

Review

Dynamic Role of Phospholipases A2 in Health and Diseases in the Central Nervous System

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Abstract: Phospholipids are major components in the lipid bilayer of cell membranes. These molecules are comprised of two acyl or alkyl groups and different phospho-base groups linked to the glycerol backbone. Over the years, substantial interest has focused on metabolism of phospholipids by phospholipases and the role of their metabolic products in mediating cell functions. The high levels of polyunsaturated fatty acids (PUFA) in the central nervous system (CNS) have led to studies centered on phospholipases A2 (PLA2s), enzymes responsible for cleaving the acyl groups at the *sn*-2 position of the phospholipids and resulting in production of PUFA and lysophospholipids. Among the many subtypes of PLA2s, studies have centered on three major types of PLA2s, namely, the calcium-dependent cytosolic cPLA2, the calcium-independent iPLA2 and the secretory sPLA2. These PLA2s are different in their molecular structures, cellular localization and, thus, production of lipid mediators with diverse functions. In the past, studies on specific role of PLA2 on cells in the CNS are limited, partly because of the complex cellular make-up of the nervous tissue. However, understanding of the molecular actions of these PLA2s have improved with recent advances in techniques for separation and isolation of specific cell types in the brain tissue as well as development of sensitive molecular tools for analyses of proteins and lipids. A major goal here is to summarize recent studies on the characteristics and dynamic roles of the three major types of PLA2s and their oxidative products towards brain health and neurological disorders.

Keywords: phospholipases A2; central nervous system; lysophospholipids; oxidized fatty acids; oxylipins; stroke; Alzheimer's disease



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1. Introduction

Phospholipids are the major component of the membrane lipid bilayer in mammalian cells. These molecules are comprised of two acyl or alkenyl chains, a glycerol backbone and several different phospho-base groups (ethanolamine, choline, serine and inositol). Membrane phospholipids are substrates of phospholipases A1, A2, C and D, enzymes producing small molecules that serve as mediators with important functional roles in cell metabolism (Figure 1). While phospholipases A1 (PLA1s) and PLA2s are responsible for cleavage of the acyl groups at the *sn*-1 and *sn*-2 positions of glycerophospholipids, respectively, their actions also result in the production of lysophospholipids (phospholipids with one acyl chain), molecules known to possess detergent-like properties. PLA2s are comprised of a large group of superfamily (more than 50 subtypes) based on their calcium dependence and cellular localization. These enzymes not only play important role in remodeling cell membrane structure and homeostasis, but also engage in different aspects of cell metabolism through specific signaling pathways [1,2]. Over the years, substantial

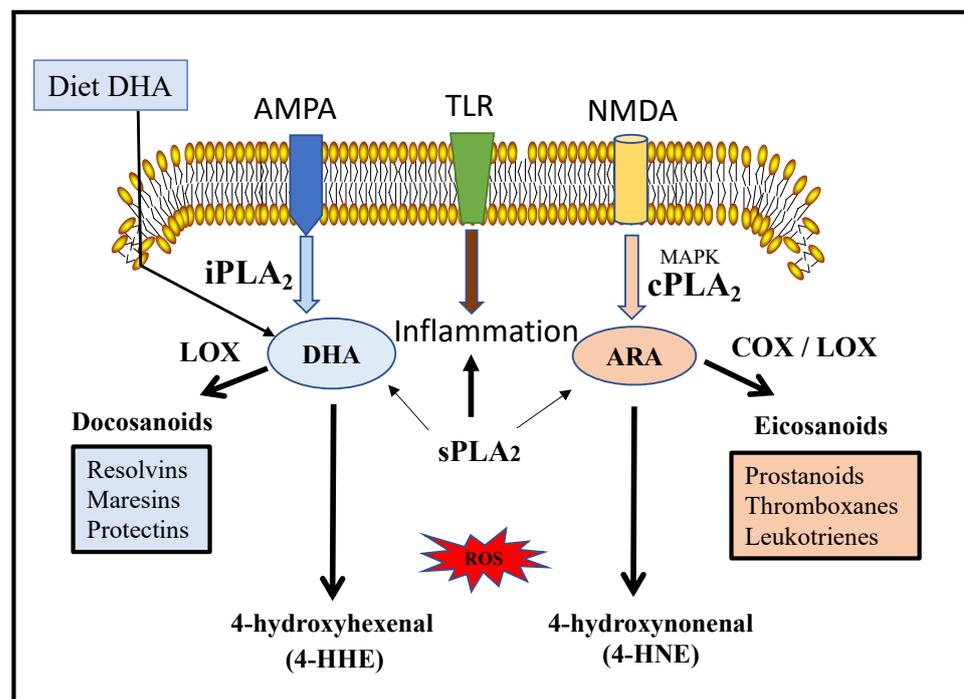


Figure 2. Receptor- signaling pathways for iPLA₂, sPLA₂ and cPLA₂ leading to production of docosahexaenoic acid (DHA) and arachidonic acid (ARE). In turn, DHA and ARA are metabolized by cyclooxygenases (COX) and lipoxygenases (LOX) to produce docosanoids and eicosanoids and undergo peroxidation to produce 4-hydroxyhexenal (4-HHE) and 4-hydroxynonenal (4-HNE), respectively. Abbreviations: AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor, TLR, Toll-like receptors, NMDA, N-methyl-D-aspartate receptor.

2. Structure and Function of cPLA₂

Cytosolic phospholipases A₂ (cPLA₂s) are intracellular enzymes with 749 amino acids and a molecular weight around 85 kDa. The cPLA₂ family is comprised of six isoforms, namely, cPLA₂ α , β , γ , δ , ϵ and ζ [1]. Except for cPLA₂ γ , which lacks the C-domain, other cPLA₂s subgroups are characterized by the presence of a highly conserved C2 domain for binding Ca²⁺ and the C-terminal domain containing the catalytic active site using the Ser-Asp dyad for catalysis [7]. The catalytic domain also contains a number of serine residues and Ser505, 515 and 727 are susceptible for phosphorylation by a number of protein kinases including the Mitogen-activated protein kinases (MAPKs), Ca²⁺ /calmodulin-dependent protein kinase II (CAMKII) and mitogen-activated protein interacting kinases (MNK1) [8]. Phosphorylation of cPLA₂ increases phospholipid binding at low calcium concentration and facilitates translocation of enzyme in the cytoplasm to different intracellular organelles including the nuclear, mitochondrial, lysosomal and the plasma membranes [9]. cPLA₂ also interacts with other lipid molecules, such as ceramide-1-phosphate and phosphatidylinositol bisphosphate (PIP₂), although how these lipids modulate enzyme activity remains to be further investigated [8]. More recently, lactosylceramide (LacCer) has been found to bind cPLA₂ in the C-2 domain and in CHO-W11A cells, LacCer could trigger cPLA₂ activity resulting in the release of ARA [10]. In a study with astrocytes, increase in cPLA₂ activity due to LacCer was linked to promotion of inflammation and neurodegeneration in the mouse model of experimental autoimmune encephalomyelitis (EAE) [11]. Interestingly, besides binding with cPLA₂, LacCer can also interact with NADPH oxidase to generate reactive oxygen species (ROS) and subsequently engage in inflammatory diseases such as atherosclerosis and cancer [12].

Among many subtypes of cPLA₂s, cPLA₂ α is probably the most studied. This cPLA₂ appears to be present ubiquitously in all brain cells, including neurons, astrocytes and microglia [5]. In an in vitro study with primary neurons, stimulation of neurons with the

excitatory glutamate receptor could result in rapid activation of the Ras/Raf/MEK/ERK pathway and subsequently phosphorylation of cPLA2 [13]. In microglial cells, stimulation of the Toll-like receptor with lipopolysaccharide (LPS) could induce ERK1/2-dependent cPLA2 phosphorylation and upregulation of the inflammatory pathway involving NF- κ B [14,15]. A more recent study using quantitative proteomics also identifies upregulation of NF- κ B associated inflammatory proteins upon treatment of microglial cells with LPS [16]. Taken together, these studies demonstrate the role of protein kinases for phosphorylation of cPLA2 in neuronal excitation and glial inflammation.

Substantial evidence has indicated cPLA2 to preferably target phosphatidylcholine (PC) and release ARA and lysophosphatidylcholine (LPC) [17]. ARA is a key substrate of cyclooxygenases (COX), lipoxygenases (LOX) and cytochrome P450 and depending on the cell type, these reactions result in synthesis of oxygenated products such as prostaglandins, leukotrienes and thromboxane B2 (Figure 2). Except for lipoxin, these ARA-derived lipid mediators are known to mediate inflammatory responses through acting on receptors in a cell-specific manner. Studies to elucidate the role of cPLA2 on neuro-inflammatory events include using genetic deletion, antisense oligonucleotides and cPLA2 specific inhibitors [18–22]. In studies using cell and animal models, arachidonyl trifluoromethyl ketone (AACOCF3 or ATK) has been successfully used to suppress cPLA2 activity and production of eicosanoids [17,23,24]. AACOCF3 also mitigates cPLA2-induced pathology in cardiovascular disease in mouse model, in human aortic smooth muscle cells [25] and in type II alveolar epithelial cells exposed to cigarette smoke condensate [26].

3. cPLA2 in Cerebral Ischemia, Spinal Cord and Traumatic Brain Injury

3.1. Cerebral Ischemia

Early studies have implicated the role of PLA2 in the rapid release of PUFA in brain due to different forms of brain injuries [27]. Studies with animal models have demonstrated increases in oxidative stress, neuronal excitation and glial cell activation, which are factors contributing to stimulation of cPLA2 in cerebral ischemia. However, due to the complex cellular makeup of the brain tissue, studies to examine the role of PLA2 in neurons, astrocytes and microglial in animal models of ischemic stroke have not been forthcoming. Under the ischemic condition, PLA2-induced release of PUFA is exacerbated by the lack of oxygen supply and decrease in ATP required for conversion of the fatty acids to their acyl-CoA. Consequently, perturbation of the deacylation-reacylation cycle mediated by phospholipases A2 and acyltransferases is an important factor for alterations of cellular phospholipids and PUFA during cerebral ischemia [1,28]. Interestingly, stroke-mediated increase in PUFA in brain can also be observed in plasma, thus making analysis of PUFA in plasma a useful marker for assessing the extent of brain damage in stroke patients [29].

3.2. Traumatic Brain Injury (TBI)

Stimulation of cPLA2 and the resulted release of ARA and lipid mediators are important factors leading to inflammation and pain in TBI. In a mouse cortical impact model, administration of AACOCF3, the cPLA2 inhibitor, could mitigate impaired autophagy that led to neuronal cell death [9]. AK106-001616, another selective inhibitor of cPLA2 could reduce the prostaglandin E2 (PGE2) and leukotriene B4 (LTB4) production in cells and in models of inflammation, neuropathic pain and pulmonary fibrosis [30]. These studies demonstrated the important role of cPLA2 in inflammatory events associated with TBI. At a subcellular level, cPLA2 was found to play a role in TBI-induced changes in lysosomal membrane permeability, leading to subsequent neuronal impairment [9]. In this study, increase in phosphorylation of cPLA2 was detected as early as 1 h after TBI and analysis of lysosomal membranes indicated decreases in phospholipids with PUFA, such as phosphatidylcholine (PC) 18:0/20:4, PC 18:0/22:6, phosphatidylethanolamine (PE) 16:0/22:6 and PE-p 18:0/22:6, 16:0/22:6 and 18:0/20:4 and increases in lysophosphatidylcholine (LPC) 16:0, 18:0 and lysophosphatidylethanolamine (LPE) 18:0. Similarly, administration

of arachidonyl trifluoromethyl ketone (AACOCF₃) could normalize changes in lysosomal membrane lipids and attenuate neuronal cell death [9].

3.3. Spinal Cord Injury (SCI)

SCI is also associated with increase oxidative stress, neuroinflammation, glial activation and lipid peroxidation. In a study with a rat spinal cord contusion model, rapid elevation of p-cPLA2 was observed 2 h after injury and the increase in cPLA2 protein expression remained prominent up to 7 days after SCI [31]. In this SCI model, cPLA2 was shown to play an important role in the secondary injury cascade and inhibition of cPLA2 at 30 min postinjury could ameliorate SCI-induced motor deficits and reduce cell loss and tissue damage [32].

4. cPLA2 in Other Neurodegenerative Diseases

Alzheimer's Disease (AD)

Alzheimer's disease (AD) is a major neurodegenerative disease marked by the deposition of amyloid plaques and neurofibrillary tangles in the brain. A number of studies have implicated the role of cPLA2 in release of ARA and increase in oxidative/nitrosative pathways in AD [33–35]. The increasing focus on PLA2 is due to a link with their products to synaptic involvement in learning and memory [36–38]. In a recent study with the 5xFAD transgenic mice, changes in lipid species, such as an increase in lysophospholipids in the hippocampus, provided support to the increase in PLA2 activity in AD brain [39]. In a more recent study with the APP knock-in (App^{N-G-F/N-G-F}) mice, there was evidence for a more aggressive A β accumulation, reactive gliosis and cognitive deficits as compared to other transgenic mouse models [40,41]. The APP knock-in mice also showed increase in cPLA2 levels in the brain [42]. A study using an unbiased lipidomic approach and biochemical assessments in different AD mouse models indicated changes in the Land's cycle activity, such as an age-dependent increase in lysophosphatidylcholine level and cPLA2 activity and changes in phospholipids were marked by a progressive decline in behavior and memory [43]. However, since there are many PLA2 subtypes in different brain cells, more studies are needed to better define the lipid changes in a subcellular and subregion level. In a study with aged (16-month-old) transgenic Tg2576 AD mice, a subgroup (20%) of mice showed resilience to the spatial memory test. Genetic analysis of this subgroup unveiled the possible role of PLA2G4E (cPLA ϵ) associated with the resilience to the spatial memory [44]. This finding may have important implication as analysis of AD patients also showed a defect in this cPLA ϵ gene. Moreover, in a study with the APP/PS1 mice, administration of adeno-associated viral vector of the cPLA ϵ gene to hippocampal neurons could restore the cognitive defects in these mice [44].

There is growing evidence that amyloid beta peptide (A β) released from amyloid precursor protein (APP) can become cytotoxic upon aggregation to oligomeric form [45]. Our earlier studies with astrocytes demonstrated the ability of oligomeric amyloid beta (oA β) to activate cPLA2 and alter membrane physical properties [46] and mitochondrial function [47]. Aggregated A β _{1–42} was shown to stimulate cPLA2 phosphorylation in cortical neurons and regulation memory deficits and neuronal apoptotic cell death [13,38,48–50]. Studies further showed the ability of oA β to activate inflammatory pathways in microglia and in turn, cPLA2 played a role in microglial functions including uptake of amyloid beta [51,52]. In these studies, antisense oligonucleotide against cPLA2 could abrogate the oxidative events and neuronal damage [49]. In addition, both azelnidipine (ALP), a dihydropyridine calcium channel blocker known for its treatment of hypertension and methylarachidonyl fluorophosphate (MAFP), a cPLA2 inhibitor, also suppressed oA β -induced translocation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF κ B) p65 subunit to nuclei in cerebral endothelial cells, suggesting that cPLA₂ activation and calcium influx are essential for oA β -induced NF κ B inflammation [53].

Since apolipoprotein E4 (APOE4) has been identified as a prevalent genetic risk factor driving the development of AD, recent studies have attempted to link lipid peroxidation

products such as 4-hydroxynonal (HNE) which can bind with different APOE cysteine residues [54]. There is evidence for higher levels of cPLA2 expression in AD patients carrying APOE 3/4 as compared to APOE 3/3 genotype [55]. In this latter study, astrocytes isolated from mice transfected with human APOE4 also showed greater levels of inflammatory markers, such as reactive oxygen species (ROS) and inducible nitric oxide synthase (iNOS), as compared with mice transfected with APOE3 [55]. Furthermore, inhibition of cPLA2 could abrogate the increase in inflammation in APOE4-TR mice. Taken together, these results suggest the important role of cPLA2 in exerting greater inflammatory activities in brain of APOE4 genotype. Expectedly, more studies are needed to examine underlying mechanism(s) whereby cPLA2 and its downstream products may play a role in driving the AD pathology, especially those associated with the E4 allele.

5. Structure and Function of iPLA2

Group VI (GVI) phospholipases A2, also known as iPLA2, belong to the group of calcium-independent phospholipases A2. Currently, six subgroups of iPLA2 have been identified: GVIA (iPLA2 β ; PNPLA9), GVIB (iPLA2 γ ; PNPLA8), GVIC (iPLA2 δ ; PNPLA6), GVID (iPLA2 ϵ ; PNPLA3), GVIE (iPLA2 ζ ; PNPLA2) and GVIF (iPLA2 η ; PNPLA4) [56]. Molecular weights of these subgroups of iPLA2 range from 84 to 91 kDa, depending on the cellular localization. All GVI PLA2s have a patatin-like lipase domain and share a GXSXG catalytic motif together with multiple strings of ankyrin motif [2,57]. Among the subgroups, GVIA PLA2 (iPLA2 β) and GVIB PLA2 (iPLA2 γ) are the most studied [2].

5.1. GVIA PLA2 (iPLA2 β)

GVIA PLA2 (iPLA2 β) is an 85 kDa protein with 752 amino acids [56]. This enzyme is widely present in the peripheral organs as well as in the CNS and is thus regarded as the most prominent phospholipase playing a house-keeping role for maintaining membrane homeostasis [58]. In addition, GVIA PLA2 also plays a role in cell proliferation, cell death and signal transduction and thus posts impact on diseases including cancer, cardiovascular abnormalities, glaucoma, periodontitis and nerve degeneration [56,59]. In recent years, deficiency in iPLA2 β has been reported to elevate mitochondrial lipid peroxidation, resulting in mitochondrial dysfunction [60]. Mutation of this PLA2 also results in reduction of mitochondrial potential, leading to attenuation of calcium uptake and calcium retention capacity in mitochondria [61]. Studies on iPLA2 have been aided by the specific inhibitor, bromoenol lactone (BEL). In hippocampal pyramidal neurons, inhibition of iPLA2 by BEL increases amplitude of the AMPA receptor activity [62].

Studies on iPLA2 β indicate that this is the major phospholipase responsible for the release of DHA from glycerophospholipids [63–65]. In an earlier study, iPLA2 β ^{-/-} and iPLA2 β ^{+/+} mice infused intravenously with [1-¹⁴C]-DHA demonstrated a significant decrease in baseline activity for uptake of labeled DHA by the iPLA2 β ^{-/-} mice [64]. Studies with iPLA2 β KO mice also showed a decrease rate of incorporation of unesterified DHA from plasma into brain phospholipids and, thus, resulted in alterations of the brain fatty acids and lysophospholipids in the knockout (KO) mouse brain [66]. Interestingly, depletion of iPLA2 β is marked by an increased in mRNA and activity of cPLA2 α , suggesting presence of a compensatory metabolic link between these two types of PLA2s. iPLA2 β KO mice show minimal neuropathology during birth but with increasing age, there is evidence for motor disturbances, cerebellar neuron loss and striatal α -synuclein accumulation. In addition, the aged iPLA2 β KO mice also exhibit activations of microglia and astrocytes and increase in tumor necrosis factor α (TNF α) and iNOS) production, suggesting the role of this PLA2 in mediating oxidative and inflammatory events with increasing age [63].

5.2. iPLA2 γ

iPLA2 γ is a membrane-bound enzyme with 782 amino acids and molecular weight of 90 kDa. This enzyme has the lipase consensus sequence Gly-X-Ser-X-Gly in the C terminal and a Ser-Asp dyad active site in the catalytic domain [67]. iPLA2 γ also shows a motif

for mitochondrial localization in the N-terminal and a nucleotide binding motive together with a peroxisome localization signal at the C terminal [67]. While the S-enantiomer of BEL is known to preferably inhibit iPLA2 β , iPLA2 γ is preferably inhibited by the R-enantiomer. Interestingly, there is evidence that iPLA2 γ can interact with both diacyl and alkenyl acyl form of phosphatidylcholine (PC) and phosphatidylethanolamine (PE) as well as hydrolysis of fatty acids in either *sn*-1 or *sn*-2 position [67]. In agreement with the mitochondrial localization, iPLA2 γ KO mice show aberrant mitochondria structure with swelling and abnormal cristae in the hippocampus. Genetic deletion of iPLA2 γ also shows decrease in cardiolipin (CL), the specific phospholipid in mitochondrial membrane. There is further evidence for iPLA2 γ to target oxidized CL [68,69]. Some of these activities may be due to the putative serine residues in this molecule, rendering it susceptible to phosphorylation by protein kinases including protein kinase C (PKC) and extracellular signal-regulated kinase (ERK) [70,71]. Obviously, more studies are needed to better understand the role of these protein kinases in mediating activity of the enzyme under different conditions. iPLA2 γ deficiency is shown to enhance α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor destabilization and tau phosphorylation [72] and AMPA receptor overstimulation in hippocampus may play an important role in neuron cell death [73].

6. iPLA2 and Neurological Diseases

Mutations of GVI PLA2 gene have been shown to cause a number of neurological abnormalities including infantile neuroaxonal dystrophy (INAD), neurodegeneration with brain iron accumulation (NBIA), autosomal recessive early-onset dystonia-Parkinson disease with Lewy body pathology and accumulation of hyperphosphorylated tau [57,60,63,74]. In a study with *Drosophila*, KO of the iPLA2 β gene results in reduced survival, locomotor deficits, hypersensitivity to oxidative stress and increase in lipid peroxidation [60]. Deficiency of iPLA2-VIA in *Drosophila* also exhibits neurotransmission defects and degeneration of DA neurons [75]. In this last study, iPLA2-VIA loss is linked to the disturbance of membrane lipids leading to endoplasmic reticulum stress.

7. Structure and Function of sPLA2

sPLA2s are small molecular weight proteins (20–40 kDa) present in different mammalian organs including the CNS. This group of enzymes are transcriptionally induced in cells upon challenge by toxins and pro-inflammatory cytokines and under infectious conditions such as arthritis and sepsis. Upon transcription, active sPLA2 are subsequently secreted and thus can interact with other cells in the extracellular milieu. Under these conditions, sPLA2 are often induced together with the C-reactive protein and serve as markers of inflammation [76]. Studies have identified more than 10 isoforms of sPLA2 e.g., IB, IIA, IIC, IID, IIE, IIF, III, V, X and XIIA, which are distributed among different cell types and body organs [77]. The ribbon model of human group III sPLA2 showed three helices, one calcium binding loop, five disulfide bonds and His34 and Asp63 in the active site [77]. In the extracellular milieu, sPLA2s require high levels of calcium for activation [78]. Although sPLA2s do not seem to have much substrate specificity, their ability to release ARA can contribute to the pool of inflammatory lipid mediators similar to those produced by cPLA2 [79].

Previous studies on different groups of sPLA2 have focused mainly on their specific functions in the peripheral system. Among these isoforms, sPLA2-IIA is probably the most studied due to its implication in atherosclerosis, septic shock, peritonitis, rheumatoid arthritis and other host defense mechanisms [80]. In studies with cells, increase in sPLA2-IIA expression is shown in response to inflammatory stimuli, such as IL-1 β , IL-6, TNF α in association with the NF- κ B and signal transducer and activator of transcription 3 (STAT3) transcription pathways. There are examples of other sPLA2 subtypes playing roles in specific physiological events in the body. For example, group IIF is associated with epidermal hyperplasia, IIE in regulating hair follicle homeostasis and IID in suppression of lymphoid immune cells [81]. Since sPLA2-IIF is more hydrophobic than other sPLA2s, it

can better penetrate membranes and disrupt lipid monolayers and bilayers [82]. Together, different sPLA2s have been implicated to play important roles in mediating different body functions including epidermal hyperplasia, male reproduction, anaphylaxis colonic diseases and atherosclerosis.

A major difficulty to delineate the role of PLA2 in specific cell types in the brain is the lack of protocols/methods to isolate these cells. As a result, many studies have reverted to using immortalized cell lines. A study by Sheng et al. examined the effects of proinflammatory cytokines and LPS on induction of iNOS and sPLA2-IIA in primary and immortalized astrocytes and microglial cells [83]. In this study, proinflammatory cytokines (TNF α , IL-1 β and interferon- γ (IFN γ)) and LPS could upregulate sPLA2-IIA mRNA and protein in primary and immortalized rat astrocytes (DITNC) but not in primary or immortalized microglial cells [83]. In contrary, expression and secretion of sPLA2-IIA are observed in human microglia-like promonocytic THP-1 cells and human primary astrocytes with proinflammatory cytokines [84]. Obviously, more studies are needed to elucidate the conditions to stimulate sPLA2-IIA in different cell types in the CNS.

Studies on sPLA2-IIA in mice are also hampered due to lacking this gene in many mouse strains [85]. However, this problem is ratified by transfecting the human sPLA2-IIA gene into these mice. Interestingly, mice harboring the human sPLA2-IIA exhibit epidermal pathology [86] and increase in atherogenesis [87]. In a study, an attempt was made to analyze the eicosanoids and metabolic mediators in the cPLA2 $\alpha^{-/-}$ mice [88] and transgenic sPLA2-IIA^{TGN} (both on C57BL/6J background) to determine the metabolites from these PLA2 in the development of arthritis [79]. Results indicated no distinct separations and thus both cPLA2 and sPLA2-IIA could play a role in the production of these metabolites and development of arthritis. It is important to recognize that although this mouse strain lacks sPLA2-IIA, it does not preclude the possible presence of other sPLA2 isoforms which may provide similar physiological functions.

8. sPLA2 in Extracellular Vesicles

Early studies have identified proteins and phospholipases (A2, C and D) in bioactive vesicles (exosomes) secreted from cells. Release of these vesicles offer the possibilities to mediate intercellular signaling mechanisms [89]. sPLA2-IIA and its metabolic products are identified in the extracellular vesicles secreted from astrocytes [80]. Expectedly, these vesicles in the extracellular milieu can interact and alter functions of other cells including neurons. Studies with primary human astrocytes showed increase in sPLA2-IIA in response to pro-inflammatory mediators and the secreted sPLA2-IIA present in the conditioned medium could cause toxic effects to SH-SY5Y neuroblastoma cells [84]. sPLA2-IIA also plays an integral role in regulating vascular inflammation and increases risk of cardiovascular diseases (CVD) [90]. In fact, a baseline increase in sPLA2-IIA levels was observed in subjects with early diagnosis of acute respiratory distress syndrome [91]. In the bronchoalveolar lavage fluid, pools of sPLA2-IIA (protein and mRNA) were identified in the extracellular vesicles [91]. In astrocytes activated by cytotoxic A β , release of sPLA2-IIA was observed together with activation of calcium signals and treatment with aristolochic acid (sPLA2 inhibitor) could counteract A β -induced neurotoxicity [92].

9. sPLA2-IIA in Neurodegenerative Diseases

9.1. Alzheimer's Diseases

Despite extensive studies on sPLA2 in infectious and inflammatory diseases, relatively little is known about their role in neurodegenerative diseases. In an early study, autopsy samples from AD patients showed a 4-fold increase in levels of sPLA2-IIA mRNA in AD hippocampi as compared to non-demented elderly brains [93]. Double staining of brain sections also showed a high level of sPLA2-IIA-immunoreactivity in the glial fibrillary acidic protein (GFAP) astrocytes and in the A β -containing plaques. In this study, stimulation of cultured astrocytes with A β 42 and IL-1 β resulted in increase in sPLA2-IIA immunoactivity [93]. Furthermore, another study showed that sPLA2-IIA secreted from

astrocytes could regulate APP processing in neuronal cells [94]. Taken together, these studies demonstrated a clear correlation between sPLA2-IIA in reactive astrocytes around the amyloid plaques in AD brain.

9.2. Cerebral Ischemia

The lack of sPLA2-IIA in many mouse strains has precluded studies to examine its role in cerebral ischemia using the murine model systems. However, in a study using a rat model in which cerebral ischemia was induced by occlusion of the middle cerebral artery (MCAO), measurement of sPLA2-IIA mRNA expression indicated a biphasic increase at 30 min and at 12 h to 14 days [95]. In situ hybridization of sPLA2-IIA mRNA in the brain sections showed an early-phase increase in the affected ischemic cortex and a later phase increase mainly in the penumbral area. Immunohistochemistry and confocal microscopy of the brain sections indicated sPLA2-IIA immunoreactivity associated mainly with reactive astrocytes [95]. Administration of a nanocrystal formulation of PX-18, a sPLA2 inhibitor, exerted neuroprotective effects in a cerebral ischemia/reperfusion model in gerbils [96].

9.3. Spinal Cord Injury

A study using a spinal cord injury (SCI) model indicated localization of sPLA2-IIA in oligodendrocytes but not in astrocytes or Schwann cells [97]. In this study, sPLA2-IIA was shown to play a role in mediating oligodendrocyte death after SCI. Quantitative reverse transcription polymerase chain reaction (RT-PCR) analysis indicated upregulation of sPLA2-IIA and IIE mRNA in the rat spinal cord as early as 4 h after injury. Interestingly, besides sPLA2-IIA and IIE, other sPLA2 isoforms such as sPLA2 1B, IIC, V, X and XII, were also present in the spinal cord [97].

Recently, sPLA2 has been implicated in early spinal mechanisms of neuronal excitability and nociception. In a study with a rat nerve root compression model, administration of sPLA2 inhibitor ameliorated mechanical allodynia and attenuated the increase in inflammatory factors (IL-1 β , TNF α and IL-1 α) due to the injury [98]. These findings agree with the role of sPLA2 regulating neuronal excitability, possibly related to the glutamate signaling and inflammatory cascades. In addition, the increase in inflammatory responses, nerve root compression is also associated with neuropathic pain. Neurochemical and immunohistochemical study identified glial activation together with increases in PLA2 and 8-hydroxyguanosine (8-OHG), a marker of oxidative stress [99]. Treatment with meloxicam (a COX-2 inhibitor) not only reduced activation of astroglial cells, but also prevented neuropathic pain and the oxidative stress in the nerve compression model [99]. To further imply action of sPLA2, thioetheramide-phosphorylcholine, a sPLA2 inhibitor, was shown to attenuate mechanical allodynia and neuronal excitability in this spinal cord injury model [98]. Indeed, loading this sPLA2 inhibitor in phospholipid micelle form proved to be a promising therapeutic target for suppressing neuropathic pain [100].

10. PLA2 and Lysophospholipids

In addition to the release of *sn*-2 fatty acids, the enzymatic action of PLA2 also produces lysophospholipids which are known for their detergent-like properties. These molecules can modify properties of the membrane lipid bilayer and be transported effectively across the blood–brain barrier (BBB). In fact, recent studies suggest the use of lysophospholipids as a carrier for fatty acids. Dietary DHA administered in the form of LPC was shown to enhance brain phospholipids with DHA better than with the free fatty acid alone [101,102]. Recent studies indicated transport of DHA-lysophospholipids to brain through a specific Na-dependent transporter “major facilitator superfamily domain containing 2a (Mfsd2A)” expressed in the endothelium of the blood brain barrier (BBB) [103,104]. This transporter is also present in different mammalian species. A cryo-electron microscopic study reveals 12 transmembrane helices and an amphipathic cavity containing the Na⁺ and lysolipid binding site [105]. The important role of this transporter in brain pathology is demonstrated by a recent study showing a genetic variant of this protein to cause congenital microcephaly

and hypomyelination [106,107]. Consequently, more studies are needed to understand the physiological role of this transporter for enrichment of DHA in the brain.

Lysophospholipids are substrates for the reacylation process mediated by lysophospholipid acyltransferases and the ATP-dependent activation of acyl-CoA [28]. Considering the role of cPLA2 in the release of ARA under stimulated conditions, activity of this “Land’s cycle” is particularly important in the maintenance of ARA homeostasis in the cell [108]. Due to different types of phospholipids present in the membrane, different isoforms of lysophospholipid acyltransferases are present in the body organs to mediate phospholipid homeostasis [109]. In human monocytes, lysoPC acyltransferase 3 is found to regulate incorporation of ARA into PC [110]. In the brain, an LPI acyltransferase 1 (LPIAT1) is involved in regulating neuronal function. Variants in the membrane-bound O-acyltransferase family member 7 (*MBOAT7*) which encodes LPIAT1 is involved in intellectual disability associated with epilepsy and autism spectrum disorder (ASD) [111]. A recent review by Kita et al. also demonstrated the role of different lysophospholipid acyltransferases on mediating specific physiological and pathological functions in the neural and peripheral system [1].

In brain injury and neuro-inflammatory diseases, increases in LPC have been regarded as a lipid mediator for astrogliosis and other deleterious events associated with neurodegeneration [112]. Recently, substantial interest has been placed on lysophosphatidic acid (LPA), which is regarded to serve as a second messenger for regulating many receptor-mediated cell functions [113]. Although LPA is produced through deacylation of phosphatidic acid (PA) by PLA1 or PLA2 [114,115], there is evidence that this lysophospholipid can also be derived from LPC through autotaxin, a soluble enzyme with PLD-like activity and is present in extracellular fluids such as plasma and cerebrospinal fluid (Figure 3) [116,117]. Recent studies have unveiled the multifunctional role of LPA to act on G-protein-coupled receptors (1–9) (Figure 3) [118,119]. Interestingly, since sphingosine 1-phosphate (SIP) shares a basic structure similar to LPA, both type of lipids can also interact with multiple G-protein-coupled receptors [119]. Activation of these receptors by LPA or SIP stimulates different downstream signaling pathways responsible for regulating intracellular metabolism. Genetic ablation of LPA receptors leads to aberrant neurodegenerative diseases including AD and neuropathic pain [118,120]. Activation of LPA receptor 1 in macrophages is found to regulate pathology of multiple sclerosis [121]. Furthermore, measurement of LpaR1 expression in blood mononuclear cells is used as a marker for onset/relapse and severity in the EAE model and multiple sclerosis patients. Consequently, future studies to better define the LPA receptors and their signaling pathways should further advance understanding of the pathology of these neurological diseases.

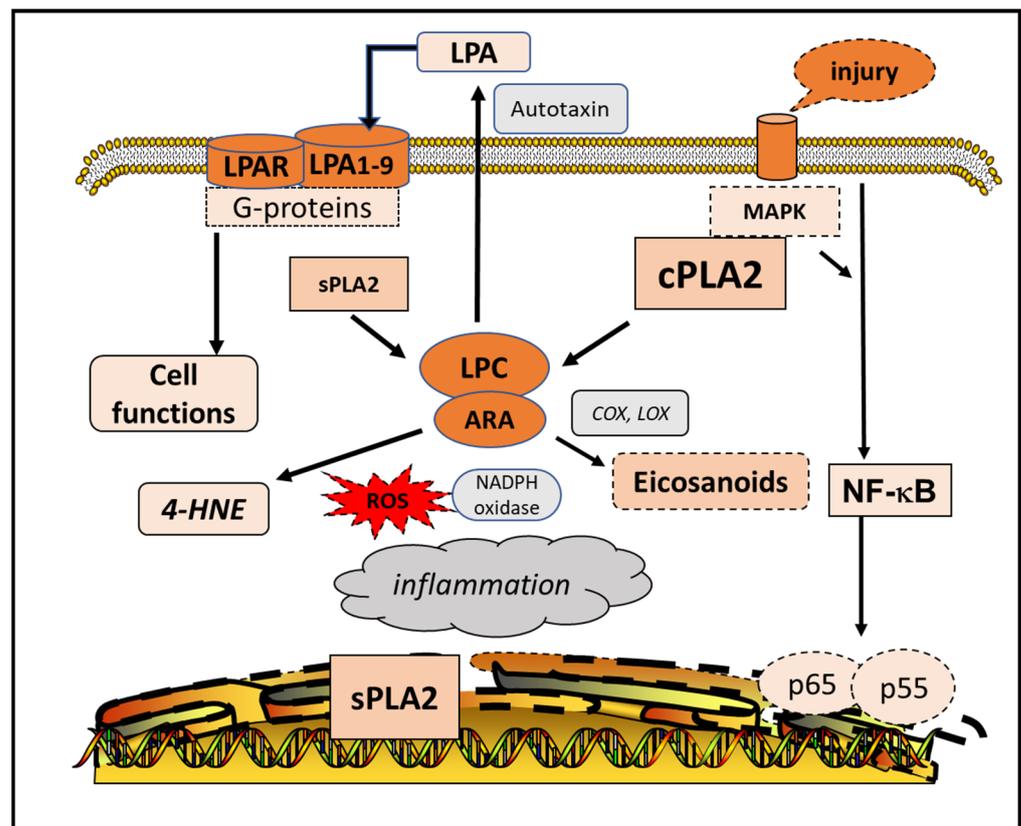


Figure 3. Role of lysophospholipids in metabolic pathways. Cell injury leads to activation of cPLA2 and NF-κB pathway and transcriptional increase in sPLA2. Activation of sPLA2 and cPLA2 result in the release of ARA and lysophosphatidylcholine (LPC). LPC is converted to lysophosphatidic acid (LPA) via the extracellular autotaxin. LPA interacts with G-protein receptors to regulate cell metabolism. Abbreviations: 4-hydroxynonenal (4-HNE), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), reactive oxygen species (ROS), mitogen-activated protein kinases (MAPK).

11. PLA2-Mediated Production of Oxylipins and Lipid Peroxidation Products

Studies on PLA2s demonstrated a Yin-Yang mechanism for the release of ARA and DHA through the cPLA2 and the iPLA2, respectively (Figure 2) [122]. Both ARA and DHA are subject to enzymatic and non-enzymatic free-radical oxidation reactions resulting in production of oxylipins. Depending on the cell types, these oxylipins are active lipid mediators and exert specific cellular effects through binding to receptors. Consequently, these mediators play an important role in regulating various biological processes such as inflammation, immunity, vascular functions, as well as a diverse set of homeostatic processes.

Stimulation of cPLA2 and release of ARA has been regarded as a major source of inflammation in cells. ARA interacts with oxidative enzymes such as cyclooxygenase (COX), lipoxygenase (LOX) and cytochrome P450 (CYP), resulting in synthesis of prostaglandins, leukotrienes and thromboxanes [123,124]. With the exception on lipoxin which is regarded as a protective mediator, most ARA-derived oxylipins exert inflammatory responses through interacting with specific cell receptors. In contrary, DHA interacts with different forms of LOX to form mediators such as resolvins, maresins and neuroprotection D1 (NPD1) [125]. As indicated in brain under ischemic insult, NPD1 exerts protective response and suppresses oxidative insults. ARA accounts for close to half of oxylipins in the brain while less than 20% of oxylipins are attributed to DHA [126]. Interestingly, the brain oxylipin profiles are not altered by changes in dietary n-3 and n-6 PUFA [127]. One possible reason is that these oxylipins are chemically unstable and thus are not stored in tissues but are synthesized de novo only on demand [128]. Nevertheless, pro-inflammatory

oxylipins derived from n-6 PUFA are associated with diseases including diabetes [129], kidney disease [130], rheumatoid arthritis and atherosclerosis [131], whereas the n-3 PUFA oxylipins are associated with suppressing inflammation and contributing to the resolution of immune responses [132,133].

Several studies have demonstrated the diverse health benefits of long n-3 PUFAs, such as the role of eicosapentaenoic acid (EPA, 20:5 n-3) and DHA in triglyceride-lowering, anti-inflammatory and antiarrhythmic effects [134,135]. However, when tested in the *in vitro* conditions, both DHA and ARA increase membrane fluidity, thus, leading to an increase in neurotropic and neuroprotective α -secretase-cleaved soluble APP (sAPP α) in neuronal cells [136]. Dietary n-3 PUFA such as fish oil supplementation have also been shown to increase in EPA and DHA as well as decrease in ARA in erythrocyte membranes [137,138]. Mouse pups nursed by mothers taking DHA supplement showed a large increase in 22:6 (n-3) and decrease in 20:4 (n-6) as compared to controls [139]. Adult mice given a DHA dietary regimen (1% DHA) also showed increase in (n-3) and decrease in (n-6) phospholipid species [140]. In a study with Wistar rats, oral administration of fish oil (38% of DHA and 46% of EPA) for 30 days also showed significant increases in PC and PE with DHA and decreases in PC and PE with ARA in the cortex, hippocampus and striatum [141]. These results indicate that DHA supplement not only increases n-3 fatty acids but suppresses n-6 fatty acids in the membrane phospholipids. In relation with the changes in fatty acids, dietary n-3 PUFA also increases n-3 PUFA derived oxylipins and decreases n-6 PUFA oxylipins in the hippocampus [142]. More studies on analysis of the oxylipins are needed to verify changes in oxylipin patterns upon dietary DHA supplement.

12. Peroxidation of ARA and DHA

In addition to reactions with oxygenases, PUFAs are also substrates of non-enzymatic reactions by oxygen free radicals, producing two oxygenated products, namely, 4-hydroxyhexenal (4-HHE) from DHA and 4-hydroxynonenal (4-HNE) from ARA [122]. These bioactive aldehydes are likely present in low levels, but they are metabolic active and able to alter cell metabolism by forming adducts with proteins, phospholipids and nucleic acids [143]. Because different PLA2s show preferences for release of DHA and ARA, it is of interest to follow their peroxidation products. In a study with BV-2 microglia cells, LPS was shown to activate cPLA2 and, thus, releasing ARA and production of 4-HNE [144]. In contrary, increase in 4-HHE but not 4-HNE was observed upon treating cells with DHA. In fact, studies with animal models also demonstrated increase in 4-HHE in brain and other organs upon supplementation with DHA [139]. Interestingly, while dietary DHA alters PUFA in phospholipids in all brain regions, the increase in 4-HHE is found mainly in cerebral cortex and hippocampus, suggesting that these two brain regions are more sensitive in the oxidative pathway [139]. The importance of the hippocampus in lipid peroxidation is demonstrated in a study in which aged mice were supplemented with n-3 PUFA [145]. Changes in lipid peroxidation in the aged mice were associated with enhancement of cellular plasticity in the hippocampus and better object recognition memory. In another study, a short-term n-3 PUFA diet to aged mice showed protection against neuroinflammation and restored spatial memory, events also attributed to special function of the n-3 PUFA in the hippocampal region [146]. In a study with healthy human subjects, supplementation of different levels of DHA also resulted in a dose-related increase in 4-HHE levels in the plasma [147].

Although more studies are needed to investigate the physiological role of 4-HHE in brain, studies with microglial cells indicated that 4-HHE is ten times more potent than DHA in its ability to mitigate LPS-induced inflammation in these cells [144]. In addition, 4-HHE was also 10 times more sensitive to stimulate the antioxidant stress response involving Nrf2 and induction of HO-1, a powerful antioxidant enzyme [144]. Another study with vascular endothelial cells also indicated ability for 4-HHE to enhance the adaptive response pathway involving Nrf2 [148,149]. Although 4-HNE is produced upon stimulation of cPLA2 and peroxidation of ARA in animals and cell models of oxidative stress, the physiological role

of this aldehyde *in vivo* remains to be examined [150,151]. In our studies with cell models, exogenous application of 4-HNE up to 10 μ M range showed protective effects similar to the 4-HHE [144]. Using the microglia model, we also reported that 4-HHE was more effective than DHA to counteract activation of cPLA2 and upregulation of iNOS and TNF α by the toxic oligomeric A β [52].

The neuroprotective effects of DHA can be, in part, attributed to its bioactive metabolites. The review by Kuda stated over 70 biologically active DHA-derived metabolites derived from enzymic metabolism, oxygenation and conjugation of DHA [152], yet many of their potential effects have not been tested. Due to the recent advancements in organic synthesis [153], it is possible to study the direct effects of some fatty acid-derived metabolites in the biological systems. For example, neuroprotectin D1, an enzymatically oxidized product of DHA, is known to induce neuronal survival and downregulation of amyloidogenic processing in AD cellular models [154]. The 4(RS)-4-F_{4t}-neuroprostane (4-F_{4t}-NeuroP), a non-enzymatic product derived from oxidation of DHA, has been reported to offer protective effects through decreasing cytochrome c release and caspase 3 activity in ventricular tissue after ischemia/reperfusion [155]. In our recent studies, this compound suppresses oxidative stress, inflammation and mitochondrial dysfunction in LPS-stimulated microglia (unpublished data).

13. Phospholipase Products through Lipidomics and Advanced Mass Spectrometry Analysis

13.1. Phospholipid Species

The membrane lipid bilayer is comprised of different types of phospholipids, namely PC, PE, PI and PS. In the brain, the PE phospholipids tend to have high levels of alkenylacyl group—plasmalogen. Although plasmalogens are enriched in myelin and the white matter, little is known about their interaction with PLA2 due partly to difficulty to separate the alkenylacyl group from the diacyl group. In the past, phospholipids were separated by one or two dimension thin-layer chromatography [156]. Although most thin-layer protocols lack sensitivity and cannot separate the alkyl/alkenyl linkages from the acyl linkages, improved lipidomic protocols can offer sensitivity and separation of molecular species of individual phospholipid [157]. Using the shotgun lipidomic analysis, our recent study indicated DHA supplements can alter phospholipid species in brain, heart and plasma [140]. Lipidomic analyses of phospholipid species in human plasma have proved to be useful in revealing changes in lipids associated with different neurological diseases and injury [158].

13.2. Oxylipins

Improved methods for analysis of oxylipins have unveiled the complexity of these compounds in different cell systems. In the past, radioimmunoassay [159] and enzyme-linked immunosorbent assay [160] are the most widely used techniques for analysis of oxylipins. This approach is problematic because it requires specific antibodies and due to the structural similarity of oxylipins, it is unlikely that antibodies alone can sufficiently distinguish them [161]. Over the years, new chromatography-mass spectrometry-based methods such as liquid chromatography-mass spectrometry (LC-MS) or gas chromatography-mass spectrometry (GC-MS) have developed [162]. LC-MS/MS method offers a cost effective and more sensitive alternative method for oxylipins analysis amidst challenges such as the small mass range occupied by the diverse lipid classes, the structural isomers and their low abundance together with inherent instability in biological fluids [163,164]. Ultrahigh performance liquid chromatography (UHPLC) coupled to tandem MS/MS instruments have demonstrated high resolution, speed and sensitivity for analyzing oxylipins in biological samples and also with good selectivity and low detection limits [162]. Nevertheless, the scope of this approach is limited due to availability of commercial standards. Although recent targeted metabolomic LC-MS approaches with high sensitivity has been used to quantify over 100 oxylipins [164], the combination of UHPLC chromatographic separation and (multiple reaction monitoring) MRM transitions performed on a triple quadrupole

(QqQ) mass spectrometer allow 184 eicosanoid metabolites to be separated and quantified in a 5 min running time [165]. In a recent study, Watrous et al. use a non-targeted mass spectrometry approach in conjunction with chemical networking of spectral fragmentation patterns to identify over 500 discrete chemical signals highly consistent with known and putative eicosanoids and related oxylipins in human plasma, including 46 putative molecules not previously described [166]. Future studies with improved technology will advance identification of these oxylipins and aid discovery of their physiological functions.

14. Summary and Future Directions

This review has provided a comprehensive coverage of recent knowledge of the three major types of PLA2, namely, cPLA2, iPLA2 and sPLA2. This review also places emphasis on the Yin-Yang metabolism for metabolism of ARA and DHA, leading to production of peroxidative products and oxylipins which can be inflammatory and protective. A summary of the PLA2 subtypes and their properties as well as specific implication on neurological diseases is listed in Table 1. In addition, Table 1 also includes recent studies unveiling the role of lysophospholipids and possible role to enrich brain phospholipids with DHA. Lastly, with the aid of advance proteomics, lipidomics and sensitive LC–MS techniques, future studies will be able to provide new and important information for specific PLA2 and their metabolites in specific cell types and implication for health and diseases.

Table 1. Characteristic features of PLA2 and their metabolites.

Title	Activities and Functions	References
A. cPLA2	1. Phosphorylation by mitogen-activated protein kinases (MAPK)	[8,13–15]
	2. Translocation from cytoplasm to different intracellular components	[9]
	3. Neuronal excitation and glial activation	[13–16]
	4. Preference for release of ARA and inflammatory pathways	[17]
	5. Involvement in stroke, spinal cord and traumatic brain injury	[27,28,31,32]
	6. Involvement in AD	[33–42]
	7. Activation by oligomeric A β	[46,48–53]
	8. Inhibitors—arachidonyl trifluoromethyl ketone (AACOCF3 or ATK)	[17,23,24,53]
B. iPLA2	1. Multiple strings of ankyrin motif—binding with other proteins	[2,56,57]
	2. iPLA2 β —most prominent phospholipase playing a house-keeping role—regulation of mitochondrial function	[58,60,61]
	3. iPLA2 γ —has motif for mitochondrial localization	[67]
	4. Preference for the release of DHA	[63–65]
	5. Action on cardiolipins	[68,69]
	6. Regulation of AMPA neurons	[72,73]
	7. Specific inhibitor, bromoenol lactone (BEL)	[62]
	8. Mutations of GVI PLA2 gene—infantile neuroaxonal dystrophy (INAD) and neurodegeneration with brain iron accumulation (NBIA)	[57,60,63,74]

Table 1. Cont.

Title	Activities and Functions	References
C. sPLA2		
1.	Small molecular weight proteins (20–40 kDa)—more than 10 isoforms	[77]
2.	Transcriptionally induced upon challenge by toxins and pro-inflammatory cytokines -inflammation	[76,80,83]
3.	Require high levels of calcium for activity in extracellular milieu	[78]
4.	Presence in extracellular vesicles secreted from astrocytes	[84,89,90]
5.	Many mouse strains lack the sPLA2-IIA gene	[85]
6.	Diseases—AD, cerebral ischemia, spinal cord injury	[93–99]
7.	Inhibitors: thioetheramide-phosphorylcholine	[100]
D. Lysophospholipids		
1.	DHA-LPC—effectively transported to brain	[101,102]
2.	DHA-lysophospholipids—transported to brain through a specific Na-dependent transporter “Mfsd2A”	[103–105]
3.	Different isoforms of lysophospholipid acyltransferases engage in the “diacylation-reacylation” cycle	[108–110]
4.	LPA—pathways for synthesis	[114–117]
5.	LPA—interaction with G-protein-coupled receptors leading to different downstream signaling pathways	[120]
E. ARE, DHA, oxylipins, 4-HNE and 4-HHE		
1.	Yin-Yang mechanism for the release of ARE and DHA	[122]
2.	Enzymatic and non-enzymatic free-radical oxidation reactions for production of oxylipins.	
3.	ARA—interaction with cyclooxygenase (COX), lipoxygenase (LOX) and cytochrome P450 (CYP) for synthesis of prostaglandins, leukotrienes and thromboxanes, oxylipins that are inflammatory	[123,124]
4.	DHA—interact with different forms of LOX to form protective mediators such as resolvins, maresins and neuroprotection D1	[125]
5.	Non-enzymatic free radical reactions—4-hydroxyhexenal (4-HHE) from DHA and 4-hydroxynonenal (4-HNE) from ARA	[122]
6.	Neuroprostanes	[155]
7.	Alkenyl aldehydes—bioactive and form adducts with proteins, phospholipids and nucleic acids	[143]
8.	4-HNE—downstream from stimulation of cPLA2 and ARA	[144]
9.	4-HHE—increase in brain upon dietary DHA	[139,144]

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