cytokines propagate inflammation through the activation of phospholipases A_2, cyclooxygenases, and lipoxygenases. This results in the release of AA from neural membrane glycerophospholipids and generation of pro-inflammatory, pro-thrombotic, and vasoconstricting compounds, including prostaglandins, leukotrienes, thromboxanes, and anti-inflammatory lipoxins (Phillis *et al.* 2006). The activation of phospholipases A_2 by cytokines also generates DHA that is subsequently metabolized to resolvins and neuroprotectins. These lipid mediators are anti-inflammatory and are associated with resolution of inflammatory process. Collective evidence suggests that AA and DHA play important roles in pro-and anti-inflammatory processes. Therefore, their ratio in the diet can modulate neuroinflammation. The ancient human diet had a ratio of AA/DHA of 1 : 1, but modern diets contain a AA/DHA ratio of 15 : 1 (Weylandt and Kang 2005). This dramatic increase in the AA/DHA ratio has resulted in high levels of AA in neural membranes. Excess AA generates high levels of prostaglandins, leukotrienes, and thromboxanes resulting in neuroinflammation. Based on the recent literature, the dietary intake of food rich in DHA can decrease or prevent inflammatory processes in brain tissue and can be beneficial for the neuroinflammation associated with acute neural trauma and neurodegenerative diseases.

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