

Chapter 2

Recent Development on the Neurochemistry of Docosanoids

2.1 Introduction

Neuroprotectins and resolvins are subfamilies of endogenous oxygenated metabolites derived from n-3 or ω -3 fatty acids (eicosapentaenoic acid, 20:5, EPA and docosahexaenoic acid, 22:6, DHA) (Serhan et al., 2000, 2002; Hong et al., 2003; Marcheselli et al., 2003). EPA not only modulates neuronal activity, but also participates in balancing the immune function by reducing arachidonic acid (20:4, ARA) level on cell membrane and prostaglandin E_2 (PGE₂) synthesis (Farooqui, 2009). DHA is a major structural membrane fatty acid. At the subcellular level, highest concentration of DHA is found in synaptic membranes followed by mitochondria and microsomes (Scott and Bazan, 1989). The presence of DHA in neural membranes significantly alters many basic membrane properties, including acyl chain order and fluidity, elastic compressibility, phase behavior, permeability, fusion, flipflop, and protein activity. DHA also plays important roles in gene expression, and neurotransmission, associated with serotonin, norepinephrine and dopamine receptors. This may be related to the etiology of mood and cognitive dysfunction in neuropsychiatric and neurodegenerative diseases (Farooqui, 2009). In addition, treatment of hippocampal neuronal cultures with DHA reduces glutamate-mediated neurotoxicity (Wang et al., 2003). Changes in the polyunsaturated fatty acid (PUFA) composition of neuronal membranes may lead not only to alterations in the physical characteristics of the neural membrane, but also functional changes in the activity of receptors and other proteins embedded in the membrane glycerophospholipid bilayer. Both of these processes alter physicochemical membrane properties. Beyond their structural importance in neural and retinal membranes, DHA and EPA are involved in the synthesis and functions of neurotransmitters, and in the modulation of the immune system (Farooqui, 2009, 2010a). Neuronal membranes contain phospholipid pools that are reservoirs for the synthesis of specific lipid messengers on neuronal stimulation or injury. These messengers in turn participate in signaling cascades that can either promote neurodegeneration or neuroprotection. DHA and EPA-derived metabolites also improve

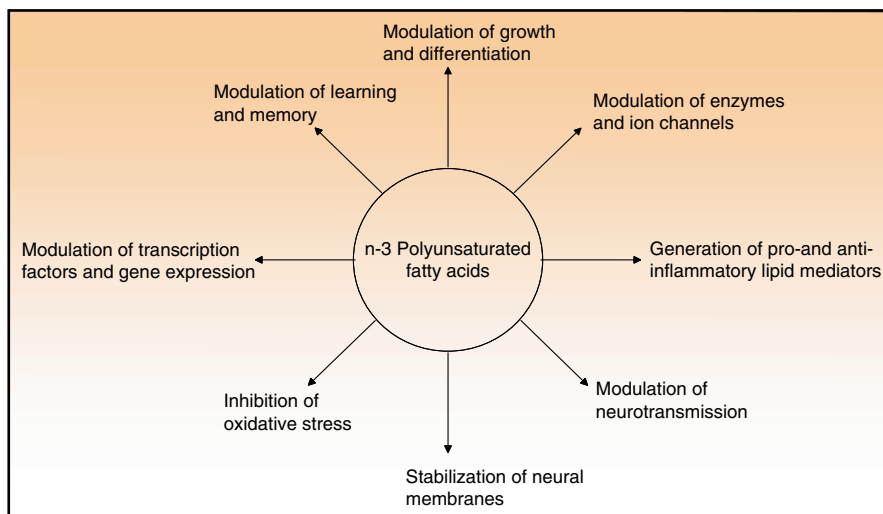


Fig. 2.1 Role of polyunsaturated fatty acids in brain

biological functions such as signal transduction, ion channeling and ligand binding to nuclear receptors (Fig. 2.1). Collective evidence suggests that dietary PUFAs regulate both eicosanoids and proinflammatory cytokine production. DHA and EPA are anti-inflammatory while ARA (n-6 fatty acids) and its metabolites are proinflammatory. Inappropriate amounts of dietary n-6 and n-3 fatty acids may lead to abnormal inflammatory and immune responses because of their abundance in the brain. An adequate ratio of n-6 and n-3 fatty acids may promote a healthier balance between n-6-and n-3 PUFA-derived lipid mediators, which may maintain optimal neural membrane function (Farooqui, 2009).

2.2 Importance of n-3 Polyunsaturated Fatty Acids in the Brain

n-3 polyunsaturated fatty acids are essential for brain growth and development. They play an important role throughout life, as critical modulators of neuronal function and regulation of neuroinflammatory and oxidative stress-mediated mechanisms in the normal CNS during aging and chronic neurological diseases. Inadequate levels of DHA in brain during development and old age induce cognitive deficits such as memory loss and learning disability in experimental animals. Thus, the inadequacy of DHA in neural membranes may contribute to cholinergic, dopaminergic, and glutamatergic receptor dysfunction in synapses associated with the hippocampal neurons, and growing evidence suggests that low levels of DHA in the brain are associated not only with neurotraumatic, neurodegenerative and neuropsychiatric diseases, but also with peroxisomal disorders (Farooqui, 2009). DHA, the

major n-3 fatty acid found in neurons, has taken on a central role as a target for therapeutic intervention in neurotraumatic, neurodegenerative, and neuropsychiatric diseases (Farooqui, 2009, 2010a). DHA acts as a ligand for the PPAR- γ and the RXR receptors. In conjunction with these receptors, which act as transcription factors, DHA modulates various neurochemical processes that maintain cellular homeostasis by modulating lipid metabolism, neural cell differentiation, and apoptosis (Farooqui, 2009). DHA downregulates protein kinase C, Ras, and NF- κ B; activates the Jak/Stat pathway, and sustains phosphorylation of EGFR. DHA attenuates the transcription of NF- κ B-dependent genes. Thereby the COX-2/PGE₂-dependent generation of pro-angiogenic vascular endothelial growth factor and levels of anti-apoptotic bcl-2 and bcl-X(L) are reduced. Eicosanoid-independent pro-apoptotic pathways include enhanced lipid peroxidation, modulation of mitochondrial calcium homeostasis, and enhanced production of reactive oxygen species (ROS) as well as activation of p53. In brain, DHA also restores levels of cerebellar phospho (p)-AKT, phospho-extracellular regulated kinase (p-ERK) and phospho-c-Jun N-terminal kinase (p-JNK) supporting their role in down-regulation of neuronal apoptosis (Sinha et al., 2009). n-3 PUFAs also quench gene expression of cyclooxygenase-2 and other enzymes, thereby diminishing the formation of proinflammatory eicosanoids. In addition, n-3 PUFAs scavenge of free radicals, which diminish inflammatory response and oxidation of lipoprotein particles, notably low-density lipoproteins. DHA also suppresses insulin/neurotrophic factor signaling deficits, neuroinflammation, and oxidative damage that may contribute synaptic loss and neuronal dysfunction in old age and demented subjects (Cole and Frautschy, 2010). Finally, DHA increases brain levels of neuroprotective brain-derived neurotrophic factor and reduces the (n-6) fatty acid arachidonate and its oxidative metabolites. The cross-talk among these molecular processes has distinct neuroprotective effects not only through the stabilization of neural membranes, modulation of ion channels and receptors, but also through inhibition of inflammatory processes and generation of anti-inflammatory lipid mediators (Farooqui et al., 2007; Farooqui, 2009).

Dietary intake of ARA, EPA, and DHA results in incorporation of these PUFAs in neural membranes. EPA is readily incorporated into membrane phospholipids with a considerable amount present in mitochondrial cardiolipin. The incorporation of EPA in mitochondrial membranes is accompanied by a decrease in mitochondrial membrane potential, and increase in lipid peroxide and ROS generation (Colquhoun, 2009). DHA incorporates into ethanolamine and serine glycerophospholipids, which are located in the inner leaflet of lipid bilayer. The ethanolamine glycerophospholipids include phosphatidylethanolamine and ethanolamine and choline plasmalogens. These lipids are closely associated not only with the stability of synapse and functioning of various receptors but also with membrane fluidity and permeability (Farooqui et al., 2008), whereas DHA-enriched phosphatidylserine (PtdSer) is an essential cofactor for the activation of several proteins including, protein kinase C, Raf-1 kinase, Akt, which translocate from cytoplasm to the membrane for their activation, supporting the view that translocation of these kinases may target signaling events modulated by the DHA-mediated neuronal specific increase of PtdSer (Kim et al., 2010). PtdSer also modulates activities of diacylglycerol kinase, nitric

oxide synthase, and Na^+ , K^+ -ATPase (Ikemoto et al., 2000; Farooqui, 2009). Ester-linked ARA, EPA, and DHA are mobilized by PLA_2 to generate free ARA, EPA, and DHA (Hirashima et al., 1992; Farooqui and Horrocks, 2007; Green et al., 2008; Farooqui, 2010b), which can act as substrates for cyclooxygenase and lipoxygenase to produce lipid mediators (eicosanoids, resolvins, and protectins/neuroprotectins) (Nieves and Moreno, 2006; Cherian, 2007; Farooqui and Horrocks, 2007). Compared to DHA, levels of EPA in brain tissue are quite low. This may be due to rapid β -oxidation of EPA following its uptake by the brain tissue (Chen et al., 2009a). In rat hepatocytes L-carnitine, a long chain fatty acid mitochondrial matrix transporter, not only increases β -oxidation of EPA, but only marginally elevates the oxidation of ARA and alleviates competitive inhibition of ARA-dependent PGE_2 synthesis and COX-2 expression by EPA. It is suggested that L-carnitine modulates the competition between ARA and EPA in PG synthesis in liver cells by enhancing oxidation of EPA. This suggests that the beneficial effects of n-3 PUFA, especially EPA, are modulated by the cellular oxidation capacity (Du et al., 2010).

Supplementation of diet containing EPA not only antagonizes the synthesis of PGE_2 from ARA, but also reduces IL-1 β -mediated increase in levels of PGE_2 , elevation in corticosterone, and upregulation in nerve growth factor expression in olfactory bulbectomized rat model of depression (Song et al., 2004). Furthermore, IL-1 β -mediated suppression of the antiinflammatory cytokine IL-10 is also blocked by the ethyl-EPA treatment. Collectively, these results indicate that ethyl-EPA treatment has beneficial effects on neurotraumatic, neurodegenerative, and neuropsychiatric (cognitive and affective disorders) in which inflammation and oxidative stress play a critical role (Song et al., 2004, 2009; Farooqui, 2009).

2.3 EPA-Derived Lipid Mediators in the Brain

The lipid mediators derived from EPA include 3-series of prostaglandins and thromboxanes, 5-series of leukotrienes, and E series resolvins (Resolvin E_1 or RvE_1) (Serhan et al., 2000, 2002). The oxidized metabolites of EPA possess antiinflammatory and antiproliferative effects (Table 2.1). The oxidation of EPA by COX and LOX enzymes results in the production of 3-series of prostaglandins and thromboxanes and the 5-series of leukotrienes (Fig. 2.2). These eicosanoids have different biological properties than the corresponding analogs generated by the oxidation of ARA. For example, TXA_3 is less active than TXA_2 in aggregating platelets and constricting blood vessels (Calder and Grimble, 2002; Calder, 2009). In addition to generating less active lipid mediator, EPA exerts its effects on other aspects of inflammation like leukocyte chemotaxis and inflammatory cytokine production. Some of these effects are likely due to changes in nuclear factor- κB -mediated gene expression, e.g. adhesion molecule in microglia, astrocytes, and in visceral inflammatory and immune cells. In contrast, recent studies on the effects of prostaglandins (PGE_2 and PGE_3) and leukotrienes (LTB_4 and LTB_5) on endothelium permeability and mononuclear adhesion and migration across endothelial cell

Table 2.1 Activities of resolvins and protectins/neuroprotectins/maresin in neural and non-neural systems

Parameter	Resolvins and protectins	Reference
Aggregation	Antiaggregatory	Serhan et al., 2000, 2002, 2009; Serhan, 2005; Farooqui, 2009
Thrombotic activity	Antithrombotic	Serhan et al., 2000, 2002, 2009; Serhan, 2005; Farooqui, 2009
Inflammation	Antiinflammatory	Serhan et al., 2000, 2002, 2009; Serhan, 2005; Farooqui, 2009
Lipid status	Hypolipidemic	Serhan et al., 2000, 2002, 2009; Serhan, 2005; Farooqui, 2009
Cell death nature	Antiapoptotic	Serhan et al., 2000, 2002, 2009; Serhan, 2005; Farooqui, 2009
Effect on excitotoxicity	Antiexcitotoxic	Serhan et al., 2000, 2002, 2009; Serhan, 2005; Farooqui, 2009
Pain sensitivity	Antinociceptive	Serhan et al., 2000, 2002, 2009; Serhan, 2005; Farooqui, 2009

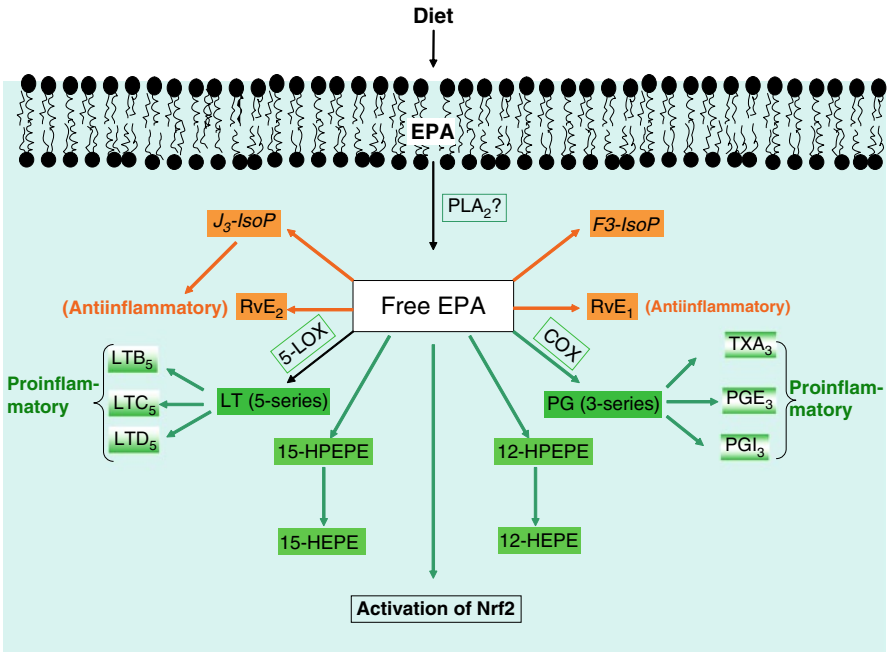


Fig. 2.2 Generation of EPA-derived lipid mediators in neural and non-neural tissues. Phospholipase A₂ (PLA₂); 5-lipoxygenase (5-LOX); resolving E₁ (RvE₁); resolving E₂ (RvE₂); 3-series of prostaglandins and thromboxanes (PGE₃ and PGI₃); 5-series of leukotrienes (LTB₅, LTC₅, and LTD₅); 15-hydroperoxy-5,8,11,13,15-eicosapentaenoic acid (15-HPEPE); 12-hydroperoxy-5,8,11,13,12-eicosapentaenoic acid (12-HPEPE); 12-hydroxy-5,8,10,14-eicosatetraenoic acid (15-HETE), and 15-hydroxy-5,8,10,14-eicosatetraenoic acid (12-HETE); cyclopentenone-IsoP molecules-derived from EPA (J₃-IsoP); F-ring IsoP-like compounds derived from EPA (F₃-IsoPs); and Nuclear factor (erythroid-derived 2)-like 2 (Nrf2)

cultures indicate that PGE_3 produces more pronounced effect on trans-endothelial Evans Blue-albumin (EBA) permeability than PGE_2 , and these effects are antagonized by EP_1 and EP_2 antagonists (Moreno, 2009). LTB_4 and LTB_5 produce a slight effect on EBA extravasation. Collective evidence suggests that the enhancement of endothelial permeability in the presence of polymorphonuclear (PMN) cells is modulated by interplay between leukotrienes and prostaglandins (Moreno, 2009; Yin et al., 2007). n-3 PUFAs also decrease the production of the classic inflammatory cytokines tumor necrosis factor, interleukin-1, and interleukin-6 and the expression of adhesion molecules involved in inflammatory interactions between leukocytes and endothelial cells. These latter effects may occur by eicosanoid-independent mechanisms, including modulation of the activation of transcription factors involved in inflammatory processes. The anti-inflammatory actions of long chain n-3 fatty acid-induced effects may be of therapeutic use in conditions with an acute or chronic inflammatory component. EPA and ARA compete for the same COX enzymes (Zhao et al., 2004; Phillis et al., 2006), but the rate of oxidation of EPA is only 10% of the ARA. Although EPA significantly inhibits COX-1-mediated oxidation of ARA (Wada et al., 2007; Schmitz and Ecker, 2008), the oxidation of ARA by COX-2 is only modestly inhibited by EPA. EPA-derived eicosanoids antagonize the pro-inflammatory effects of ARA-derived eicosanoids. EPA and ARA are ligands/modulators for the nuclear receptors NF- κB , PPAR and SREBP-1c, which modulate various genes of inflammatory signaling and lipid metabolism. In addition, the n-3/n-6 PUFA ratio of neural membranes and microdomains strongly influences membrane function and numerous cellular processes such as cell death and survival (Wada et al., 2007; Schmitz and Ecker, 2008; Yin et al., 2007).

EPA is a precursor for resolvins E series (Arita et al., 2006, 2007), including resolvin E_1 (RvE_1 ; (5S,12R,18R)-trihydroxy-6Z,8E,10E,14Z,16E-eicosapentaenoic acid) and resolvin E_2 (15S,18R-dihydroxy-EPE) (Fig. 2.3). EPA is oxidized to 18R-hydroxyeicosapentaenoic acid (18R-HEPE) by endothelial cell cyclooxygenase-2 (COX-2). Aspirin acetylates COX-2 and the acetylated enzyme no longer produces prostaglandins, but can still convert EPA to 18R-HEPE. During cell-cell interactions, 18R-HEPE is released to neighboring leukocytes for subsequent conversion by 5-LOX to RvE_1 via a 5(6) epoxide-containing intermediate. RvE_1 is present in human whole blood, and its levels can be increased by ingestion of aspirin (Serhan et al., 2000; Arita et al., 2006, 2007). RvE_1 is transformed into several metabolic products, including 20-hydroxy- RvE_1 , 20-carboxy- RvE_1 , 19-hydroxy- RvE_1 , 18-oxo- RvE_1 and 10,11-dihydro- RvE_1 by human PMNs and whole blood as well as in murine inflammatory exudates, lungs, spleen, kidney, and liver (Seki et al., 2009, 2010). Among these products, 20-carboxy- RvE_1 , 18-oxo- RvE_1 , and 10,11-dihydro- RvE_1 are essentially biologically inactive and may serve as inactive biomarkers of RvE_1 metabolism in vivo. In contrast, 20-hydroxylated product of RvE_1 has some of the activity of RvE_1 , suggesting that more metabolites of RvE_1 are generated during inflammatory response.

RvE_1 and RvE_2 produce potent anti-inflammation/pro-resolution effects in vivo (Arita et al., 2006) via specific G protein-coupled receptors (see below). RvE_1 suppresses the activation of NF- κB by tumor necrosis factor- α (TNF- α) through

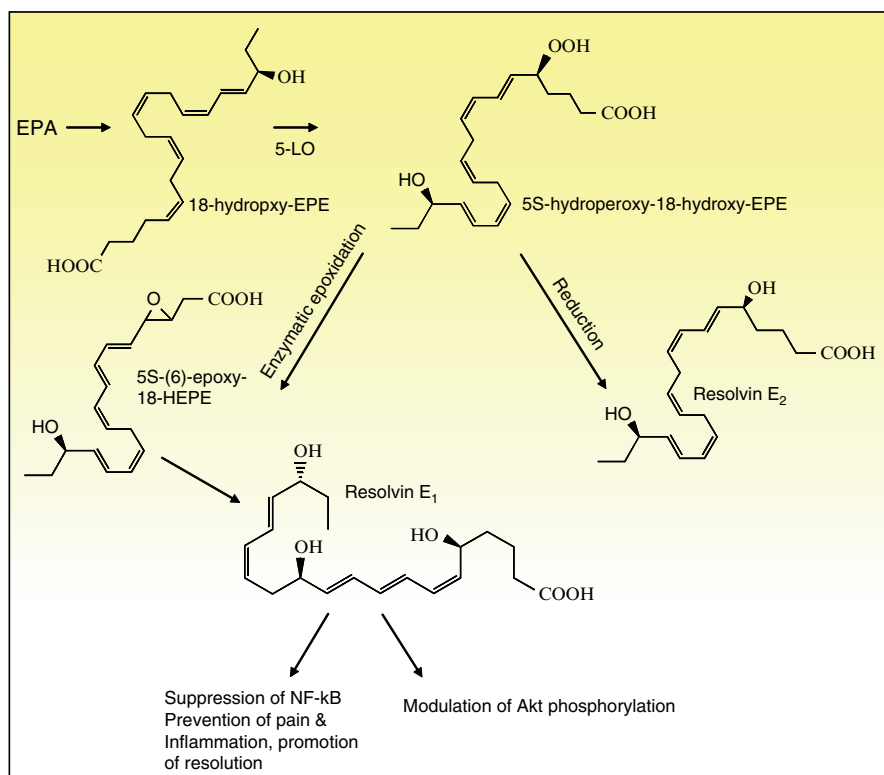


Fig. 2.3 Synthesis of RvE₁ and RvE₂ from EPA and proposed roles of RvE₁ in brain. Dietary EPA is converted to RvE₁ by the action of 5-lipoxygenase (5-LOX). After aspirin treatment, RvE₁ synthesis occurs even in the absence of inflammation. Aspirin inactivates COX-2 but allows the synthesis of the intermediate 18*R*-hydroxy-EPA which is converted to RvE₁ through the action of 5-LOX. In nonneural cells, RvE₁ interacts with ChemR23 receptor (a specific seven-transmembrane G protein-coupled receptor) and inhibits inflammation by down-regulating NF-κB activation and blocking the generation of proinflammatory mediators (Adapted from Serhan et al., 2008)

binding to human polymorphonuclear leukocyte (PMN) (Arita et al., 2007). Intrathecal RvE₁ injection blocks spontaneous pain and heat and mechanical hypersensitivity evoked by intrathecal capsaicin and TNF-α. RvE₁ mediates its anti-inflammatory activity not only by decreasing neutrophil infiltration, paw edema, but also by inhibiting the expression of proinflammatory cytokine (Xu et al., 2010). In addition, RvE₁ not only abolishes transient receptor potential vanilloid subtype-1 (TRPV1)- and TNF-α-mediated excitatory postsynaptic current increases, but inhibits TNF-α-mediated *N*-methyl-D-aspartic acid (NMDA) receptor hyperactivity in spinal dorsal horn neurons via inhibition of the extracellular signal-regulated kinase (ERK) signaling pathway (Xu et al., 2010). It is suggested that resolvins may normalize the spinal synaptic plasticity associated with pain hypersensitivity (Fig. 2.4). In addition, resolving E₁ also prolongs the survival of solid organ transplants (Levy et al., 2010).

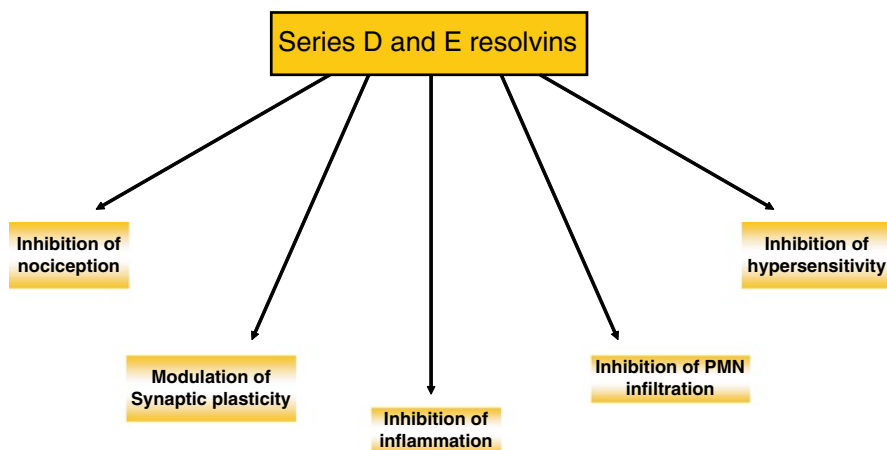


Fig. 2.4 Roles of resolvins in neural and non-neural tissues

RvE₁ mediates its actions through specific seven-membrane spanning G protein-coupled receptors, which are expressed on dendritic cells and monocytes. These receptors are called as ChemR23 receptors (Ohira et al., 2010). RvE₁ modulates the phosphorylation of Akt in a time- and dose-dependent manner in human ChemR23-transfected Chinese hamster ovary cells (Ohira et al., 2010). RvE₁ not only stimulates the phosphorylation of Akt, but also phosphorylates a downstream 30-kDa protein, which is identified as a ribosomal protein S6. The phosphorylation is blocked by a phosphatidylinositol 3-kinase (PtdIns 3K) inhibitor (wortmannin) and an ERK inhibitor (PD98059) but not by a p38-MAPK inhibitor (SB203580). Recent studies on RvE₁ metabolome indicate that RvE₁ is metabolized to several novel products by human polymorphonuclear leukocytes and whole blood as well as in murine inflammatory exudates, spleen, kidney, and liver. The new RvE₁-derived products include 19-hydroxy-RvE₁, 20-carboxy-RvE₁, and 10,11-dihydro-RvE₁. The metabolomic profiles of RvE₁ were species-, tissue-, and cell type-specific (Hong et al., 2008). Direct comparisons between RvE₁ and RvE₁-derived products indicate that 10,11-dihydro-RvE₁, 18-oxo-RvE₁, and 20-carboxy-RvE₁ display reduced bioactivity *in vivo*. At concentrations as low as 1 nM, RvE₁ stimulates macrophage phagocytosis. In addition, RvE₁ enhances phagocytosis of zymosan A by human macrophages, which are inhibited by PD98059 and rapamycin (mTOR inhibitor). Collectively, these studies indicate that RvE₁ initiates direct activation of ChemR23 and signals receptor-dependent phosphorylation. These phosphorylation-signaling pathways identified for RvE₁ receptor–ligand interactions emphasize the importance of endogenous pro-resolving agonists in resolving acute inflammation (Ohira et al., 2010).

The oxidation of RvE₁ by NAD⁺-dependent hydroxyprostaglandin dehydrogenase to the oxo product (18-oxo-RvE₁) results in inactivation of RvE₁ activity. Based on detailed pharmacological investigations on the effect of RvE₁, it is suggested that

the binding of RvE₁ to BLT₁ receptor mediate the resolution of inflammation (Arita et al., 2006, 2007). RvE₂ is synthesized from EPA by human PMNs and produces similar actions as RvE₁. When given together, the protective actions of RvE₁ and RvE₂ are additive at low doses, suggesting distinct receptors for RvE₂ and RvE₁ (Tjonahen et al., 2006). Collective evidence suggests that both RvE₁ and RvE₂ contribute to the beneficial actions of EPA in human diseases. RvE₁ and RvE₂ dramatically reduce dermal inflammation, peritonitis, dendritic cell migration, and interleukin production.

Similarly, in experimental model of pneumonia in mice, RvE₁ significantly decreases lung tissue levels of several proinflammatory chemokines and cytokines, including IL-1 β , IL-6, HMGB-1, MIP-1 α , MIP-1 β , keratinocyte-derived chemokine, and MCP-1, in a manner independent of the anti-inflammatory mediators IL-10 and lipoxin A4. In addition, animals treated with RvE₁ show a marked improvement in survival suggesting that RvE₁ administration may represent a novel therapeutic strategy for acute lung injury and pneumonia (Seki et al., 2010).

Non-enzymic oxidation of EPA generates cyclopentenone-IsoP (A_3/J_3 -IsoPs) (Brooks et al., 2008). Like ARA-derived IsoPs, the A_3/J_3 -IsoPs are formed in situ esterified in phospholipids and are then released in the free form by a PAF hydrolase like PLA₂. It is suggested that A_3/J_3 -IsoPs are generated after rearrangement of their endoperoxides precursors to molecules with E- and d-prostane rings that subsequently dehydrate. The oxidation products of EPA activate the Nrf2 transcription factor (a member of the basic leucine-zipper NF-E2 family) that induces antioxidant responses in reactive electrophiles-mediated induction of gene transcription (Gao et al., 2006, 2007). These genes include glutathione S-transferase, NADPH:quinone oxidoreductase 1, UDP-glucuronosyltransferase, gamma-glutamate cysteine ligase, and hemeoxygenase-1. They mediate detoxification and/or to exert antioxidant functions, thereby, protecting cells from genotoxic damage. The non-enzymic products of EPA interact with the ubiquitin ligase adaptor protein Keap1 (a BTB-Kelch protein), the direct inhibitor of Nrf2, initiating Keap1 dissociation from Cullin3 to yield Nrf2 translocation and activation causing induction of Nrf2-directed gene expression. Binding of Keap1 to Nrf2 directs the ubiquitination and proteasome-dependent degradation of Nrf2. Inhibition of Nrf2 ubiquitination results not only in Nrf2 accumulation, but also in increased ARE-directed gene expression, and an enhanced ability to respond to oxidant stress (McMahon et al., 2003). It is proposed that molecules containing an α,β -unsaturated carbonyl moiety, specifically J_3 -IsoPs, may be responsible for eliciting this biological activity (Gao et al., 2007). Thus, both enzymic and non-enzymic oxidation products of EPA modulate signal transduction processes associated with anti-inflammatory responses in neural and non-neural systems.

In addition, EPA is also metabolized by cytochrome P450 (CYP2C/2J)-isoforms, which convert EPA into 17,18-epoxyeicosatetraenoic (17,18-EEQ) acid. These omega-3 epoxides are highly active as antiarrhythmic agents. They suppress Ca²⁺-induced increased rate of spontaneous beating of neonatal rat cardiomyocytes, at low nanomolar concentrations (Arnold et al., 2010). Dietary EPA/DHA supplementation of rats results in substantial replacement of ARA by EPA in membranes from

heart, kidney, liver, lung, and pancreas, with less pronounced effects in brain. Changes in fatty acids are accompanied by concomitant changes in endogenous CYP metabolite profiles (e.g. altering the epoxyeicosatrienoic acids (EETs):17, 18-epoxyeicosatetraenoic (17,18-EEQ) and 19,20-epoxydocosapentaenoic acid (19,20-EDP) ratio from 87:0:13 to 27:18:55 in the heart). Collectively, these studies demonstrate that CYP-enzymes efficiently convert EPA to novel epoxy- and hydroxy-metabolites that may mediate some of the beneficial cardiovascular effects of dietary omega-3 fatty acids (Arnold et al., 2010).

2.4 DHA-Derived Lipid Mediators in the Brain

DHA is a precursor of D-series resolvins. The action of 15-LOX-like enzyme converts endogenous DHA into 17S-hydroperoxy-DHA (17S-H(p)DHA). This biosynthetic intermediate is transformed into several bioactive compounds, including resolvin D1-D6 (RvD₁, RvD₂, RvD₃, RvD₄, RvD₅, and RvD₆) (Figs. 2.5 and 2.6). There are

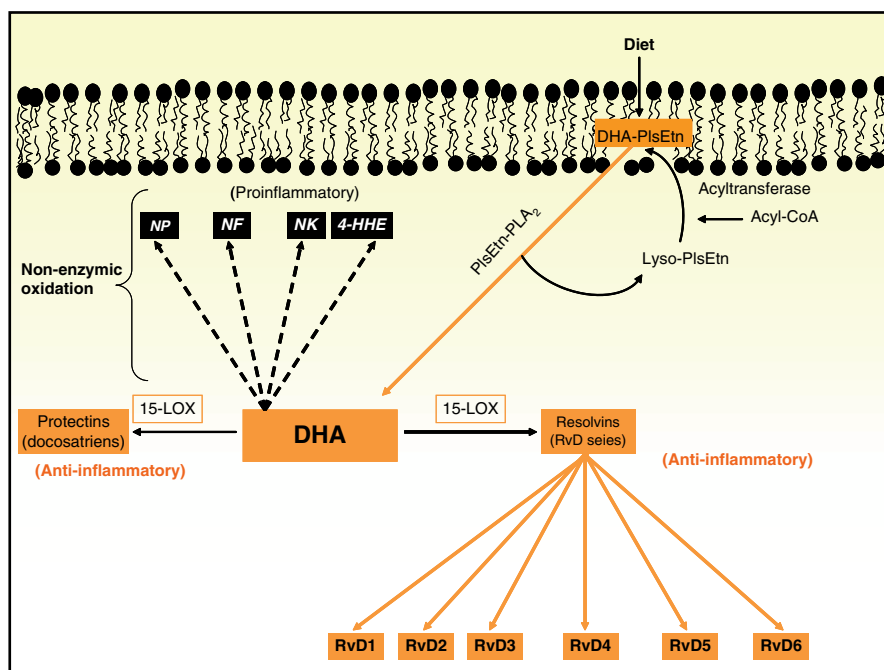


Fig. 2.5 Generation of enzymic and non-enzymic lipid mediators from DHA. Plasmalogen (*PlsEtn*); Plasmalogen-selective PLA₂ (*PlsEtn-PLA₂*); lyso-ethanolamine plasmalogen (*lyso-PlsEtn*); neuroprostane (*NP*); neurofuran (*NF*); neuroketal (*NK*); 4-hydroxyhexenal (*4-HHE*); Resolvin D (*RvD*)

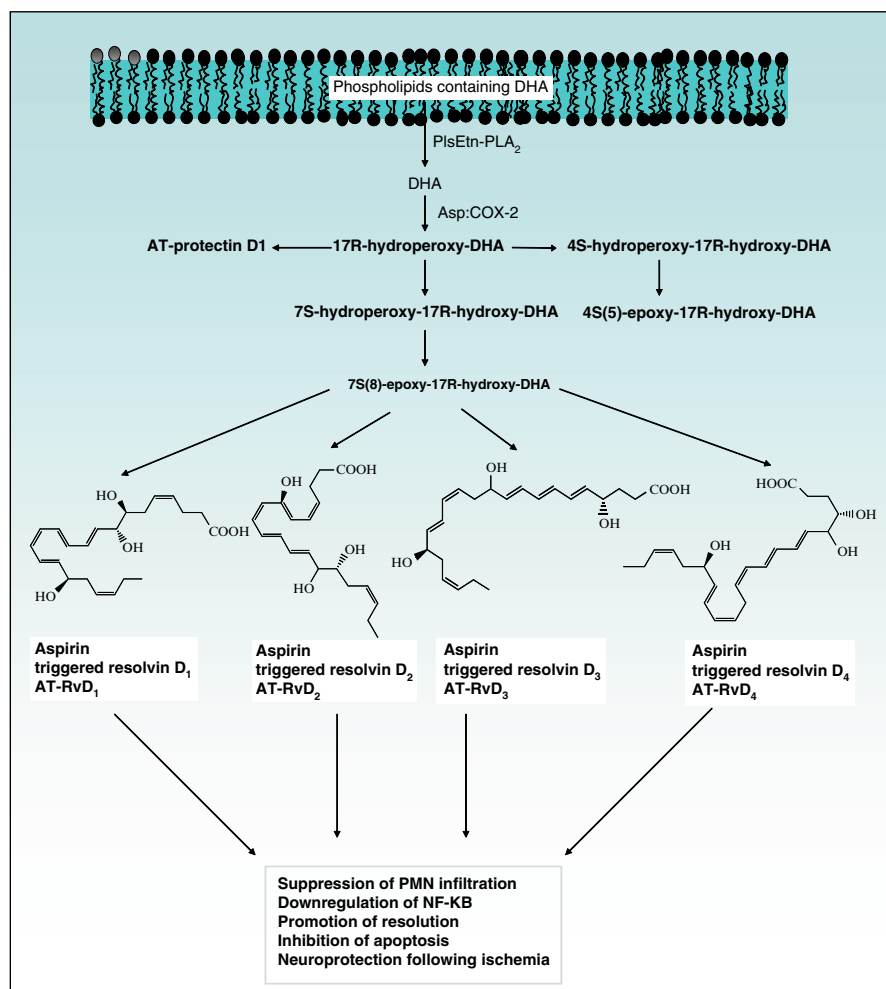


Fig. 2.6 Generation of resolvins D series from DHA in non-neural cells. DHA is released from PtsEtn by plasmalogen-selective PLA₂. Free DHA is metabolized in aspirin-COX-2 dependent manner into ATRvD₁, ATRvD₂, ATRvD₃, and ATRvD₄ through 7S(8)-epoxy-17R-hydroxy-DHA formation. Similar synthesis may occur in neural cells (Adapted from Serhan, 2005; Serhan et al., 2008)

also aspirin-triggered forms of D series resolvins (AT-Rv), which are also enzymically derived from DHA through a pathway with sequential oxygenation initiated by aspirin-acetylated COX-2 (Serhan and Chiang, 2008). For the biosynthesis of AT-RvDs, DHA is initially transformed into 17R-hydroxy-DHA. The stereochemistry at carbon 17 is maintained, so each AT-RvD carries a 17R alcohol group configuration, resulting in a distinct series of compounds. The complete stereochemistry of RvD₁ (7S,8R,17S,-trihydroxy-4Z,9E,11E,13Z,15E,9Z-docosahexaenoic acid) and

AT-RvD₁ (7S,8R,17R-trihydroxy-4Z,9E,11E,13Z,15E,19Z-docosahexaenoic acid has also been studied) (Serhan, 2005; Ariel and Serhan, 2007). These lipid mediators not only antagonize the effects of eicosanoids, but also modulate leukocyte trafficking and down-regulate the expression of cytokines in glial cells. They possess potent anti-inflammatory, neuroprotective and pro-resolving properties (Hong et al., 2003; Marcheselli et al. 2003; Serhan, 2005). Biosynthesis of neuroprotectin D₁ (NPD₁) involves the release of DHA by PlsEtn-PLA₂ or from PtdSer by Ptdser-selective PLA₂ or cPLA₂. Free DHA undergoes lipoxygenation and epoxidation followed by hydrolysis to form NPD₁. Thus far, binding sites for NPD₁ have been identified in retinal pigment epithelium cells and polymorphonuclear cells (Niemoller and Bazan, 2010) (Fig. 2.7). Like DHA, docosapentaenoic acid n-6 (DPAn-6; 22:5) also generates resolvins called 17S-HDPAn-6 (17S-hydroxydocosa-4Z,7Z,10Z,13Z,15E-pentaenoic acid) and 10S,17S-HDPAn-6 (10S,17S-dihydroxydocosa-4Z,7Z,11E,13Z,15E-pentaenoic acid). These resolvins like DHA-derived D series resolvins produce potent anti-inflammatory effects (Dangi et al., 2010). However, DPA-derived metabolites are not strong inhibitors of cytochrome-P450 enzymes. In brain tissue, initiation, intensification, and resolution of inflammation requires a distinct micro-environments composed of astrocytes, microglia endothelial cells, and highly specialized extracellular matrix (ECM) components of neural cells. At the conclusion of the inflammatory response, above neural cells also contribute to the process resolution by (a) the withdrawal of survival signals, (b) the normalization of chemokine gradients, and (c) the synthesis of lipoxins, resolvins and neuroprotectins inducing resolution programs that allow infiltrating cells to undergo apoptosis. The dysregulation of lipoxin, resolvin, and neuroprotectin may lead to persistent chronic inflammation, which can be remarkably stable.

2.4.1 17S D Series Resolvins

Resolvins act through specific receptors found in neural and non-neural cells. They are called as resolvin D receptors (resoDR₁) (Serhan et al., 2006a, b; Serhan et al. 2008a, b). ResoDR₁ induce potent anti-inflammatory and immunoregulatory activities. D series resolvin not only block the production of pro-inflammatory mediators, but also regulate the trafficking of leukocytes cells at the sites of inflammation (Serhan et al., 2008; Hong et al., 2003) and inhibit the expression of cytokines and modulate inflammation. Studies on characterization of ResoDR₁ are currently in progress.

2.4.2 Protectins and Neuroprotectin

15-LOX converts DHA into protectin D₁ through epoxide intermediate with epoxy group at the 16(17) position. The synthesis of PD₁ with complete stereochemistry

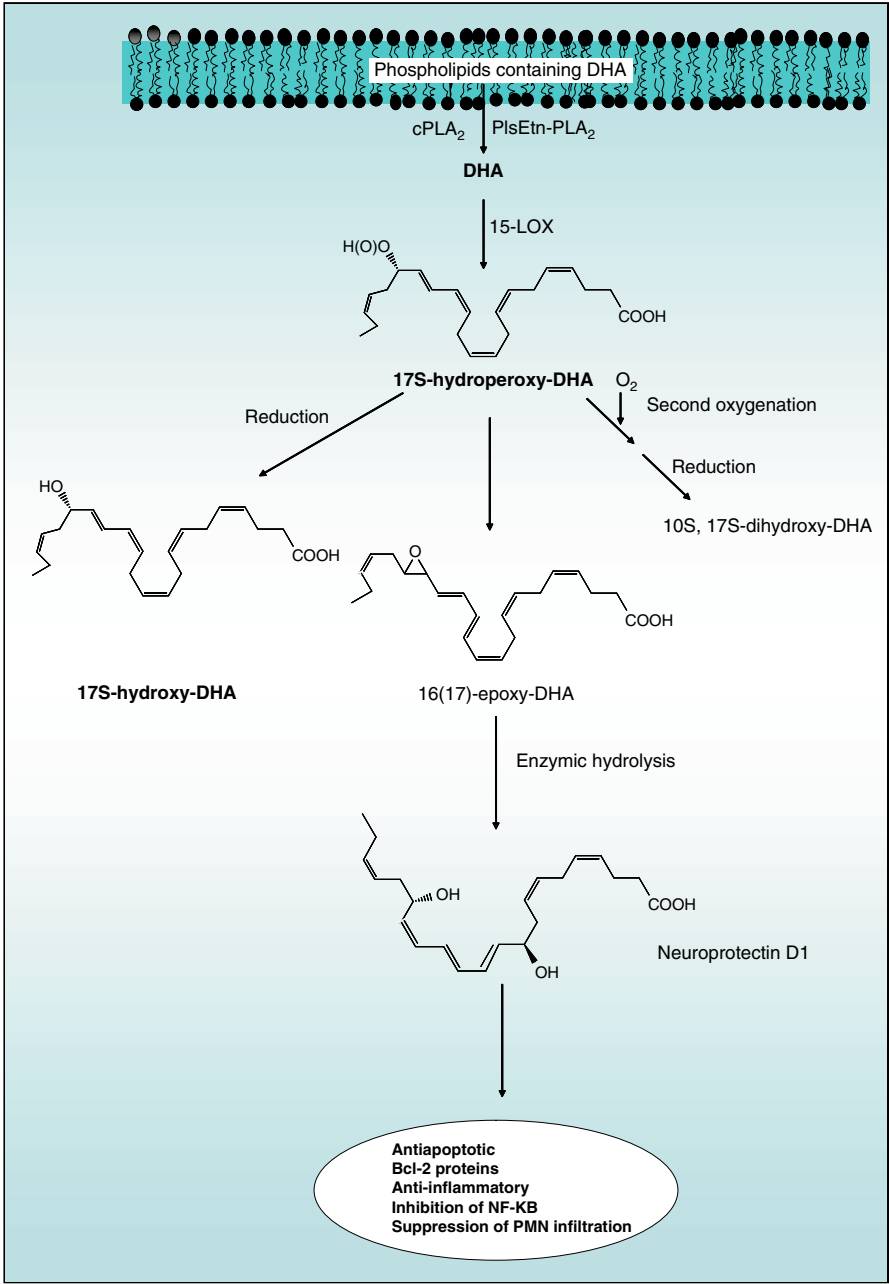


Fig. 2.7 Generation of neuroprotection D1 from DHA in brain. DHA is hydrolyzed from PlsEtn by PLA_2 . It undergoes lipoxygenation, epoxidation and hydrolysis to generate NPD_1 (Adapted from Serhan et al., 2008 and Marcheselli et al., 2010)

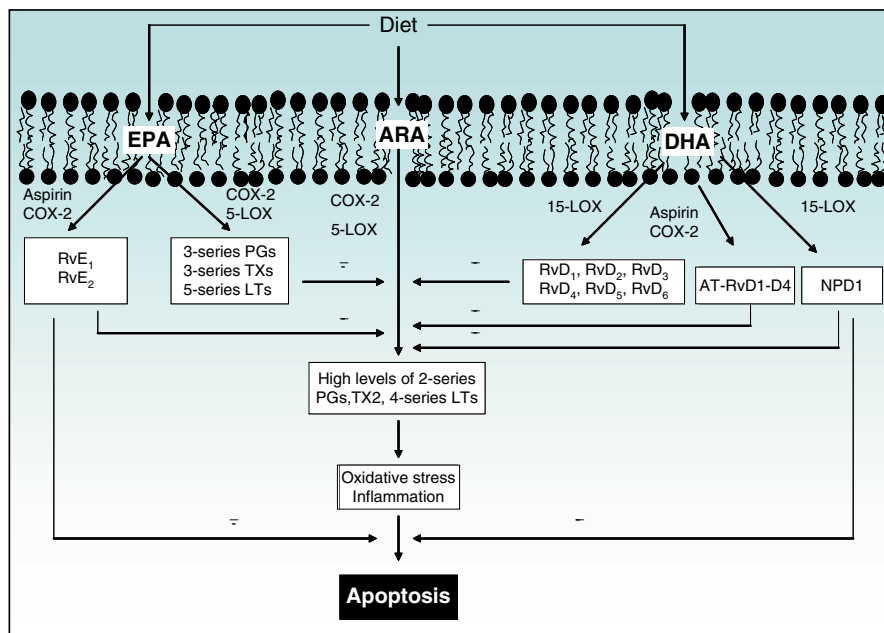


Fig. 2.8 Regulation of inflammation, oxidative stress, and apoptotic cell death by resolvins and neuroprotections

of PD₁ has been established and confirmed by total organic synthesis, showing that PD₁ is 10R,17S-dihydroxy-docosa-4Z,7Z,11E,13E,15Z,19Z-hexaenoic acid (Serhan et al., 2000, 2002, 2006b; Hong et al., 2003; Marcheselli et al., 2003). The reaction sequence of biosynthesis for PD₁ via the epoxide intermediate distinguishes it from the formation of the double dioxygenation product 10S,17S-dihydroxy-DHA. PD₁ is more potent than DHA in neuroprotective action. In sharp contrast, PD₁ positional isomers, including 4S,17S-diHDHA or 7S,17S-diHDHA, display less potent and non-selective actions. The occurrence of PD₁ has also been reported in brain, where it is called as neuroprotectin D₁ (10R, 17S-dihydroxy-docosa-4Z,7Z,11E,13E,15Z,19Z-hexaenoic acid, NPD₁) (Hong et al., 2003). Tritium-labeled NPD₁ (³H]-NPD₁) binds to ARPE-19 cells with high-affinity (K_d 31.3 ± 13.1 pmol/mg of cell protein). The stereospecific NPD₁ interactions with these cells provide potent protection against oxidative stress-mediated apoptosis (Fig. 2.8). ³H-NPD₁/PD₁ also shows specific and selective high affinity binding with isolated human neutrophils (K_d approximately 25 nM). Neither resolvin E₁ nor lipoxin A₄ compete for ³H-NPD₁/PD₁ specific binding with human neutrophils. Collectively, these results indicate that stereoselective specific binding of NPD₁/PD₁ with retinal pigment epithelial cells as well as human neutrophils may occur through specific receptors in both the immune and visual systems (Marcheselli et al., 2010). Although the isolation and characterization of 10(S),17(S)-dihydroxy-docosahexa-4Z,7Z,11E,13Z,15E,19Z-enoic acid, a main dihydroxy conjugated triene derived

from the lipoxygenation of DHA has also been reported, but nothing has been reported on its interactions with neural and non-neural cells. It is an isomer of protectin/neuroprotectin D1 (PD1/NPD1) and has been named PDX (Chen et al., 2009b). This metabolite inhibits human blood platelet aggregation at submicromolar concentrations.

Like resolvins, the neuroprotectins block the infiltration of PMN (Serhan et al., 2006b) (Figs. 2.4 and 2.7). They down-regulate the expression of cytokines in the glial cells (Hong et al., 2003; Serhan et al., 2006b). NPD₁ reduces retinal and corneal injury (Mukherjee et al., 2004; Gronert et al., 2005) and produces neuroprotective effect in ischemic injury (Marcheselli et al., 2003). Similarly, NPD₁ promotes neural cell survival via the induction of antiapoptotic and neuroprotective gene-expression programs that suppress A β 42-mediated neurotoxicity in Alzheimer disease (AD) (Lukiw et al., 2005; Bazan, 2009a, b). DHA and NPD1 protect synapses and decrease the number of activated microglia in the hippocampal system (Pomponi et al., 2008). Although the molecular mechanisms associated with the above processes are not fully understood. However, it is becoming increasingly evident that NPD₁ not only inhibits IL-1 β -stimulated expression of COX-2, but also regulates apoptotic signaling at the level of mitochondria, inducing the release of cytochrome *c* and activating effector enzyme, caspase-3 (Table 2.2). In addition in rat-infused with A β , DHA and its oxidative metabolites attenuate elevation in levels of lipid peroxides and ROS in the cerebral cortex and the hippocampus, indicating that DHA and its metabolites facilitate neuroprotection by down-regulating γ -secretase activity, an enzyme that liberates A β from soluble amyloid precursor protein- α (Lukiw et al., 2005). Furthermore, soluble amyloid precursor protein- α stimulates the synthesis of NPD₁ (Lukiw et al., 2005; Bazan, 2009a, b). Activities of key PLA₂ (PLsEtn-PLA₂ and cPLA₂) and 15-LOX, enzymes required for NPD₁ biosynthesis, are markedly increased in the AD hippocampal CA1 region (Farooqui et al., 1997, 2006; Farooqui, 2010b; Bazan, 2009a). Collective evidence suggests that DHA and its oxidative metabolites limit the generation and accumulation of the A β peptide, which is closely associated with the pathogenesis of AD. DHA and its metabolites also suppress several signal transduction pathways induced by A β , including two major kinases that phosphorylate the microtubule-associated protein tau and promote neurofibrillary tangle pathology (Farooqui, 2009).

It is recently shown that in macrophages DHA is also metabolized through a 14-LOX pathway resulting in generation of 7,14-dihydroxydocosa-4Z,8,10,12,16Z,19Z-hexaenoic acid. This metabolite is called as maresin (MaR1) (Fig. 2.9). This metabolite not only terminates PMN infiltration, but also stimulates macrophage phagocytosis. An isomer of MaR1, 7S,14S-diHDHA, acts less potently than MaR1. This suggests that these DHA-derived metabolites may be stereoselectively regulate catabasis and facilitate arrival of tissues to homeostasis (Serhan et al., 2009).

In retina, epithelium-derived factor acts as an agonist and induces the synthesis of NPD₁ and thus promoting NPD₁-mediated paracrine and autocrine signal transduction processes. Also, DHA and epithelium-derived factor not only synergistically activates NPD₁ generation and antiapoptotic protein expression, but also

Table 2.2 Effects of resolvins and neuroprotectins in animal models of neural and non-neural diseases

Animal model	Effect of resolvins/ neuroprotectin	Molecular mechanism	Reference
Stroke	Beneficial	Decrease in proapoptotic Bcl-2 expression and inhibition of caspase-3; induction of neuroprotective gene-expression	Serhan et al., 2000, 2002; Mukherjee et al., 2007; Bazan, 2009a, b
Alzheimer disease	Beneficial	Decrease in proapoptotic Bcl-2 expression and inhibition of caspase-3; induction of neuroprotective gene-expression	Serhan, et al., 2000, 2002; Mukherjee et al., 2007; Bazan, 2009a, b
Inherited retinal degeneration	Beneficial	Decrease in proapoptotic Bcl-2 expression and inhibition of caspase-3; induction of neuroprotective gene-expression	Serhan, et al., 2000, 2002; Bazan, 2009a, b
Periodontal disease	Beneficial	Inhibition of proinflammatory cytokine expression	Serhan et al., 2000, 2002; Serhan, 2008; Seki et al., 2009
Inflammatory bowel disease	Beneficial	Inhibition of proinflammatory cytokine expression	Serhan et al., 2000, 2002; Serhan, 2008; Seki et al., 2009
Asthma	Beneficial	Inhibition of proinflammatory cytokine expression	Serhan et al., 2000, 2002; Seki et al., 2009
Bacterial pneumonia	Beneficial	Inhibition of proinflammatory cytokine expression	Serhan et al., 2000, 2002; Seki et al., 2010
Acute lung injury	Beneficial	Inhibition of proinflammatory cytokine expression	Serhan et al., 2000, 2002; Seki et al., 2010

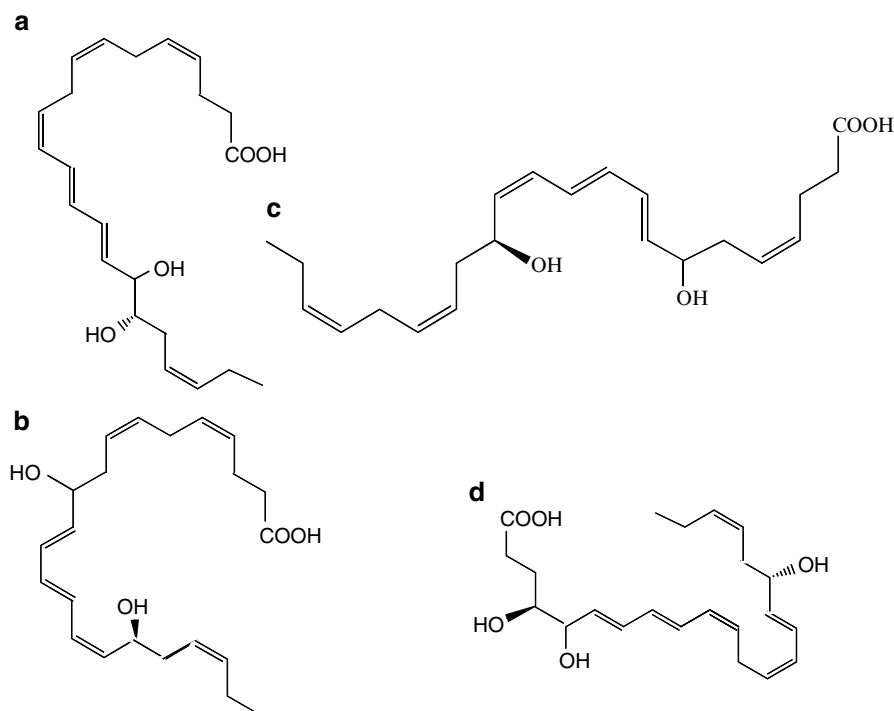
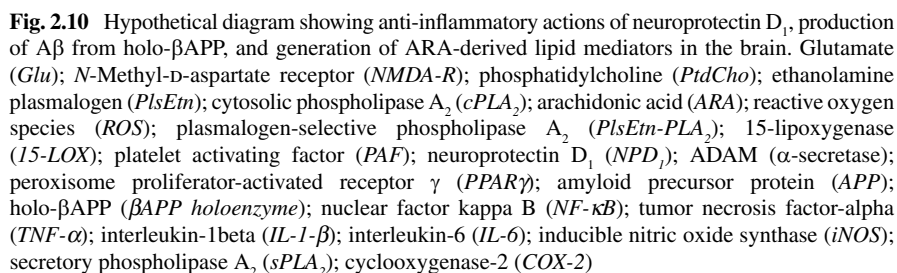


Fig. 2.9 Chemical structures of docosahexaenoic acid and docosanoids. 16,17S-docosatriene (a); 10,17S-docosatriene (b); maresin (c); and 4S,17S-resolvin (d). These metabolites inhibit inflammation by retarding the actions of eicosanoids

down-regulates proapoptotic Bcl-2 protein expression and activation of caspase 3 during oxidative stress (Mukherjee et al., 2007). NPD_1 also promotes AKT translocation and activation and interacts with PPAR-gamma family of ligand-activated nuclear receptors, which may be involved in various aspects of neuroinflammation and neurodegeneration (Palacios-Pelaez et al., 2010; Niemoller and Bazan, 2010; Farooqui, 2010a, c). Receptors for NPD_1 have not been characterized in brain tissue, but their occurrence has been suggested (Hong et al., 2003; Marcheselli et al., 2003; Mukherjee et al., 2004). Thus, NPD_1 -mediated regulation targets upstream events of brain cell apoptosis and modulation of neuroinflammatory signaling promote the cellular homeostasis, and restoration of brain damage through above-mentioned mechanisms. This is tempting to speculate that the generation of DHA-derived resolvins, neuroprotectins, maresin, and synthesis of ARA-derived lipoxins may be internal neuroprotective mechanisms that block neuroinflammation and apoptosis-mediated brain damage caused by neurotraumatic and neurodegenerative diseases (Serhan, 2005; Bazan, 2009a, b; Farooqui, 2010b).

Investigators are using lipidomics, proteomics and genomics techniques to identify and determine levels of ARA, EPA and DHA-derived lipid mediators (F_2 -isoprostanes, eicosanoids, lipoxins, resolvins, and NPD_1) (Serhan et al., 2006b,

2008; Ariel and Serhan, 2007; Brooks et al., 2008; Bazan, 2009a, b) and developing diagnostic test in cerebrospinal fluid (CSF) from patients with acute neural trauma, neurodegenerative, and neuropsychiatric diseases. The use of proteomic strategies for characterizing resolvin and neuroprotectin metabolizing enzymes in subcellular organelles of human brain and CSF may provide new information on properties and therapeutic targets. Resolvin and neuroprotectin synthesizing and catabolizing enzymes not only control the levels of these lipid mediators in normal and diseased brain, but also modulate physiology and pathology of chronic brain diseases. Collectively, these studies suggest that combining lipidomics, proteomics, and genomics techniques may greatly enhance the existing knowledge of molecular mechanism associated with homeostasis between inflammation inducing mediators (eicosanoids and platelet activating factor) and inflammation blocking lipid mediators (lipoxins, resolvins, and neuroprotectins) in neural trauma, neurodegenerative and neuropsychiatric diseases (Serhan et al., 2006b, 2008; Brooks et al., 2008; Bazan, 2009a, b; Farooqui, 2010a). Information about the temporal and spatial positioning of inflammation inducing and inflammation blocking pathways in brain may not only be dictated by anti-inflammatory drugs but also by the diet. The Western diet has extremely high levels of omega-6 fatty acids with ARA to DHA of about 20:1. The Paleolithic diet on which human beings have evolved, and lived for most of their existence, had a ratio of 2–1:1, and was high in fiber, rich in fruits, vegetables, lean meat, and fish (Simopoulos, 2002, 2008; Cordain et al., 2005). The high intake of ARA enriched food in Western diet not only elevates levels of eicosanoids and platelet activating factor, but also upregulates the expression of proinflammatory genes including genes for cytokines (TNF- α and IL-1 β), secretory phospholipase A₂, cyclooxygenase-2, and nitric oxide synthase. In contrast, consumption of DHA-enriched diet has anti-inflammatory effects that are partly mediated by repression of genes that code for pro-inflammatory cytokines. Since Western diet is low in DHA and high in ARA, it is linked to many chronic visceral diseases as well as neurodegenerative and neuropsychiatric disorders (Simopoulos, 2002, 2008; Cordain et al., 2005; Farooqui, 2009). Enrichment of DHA in Western diet may improve inflammation and oxidative stress in neurotraumatic and neurodegenerative diseases not only through the effects of DHA on physicochemical properties of neural cell membranes, but also through modulation of genes and generation of resolvins Ds and neuroprotectins. It is worth noting that in AD transgenic mice dietary DHA restores cerebral blood volume, reduces A β deposition, and ameliorates A β pathology (Green et al., 2007). Although molecular mechanisms associated with above processes are not fully understood, recent studies indicate that in 3xTg-AD mouse models and human neuronal-glia (HNG) cells in primary culture, NPD₁ not only down-regulates A β 42-mediated expression of the pro-inflammatory enzyme COX-2 (Fig. 2.10), but also reduces the expression of B-94, a TNF- α -inducible pro-inflammatory element resulting in inhibition of apoptosis. Moreover, NPD₁ suppresses A β 42 peptide shedding by down-regulating β -secretase-1 (BACE1) while activating the α -secretase ADAM10 and up-regulating sAPP α , thus shifting the cleavage of β APP holoenzyme from an amyloidogenic into the non-amyloidogenic pathway (Zhao et al., 2011). It is also shown that anti-amyloidogenic



effects of NPD₁ are mediated in part through activation of the PPAR γ receptor, while NPD₁-induced stimulation of non-amyloidogenic pathways is PPAR γ -independent. In summary, NPD₁ potentially down-regulates inflammatory signaling, amyloidogenic APP cleavage and apoptosis, supporting the potential of this lipid mediator in rescuing human brain cells in early stages of neurodegenerations (Zhao et al., 2011). In spite of above laboratory observations, to date studies on the dietary intervention of n-3 PUFA in AD have so far failed. It is proposed that long-term DHA supplementation may not only restore signal transduction processes associated with behavioral deficits and learning activity, but also produce several neuroendocrinological and immunological effects on brain tissue, which may be beneficial in neurotraumatic, neurodegenerative, and neuropsychiatric diseases (Farooqui, 2010a, c).

2.5 Conclusion

EPA and DHA-derived lipid mediator resolvins and protectins/neuroprotectins regulate immune systems by modulating signal transduction processes associated with neuroinflammation and neurodegeneration. EPA-derived E-series resolvins (i.e., RvE₁ and RvE₂) and DHA-derived D-series resolvins (RvD₁ and RvD₂) have potent anti-inflammatory and pro-resolution properties. They retard excessive inflammatory responses and promote resolution by enhancing clearance of apoptotic cells and debris from inflamed brain tissue. These actions may underlie the beneficial effects of EPA and DHA in human health and neurotraumatic and neurodegenerative diseases.

Aspirin initiates resolution by triggering biosynthesis of specific epimers of resolvins and protectins. In addition to their synthesis in resolution, these lipid mediators also display potent protective roles in neural systems, liver, lung, and eye. Potent actions of resolvins and protectins in models of chronic human disease indicate that down-regulation in resolution pathways may contribute to the pathogenesis of many chronic neurodegenerative and visceral diseases.

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