Intracellular- and extracellular-derived Ca^{2+} influence phospholipase A$_2$-mediated fatty acid release from brain phospholipids

Angelo O. Rosa[1],[*] and **Stanley I. Rapoport**[1]

[1]Brain Physiology and Metabolism Section, National Institute on Aging, National Institutes of Health, Bldg 9, Room 1S126, 9000 Rockville Pike, Bethesda, MD, 20892. USA

Summary

Docosahexaenoic acid (DHA) and arachidonic acid (AA) are found in high concentrations in brain cell membranes and are important for brain function and structure. Studies suggest that AA and DHA are hydrolyzed selectively from the *sn*-2 position of synaptic membrane phospholipids by Ca^{2+}-dependent cytosolic phospholipase A$_2$ (cPLA$_2$) and Ca^{2+}-independent phospholipase A$_2$ (iPLA$_2$), respectively, resulting in increased levels of the unesterified fatty acids and lysophospholipids. Cell studies also suggest that AA and DHA release depend on increased concentrations of Ca^{2+}, even though iPLA$_2$ has been thought to be Ca^{2+}-independent. The source of Ca^{2+} for activation of cPLA$_2$ is largely extracellular, whereas Ca^{2+} released from the endoplasmic reticulum can activate iPLA$_2$ by a number of mechanisms. This review focuses on the role of Ca^{2+} in modulating cPLA$_2$ and iPLA$_2$ activities in different conditions. Furthermore, a model is suggested in which neurotransmitters regulate the activity of these enzymes and thus the balanced and localized release of AA and DHA from phospholipid in brain, depending on the primary source of the Ca^{2+} signal.

Keywords

Phospholipase A$_2$; calcium; arachidonic acid; docosahexaenoic acid; endoplasmic reticulum; signaling

1. Overview of the phospholipase A$_2$ families

Although PLA$_2$ enzymes have been known for over 100 years, only within the last 15 years has their importance for neurochemical processes been widely recognized [1]. These enzymes catalyze the hydrolysis of esterified fatty acids at the stereospecifically numbered (*sn*)-2 position of membrane phospholipids to release unesterified fatty acids and form lysophospholipids [2–9]. The fatty acids and their metabolic products are important for normal brain function and can alter neuropathological processes [1,10–15].

*Corresponding author (present address): Angelo Oscar da Rosa, PhD, Department of Pharmacology, MUSC, Lab: BSC 327, Office BSC: 324, 173 Ashley Avenue, Charleston, SC 29425-5050, e-mail: darosa@musc.edu, Telephone: 843-792-4457.

PLA$_2$s are classified according to their sequence homology and Ca^{2+} dependence. They belong to three main families having different catalytic sequences, and these sequences are conserved among PLA$_2$s in the same family. The three most described families are: low molecular mass secretory PLA$_2$ (sPLA$_2$), higher molecular mass Ca^{2+}-dependent cytosolic PLA$_2$ (cPLA$_2$), and "Ca^{2+}-independent" PLA$_2$ (iPLA$_2$) [24](See Table 1). Other less studied PLA$_2$ families have been described, such as platelet-activating factor-acetyl hydrolase (PAF-AH) [8,21] and lysosomal PLA$_2$ [22,23].

The sPLA$_2$ family is subdivided into groups: sPLA$_2$-IB, sPLA$_2$-IIA, sPLA$_2$-IIC, sPLA$_2$-IID, sPLA$_2$-IIE, sPLA$_2$-IIF, sPLA$_2$-III, sPLA$_2$-V, sPLA2-X, and sPLA$_2$-XII [1]. The genes for human sPLA$_2$–IB map to chromosome 12q23–24, those for group II subfamily sPLA$_2$s (IIA, IIC, IID, IIE, IIF) and for sPLA$_2$-V map to chromosome 1p34–36, and the gene for sPLA$_2$-X maps to chromosome 16p12–13 [1]. sPLA$_2$s are Ca^{2+}-dependent for catalytic activity (generally requiring millimolar Ca^{2+} concentrations) [1,25,26], consistent with their extracellular activity and millimolar Ca^{2+} concentrations in the extracellular space [27]. Evidence also points to an intracellular functional role sPLA$_2$ in caveolae-containing compartments around the nucleus of immune cells and in the nucleus of astrocytes and neurons [28–30].

The cPLA$_2$ family is subdivided into cPLA$_2\alpha$, cPLA$_2\beta$, cPLA$_2\gamma$, cPLA$_2\delta$, cPLA$_2\varepsilon$ and cPLA$_2\zeta$, which also are referred to as groups IVA, IVB, IVC, IVD, IVE and IVF, respectively. They are coded by gene on different human chromosomes, chromosome 1 (cPLA$_2\alpha$), 15 (cPLA$_2\beta$, cPLA$_2\delta$, cPLA2ε, cPLA2ζ) and chromosome 19 (cPLA$_2\gamma$), which are not the same as the chromosomes that code for the sPLA$_2$ family [31–38]. cPLA$_2$ becomes activated after translocating to the plasma membrane from the cytosol, and is constitutively membrane-bound [1,38]. Although Ca^{2+} is not necessary for cPLA$_2$ catalytic activity, nanomolar Ca^{2+} concentrations are needed for its binding to the membrane, where other enzymes that regulate the arachidonic acid (AA) cascade, including cyclooxygenases (COXs) and lipoxygenases, also are located [16].

The iPLA$_2$s have extremely different structures compared to the cPLA$_2$ and sPLA$_2$ families [39]. They occur in numerous splicing variants, only some of which are functional. iPLA$_2$s are classified as group VI and are subdivided into VIA and VIB, or into iPLA$_2\beta$ and iPLA$_2\gamma$, respectively. Each iPLA$_2$ is coded by a different chromosome, iPLA$_2\beta$ is coded by chromosome 23q13 [40] and iPLA$_2\gamma$ is coded by chromosome 7q31 [1,41]. iPLA$_2\beta$ is unique among PLA$_2$s, as it has multiple ankyrin repeats, which are common motifs found in more than 400 proteins, including cell cycle regulators and transcription factors. Ankyrin repeats have been implicated in protein–protein interactions and can influence many physiological functions [39]. A site near the C-terminus of some iPLA$_2\beta$ variants can bind to calmodulin with the help of Ca^{2+} [1,42–44].

The PAF-AHs are classified as VIIA (lipoprotein-associated- PLA$_2$), VIIB (PAF-AH II) VIIIA (PAF-Ib) and VIIIB (PAF-Ib or VIIIB forms a heterodimer with VIIIA) [5]. PAF-AH was first named for its ability to cleave the acetyl group from the *sn*-2 position of platelet activating factor (PAF); however, this enzyme can cleave oxidized lipids in the *sn*-2 position up to 9 carbons long, not just PAF. This enzyme also has been shown to access substrate in the aqueous phase, unlike the other PLA$_2$s studied [21], in a Ca^{2+}-independent fashion [6]. Type I PAF-AH is a complex of two catalytic subunits, alpha1 and alpha2, a regulatory beta subunit, and a gamma subunit [45]. Its structure is very similar to the structure of G proteins [46], whereas type II PAF-AH is a single polypeptide [47]. Type II PAF-AH is myristoylated at the N-terminus and distributed in both the cytosol and membranes. Plasma PAF-AH has a closed structure when compared to II PAF-AH, and exists in association with plasma lipoproteins [21].

Lysosomal or group XV PLA_2 is a calcium-independent PLA_2 enzyme of 25 kDa [23], which has a distinguishing characteristic of having its maximal activity in an acidic medium, and accordingly, it also is called acidic $iPLA_2$ [23,48].

This review will focus on the roles of the $cPLA_2$ and $iPLA_2$ in mammalian brain. We propose a model for receptor-mediated regulation of PLA_2 enzyme activities by Ca^{2+} signals originating from intracellular and extracellular sources, leading to the controlled, balanced and localized release of specific fatty acids as signaling molecules.

2. $cPLA_2$ and $iPLA_2$ in the brain

$cPLA_2$ is found in mammalian brain in three different forms: $cPLA_2\alpha$ (85-kDa), $cPLA_2\beta$ (114-kDa), and $cPLA_2\gamma$ (61-kDa). $cPLA_2\beta$ is found mainly in the cerebellum, whereas $cPLA_2\alpha$ and $cPLA_2\gamma$ are uniformly distributed in rat brain [16,31,33]. $cPLA_2\alpha$ is found both in astrocytes and neurons [16]. In neurons of rat brain, $cPLA_2$ has been localized at post-synaptic sites, suggesting that it is important in neurotransmission (see table 2) [17].

$iPLA_2$ is believed to account for more than 70% of brain PLA_2 activity [25]. $iPLA_2\beta$ (80-kDa) was purified from rat brain [49] and found in all brain regions, with the highest activity in striatum, hypothalamus, and hippocampus [16,49]. Similarly, two different $iPLA_2$s (110-kDa and 39-kDa) were purified from bovine brain [51,52]. $iPLA_2$ (85-kDa) also was identified in monkey brain, in the neocortex, amygdala, hippocampus, caudate nucleus, putamen, and nucleus accumbens, whereas in the thalamus, hypothalamus and globus pallidus it was lightly labeled (see table 2). On the other hand, the midbrain, vestibular, trigeminal and inferior olivary nuclei, and the cerebellar cortex were densely labeled [18]. Individual $iPLA_2$ subtypes have not been investigated in the bovine or monkey brain. The enzyme is present in astrocytes [53] and in neurons, where its localization in dendrites and axon terminals suggests that it plays a role in neuronal signaling [18].

3. The $cPLA_2$ product: Arachidonic acid and brain function

Arachidonic acid (AA, 20:4n-6), an n-6 polyunsaturated fatty acid (PUFA), comprises approximately 5–15% of total fatty acids in most tissue phospholipids [54]. It can be synthesized in the liver from dietary derived linoleic acid, or obtained directly from dietary sources [55]. AA is preferentially released from phospholipid by $cPLA_2$ [1,4,56]. It and its metabolites (prostaglandins, leukotrienes, thromboxanes, lipoxins) in brain influence synaptic signaling [57,58], neuronal firing [59], neurotransmitter release [60], activation of intracellular receptors [61], hypothalamic-pituitary function [62], nociception [63], gene expression [11], cerebral blood flow [64], circadian rhythm [65], and appetite [66], among other targets. Altered AA metabolism has been implicated in neuronal death [67] and in a number of neurological, neurodegenerative, and psychiatric disorders, including epilepsy [68], ischemia, stroke [69], HIV-associated dementia [13], amyotrophic lateral sclerosis [70], Alzheimer disease [71], Parkinson disease [72], schizophrenia [73], bipolar disorder [74–76] and depression [77,78].

4. The $iPLA_2$ product: Docosahexaenoic acid and brain function

Docosahexaenoic acid (DHA, 22:6n-3) is the most abundant n-3 PUFA in brain and is necessary for normal brain function [54]. Esterified DHA within membrane phospholipids is hydrolyzed preferentially by $iPLA_2$ [79].

Humans can obtain DHA by eating fish or fish products, or can synthesize it in the liver from circulating α-linolenic acid, through serial steps of desaturation, elongation and oxidation [55,80]42. Dietary restriction of n-3 PUFAs in animal models decreased brain DHA content while increasing concentrations of the elongation product of AA, docosapentaenoic acid

(22:5n-6) [80–82]. Rats deprived of dietary n-3 PUFAs for 15 weeks had increased brain mRNA, protein and activity levels of $cPLA_2$, $sPLA_2$ and COX-2, but decreased expression of $iPLA_2$ and COX-1 [83].

DHA has been found important for membrane function and fluidity, photoreceptor function [54], memory [84,85], problem solving [86], and developmental visual and sensory functions [54]. Some studies but not others indicate that dietary DHA supplementation is beneficial in a number of brain disorders [87,88]. In rats, dietary n-3 PUFA deprivation for 15 weeks increased aggression and depression scores on behavioral tests [89]. DHA, like AA, can be metabolized by COX and lipoxygenase enzymes and generate active compounds [90,91]. DHA products, in contrast to AA products, seem to have a beneficial effect in inflammatory and neurodegenerative conditions. Resolvins of the D series and docosatrienes, which are bioactive DHA products that possess potent anti-inflammatory, immunoregulatory [92,93], and neuroprotective actions [94], are termed neuroprotectins [90].

5. Docosahexaenoic acid as a signaling molecule: competition with arachidonic acid?

AA is well recognized as a signaling molecule [10,95–97] and there are a number of lines of evidence indicating that DHA is a signaling molecule as well [12,79,98–100].

1) DHA can be released from phospholipid following activation of neuroreceptors

Activation of serotonin (5-HT) $5-HT_{2A}$ receptors in astroglioma cells caused DHA release from membrane phospholipids [101]. Muscarinic receptor activation by arecoline also caused DHA release and plasma-derived DHA incorporation into rat brain synaptic membranes, consistent with its participation in neuronal signaling [102,103].

2) DHA exerts intracellular downstream effects

DHA increased N-methyl-D-aspartate (NMDA) function in neurons. Both DHA and AA increased entry of extracellular Ca^{2+} into neurons *via* glutamatergic NMDA receptors, and DHA also increased the probability of NMDA channel opening [104]. In another study, AA increased while DHA inhibited glutamate-induced prostaglandin release from astrocytes; DHA inhibited the AA effect [105].

Unesterified DHA can promote Ca^{2+} release from intracellular stores in the endoplasmic reticulum (ER) [106]. Ca^{2+} released from the ER can be a continuous source of Ca^{2+} for mitochondria, can activate dehydrogenases and mitochondrial ATP synthesis and energy production, and can stimulate neuroprotective signals [107]. On the other hand, Ca^{2+} uptake into mitochondria can modulate the activity of Ca^{2+} channels in the ER [108,109]. If the balance between mitochondria and the ER is disturbed, a Ca^{2+} overload in the mitochondria can trigger necrosis or apoptosis [110].

Release of Ca^{2+} from intracellular stores *via* purinergic [111] or nicotinic [112] receptors can be neuroprotective. Intracellular Ca^{2+} release induced by isoflurane [113] or fructose-1,6-biphosphate was shown to be neuroprotective [114,115]. Ca^{2+} release from the ER, induced by AA or DHA, reduced the peak of subsequent Ca^{2+} release induced by G protein activation, showing a complex relation between these two PUFAs and intracellular Ca^{2+} [100].

Neuroprotectin D_1 is a metabolite of DHA that may account for part of the opposite effects of DHA and AA. The synthesis of neuroprotectin D_1 was increased in cells exposed to the Ca^{2+} ionophore A23187 or to interleukin-1β, and depended on PLA_2 activity [98]. Both A23187 and interleukin-1β can induce Ca^{2+} release from intracellular stores [116]. However,

regulation by ER Ca^{2+} of neuroprotectin D_1 synthesis induced by A23187 or interleukin-1β has not been studied. Neuroprotectin D_1 also can inhibit β-amyloid production [117] and COX-2 expression [99]. COX-2, which appears involved in neuroinflammation and is overexpressed in the Alzheimer disease brain [118,119], converts AA to prostaglandins that also can increase β-amyloid production [120]. COX-2 also has been implicated in multiple sclerosis, amyotrophic lateral sclerosis, Parkinson disease, and Creutzfeldt-Jakob disease [14]. DHA in these conditions may modulate COX-2 activity and AA metabolite production *via* COX-2.

A DHA neuroprotective effect also is supported by evidence that $iPLA_2$ inhibition increased neuronal death induced by reactive oxygen species [121]. The data together suggest that increased $iPLA_2$ activity and DHA release can be neuroprotective.

In other contexts, $iPLA_2$ activation may have different consequences, related to its different subtypes, their location, and substrate availability in brain. In apoptotic cells, $iPLA_2\gamma$ seems necessary for mitochondrial membrane pore transition formation [122]. $iPLA_2$ is a substrate for caspase-3 (or other caspases), and is cleaved during the apoptotic process at the consensus Asp183. The resulting fragment, $iPLA_2(184$-C$)$, possesses the entire catalytic domain and seven of eight ankyrin repeats, and is functionally more active than intact $iPLA_2$ in cells [123]. On the other hand, inhibition of $iPLA_2\beta$ induced apoptosis in one study [124]. The role of DHA in apoptosis related to $iPLA_2$ inhibition is not known.

6. Ca^{2+} signaling as control mechanism of $iPLA_2$ and $cPLA_2$ activities

Preferential release of DHA and AA by $iPLA_2$ and $cPLA_2$, respectively [49,74,79], raises the possibility that the enzymes are controlled by separate mechanisms and serve different or even opposing functions [75]. For example, pharmacological studies with chronic lithium, carbamazepine and valproate in unanesthetized rats, when combined with *in vivo* kinetic fatty acid modeling and molecular biology measurements, confirmed *in vitro* findings that $cPLA_2$ is specific for AA release, whereas $iPLA_2$ is comparatively specific for DHA release from phospholipid in brain synaptic membranes [74,125,126]

$cPLA_2$ requires Ca^{2+} for its translocation and arachidonic acid release [36]. Therefore, Ca^{2+} entry through ligand-gated ion channels, such as NMDA receptors, can activate this enzyme [127,128]. In neurons, NMDA receptor activation induces Ca^{2+} entry from the extracellular space and activates $cPLA_2$, and this activation is reversed by MK-801 (an NMDA antagonist), by removing calcium from the extracellular space, or by chronically administering lithium, valproic acid or carbamazepine, mood stabilizers effective in bipolar disorder, to rats [129, 130] [131,132]. The $cPLA_2$ coupling to Ca^{2+} entry through the membrane seems to depend on its location in the cell [133]. The localization of Ca^{2+} entry appears more important than the pattern of Ca^{2+} entry. In this sense, single transients, repetitive oscillationrs or sustained plateaus of Ca^{2+} activate $cPLA_2$. Under these circumstances, $cPLA_2$ translocates to the nucleus where it promotes AA release. On the other hand, potassium-induced Ca^{2+} entry can induce depolarization and the opening of voltage-dependent Ca^{2+} channels located at sites close to neurotransmitter release. However, potassium depolarization does not activate AA release, probably because $cPLA_2$ is not located close to releasing sites [133]. In agreement with this evidence of Ca^{2+} dependence of neurotransmitter-induced $cPLA_2$ activity, 5-HT receptor activation in hippocampal neurons induced an increase in PLA_2-mediated AA release that was reversed by removing extracellular Ca^{2+} [134].

$iPLA_2$ has been considered to be Ca^{2+}-independent, because its catalytic activity was found to be independent of Ca^{2+} when studied in an incubation medium [135]. However, in fractionated cytosol, Ca^{2+} later was shown to decrease $iPLA_2\beta$ activity, probably by modifying its interaction with calmodulin [43]. Multiple contact points in the 15-kDa C-terminal portion of

iPLA$_2$β have been identified as determinants of its Ca^{2+}-dependent interaction with calmodulin [44]. Interaction between calmodulin and iPLA$_2$ inhibits iPLA$_2$ activity and is modulated by Ca^{2+} [43].

iPLA$_2$β is highly localized in the ER in areas around the cell nucleus [20] and in the cytosol; it is less expressed near plasma membranes and mitochondria [18]. iPLA$_2$β immunoreactivity has been detected around the nuclear envelope in cortical and limbic areas of the rhesus brain [18], as well in dendrites and terminals, suggesting a local roles.

As illustrated in Figure 1, Ca^{2+} can be released from intracellular ER stores in several ways. The ER has two types of membrane receptors, an inositol-1,4,5-phosphate receptor (InsP$_3$R), and a ryanodine receptor (RyR) that can receive information from the cytosol and release Ca^{2+} from the ER lumen. This signaling can be evoked by purinergic [136,137], muscarinic [138], or metabotropic glutamatergic receptors [139], so as to produce receptor-mediated inositol-3-phosphate (InsP$_3$) release and activate the InsP$_3$R. Activation of NMDA receptors [140,141], AMPA receptors [142], or even InsP$_3$Rs [143] can release Ca^{2+} by "Ca^{2+}-induced Ca^{2+} release" (CICR) through activation of RyRs. Inhibition of the reticular ATPase pump (SERCA) by thapsigargin, DBHQ (2,5-di(tert-butyl)hydroquinone), or Br(2)-TITU (1,3-dibromo-2,4,6-tris (methyl-isothio-uronium) benzene), also can cause a sustained release of Ca^{2+} from the ER by a different mechanism. Ca^{2+} is believed to be released on a continuous basis from the ER and refilled by SERCA. Blocking SERCA activity may, as a result, increase cytosolic Ca^{2+} concentrations (see Figure 1) [144]. The Ca^{2+} released from intracellular stores by ATP, A23187, thapsigargin, or arginine vasopressin may activate iPLA$_2$ [42,145], even in the presence of intracellular or extracellular Ca^{2+} chelators such as BAPTA or EGTA, which suggests that ER calcium emptying can transiently modulate the enzyme availability by releasing iPLA$_2$ from calmodulin binding [145].

Smooth muscle cells treated with the calmodulin inhibitor W-7 or with thapsigargin release AA from the same pool, suggesting that iPLA$_2$β is bound to a calmodulin, and that calmodulin acts as a sensor of reticular Ca^{2+} to regulate iPLA$_2$ activity [42,44]. The PLA$_2$ family is formed by ankyrins, and ankyrins are related to protein-protein interactions and may modulate regulation of iPLA$_2$ activity by calmodulin [39]. Moreover, thapsigargin increases iPLA$_2$β expression in purified ER [146]. Strokin et al. [79], who demonstrated the exclusive release of DHA by iPLA$_2$, also showed that the ionophore A23187 increased DHA release 11-fold and AA release only 3.9 -fold compared to their respective baselines. In those studies, extracellular Ca^{2+} may have stimulated cPLA$_2$ directly by increasing Ca^{2+} close to the plasma membrane, and have activated iPLA$_2$ indirectly by releasing Ca^{2+} from intracellular stores by a CICR. ATP-induced AA release was suppressed by removing extracellular Ca^{2+} in that study, but DHA release was unchanged. Thus ATP could have induced Ca^{2+} release from intracellular stores to selectively activate iPLA$_2$ [79,147].

This putative modulation of iPLA$_2$ activity and DHA release by ER Ca^{2+} release is further suggested by experimental studies of ischemia or oxygen and glucose deprivation (OGD). In mouse C2C12 myotubes, OGD increased 4-bromoenol lactone (BEL, an iPLA$_2$ inhibitor)-sensitive iPLA$_2$ activity that could be blocked by an siRNA against iPLA$_2$β. iPLA$_2$β protein in these cells was identified mainly at the endoplasmic reticulum, where it accumulated further during OGD, whereas the mRNA level was unchanged [148]. In agreement with these results, DHA is released during decapitation-induced ischemia [149]. Ca^{2+} entry from the extracellular space is a well-known source of intracellular Ca^{2+} during OGD. However, an important component of the Ca^{2+} increase is due to ER Ca^{2+} release, and particularly SERCA dysfunction is an important mechanism for ischemic Ca^{2+} overload [150,151]. These results suggest that OGD may activate iPLA$_2$ in the ER after ER Ca^{2+} release by the physical dissociation of iPLA$_2$ from calmodulin.

Other evidence for the activation of $iPLA_2$ by Ca^{2+} derived from the ER comes from a study of the $iPLA_2$ effect on store operated calcium entry (SOCE). SOCE is another regulatory mechanism of Ca^{2+} homeostasis. It consists in the entry of Ca^{2+} from extracellular space that is induced by Ca^{2+} released from intracellular stores [152,153]. In rat cerebellar astrocytes, $iPLA_2$ is a major regulator of SOCE. During depletion of ER Ca^{2+} stores, $iPLA_2$ is believed to be activated, resulting in opening channels in plasma membrane by the formation of lysophospholipids, which may affect the lipid environment of the channels or directly interact with them. In this regard, both depletion of ER Ca^{2+} stores and inhibition of calmodulin increased BEL-sensitive $iPLA_2$ activity in cultured cerebellar astrocytes. Furthermore, the specific antisense inhibition of $iPLA_2$ reduces the SOCE [153]. This study, using antisense to inhibit $iPLA_2$ and SOCE currents as the physiological outcome, is strong evidence that $iPLA_2$ is indeed the PLA_2 subtype that can be dissociated from calmodulin either by an inhibitor of calmodulin or by Ca^{2+} release from ER.

These results suggest Ca^2-controlled activation of $iPLA_2$ *in vivo* and different possibilities for neurotransmitter regulation of AA and DHA release and signaling, since many neurotransmitters are able to stimulate $InsP_3$ formation or CICR. Given that Ca^{2+} in the ER lumen is believed to be regulated by specific proteins, changes in intracellular Ca^{2+} concentrations can transmit signals both to the ER surface and the lumen. For example, calreticulin is an ER chaperone that can detect changes in Ca^{2+} inside the ER and interact with other proteins to integrate Ca^{2+} release with different cell functions [154]. Calmodulin, and possibly other Ca^{2+} sensitive proteins, may link ER Ca^{2+} release to $iPLA_2$ activation. Ca^{2+} from these different sources, thus, may couple neurotransmission in different ways to $iPLA_2$ and $cPLA_2$ activities, thereby regulating DHA and AA signaling.

Agonist activation of dopaminergic D_2 [155–157], serotonergic $5\text{-}HT_{2A/2C}$ [158], NMDA [130] or cholinergic muscarinic receptors [102,103] has been shown to increase AA release from rat brain membrane phospholipids *in vivo*. Muscarinic and $5\text{-}HT_{2A}$ receptor activation also increased DHA release *in vivo* or *in vitro* [101–103]. D_2 and $5\text{-}HT_{2A/2C}$ agonists can activate $cPLA_2$ by a G protein mechanism [134,159], whereas 5-HT agonists and NMDA agonists can do so by increasing cell entry of extracellular Ca^{2+}, since $cPLA_2$ is Ca^{2+}-dependent [133,134]. $5\text{-}HT_{2A}$ receptor activation also can release Ca^{2+} from $InsP_3R$ stores [160], and muscarinic agonists can increase Ca^{2+} influx into the cell to also release Ca^{2+} from intracellular stores [161]. Thus, Ca^{2+} from the two sources can separately control the activities of both $cPLA_2$ and $iPLA_2$, thereby regulating AA and DHA release from membrane phospholipids.

7. Calcium modulation of PLA_2 activity and brain pathology

In many neurodegenerative, psychiatric diseases and in conditions having increased neuronal death, the modulation exerted by DHA in docosanoid production could reduce neuronal damage (see [99] for review). Inhibition by DHA of Ca^{2+} entry through L-type calcium channels could be a beneficial effect of DHA [162]. Although a description of how differential activation of $cPLA_2$ and $iPLA_2$ by Ca^{2+} could affect pathological process is beyond the scope of this review, here we briefly present data suggesting their roles.

Alzheimer Disease

Alzheimer disease is a progressive neurodegenerative disease that can involve changes brain PLA_2 and PUFA metabolism, with evidence for marked disturbances in brain Ca^{2+} homeostasis including excess Ca^{2+} release from the ER [163–165]. AA metabolism was shown to be increased in brains of Alzheimer disease patients using positron emission tomography, presumably in relation to neuroinflammation and activation of $cPLA_2$ and $sPLA_2$ via astrocytic cytokine receptors [166,167] [168–170], whose immunoreactivity have both been reported to be increased in the postmortem Alzheimer brain [50,170]. $cPLA_2$ can be activated by entry of

extracellular Ca^{2+} into cells through ionotropic NMDA receptors [127], and NMDA binding sites were decreased in the postmortem Alzheimer disease brain [171]. $cPLA_2$ mediated AA release can be increased by the β-amyloid peptide that accumulates in the Alzheimer disease brain, probably *via* mediation of NMDA receptors [172]. Additionally, a low plasma DHA level has been associated with Alzheimer disease [173], but controlled supplementation studies have not been performed. β-amyloid can induce membrane-associated oxidative stress or form an oligomeric pore in the membrane [174], which could affect $cPLA_2$ activity. DHA may be beneficial in Alzheimer disease by decreasing β-amyloid release [175].

Cerebral Ischemia

Depolarization caused by energy failure in cerebral ischemia will lead to opening of voltage-gated Ca^{2+} channels in the membrane and excessive release of neurotransmitters [176], including glutamate. Glutamate activation of NMDA receptors normally is limited by magnesium blocking the channel, but depolarization releases magnesium and the receptor can then be opened to Ca^{2+} by the excessive glutamate [177]. In ischemia, a sustained depolarization and excess glutamate can maintain the NMDA channel open and load Ca^{2+} into the cell [176], thereby activating Ca^{2+}-sensitive enzymes including $cPLA_2$ [178–181], and causing inflammatory mediator production [178,182]. Hypoxia was shown to release both AA and DHA in rat brain, at a ratio of 3.6 to 1 [149]. In ischemia, neuroprotectin D1 and DHA were protective [183–185]. DHA can block currents of L-type of calcium channels[162], and inhibit AA induced prostaglandin production [105].

Depression

Depression has been proposed to be related to NMDA receptor overactivation [186–188], with resultant neuronal damage [189]. Thus, NMDA receptor antagonists induce an antidepressant effect in animal models [190–193] and in humans [188], and classical antidepressants can regulate NMDA receptor function [186]. Neuroinflammation likely is involved in depression [194]. Decreased plasma DHA levels were found in depressed individuals with coronary problems [195], but n-3 PUFA supplementation in depressed patients produced contradictory results [196,197].

8. $iPLA_2$ and brain disease

Neurodegeneration associated with brain iron accumulation (NBIA) comprises a heterogeneous group of disorders, and includes patients with mutations in the PLA2G6 gene encoding $iPLA_2β$ [198]. Children with PLA2G6 mutations show progressive cognitive and motor skill regression, with cerebellar ataxia and dystonia, as well as cerebellar cortical atrophy and gliosis. Mice with a targeted disruption of the $iPLA2β$ gene show severe motor dysfunction, associated with widespread degeneration of brain axons and/or synapses, accompanied by the swollen axons and vacuoles [199].

9. Conclusions

$cPLA_2$ and $iPLA_2$ are important lipid regulatory enzymes that selectively release AA and DHA, respectively, from brain membrane phospholipids. The two PUFAs and their metabolites have many physiological effects and their relative rates and brain sites of release, controlled by the two enzymes and their concentrations in phospholipid, may help to fine-tune brain physiology and metabolism and when disrupted, lead to psychiatric and neurological disease. $cPLA_2$ has been shown to depend on extracellular-derived Ca^{2+} in both *in vitro* and *in vivo* studies. Although Ca^{2+} was shown not to be necessary for $iPLA_2$ activation in some *in vitro* studies, Ca^{2+} released from the intracellular stores of the ER can activate $iPLA_2$ in cells, which suggests that activation can depend on Ca^{2+} *in vivo*. Neurotransmitters coupled to $InsP_3R$ activation or

to CICR modulate iPLA$_2$ activity by regulating intracellular Ca^{2+} stores. Further experiments are needed to elaborate the *in vivo* conditions under which this occurs.

Abbreviations

AA, arachidonic acid

AMPA, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid

BEL, 4-bromoenol lactone (inhibitor of iPLA$_2$)

DHA, docosahexaenoic acid

ER, endoplasmic reticulum

CICR, Ca^{2+}-induced Ca^{2+} release

COX, cyclooxygenase

InsP$_3$R, inositol 1,4,5-trisphosphate receptor

LOX, lipoxygenase

NMDA, N-methyl-D-aspartate

OGD, oxygen and glucose deprivation

PAF-AH, Plasma activated factor-acetyl hydrolase PLA$_2$, phospholipase A$_2$

cPLA$_2$, cytosolic phospholipase A$_2$

iPLA$_2$, Ca^{2+}-independent phospholipase A$_2$

sPLA$_2$, secretory phospholipase A$_2$

PUFA, polyunsaturated fatty acid

5-HT, 5-hydroxytrypamine (serotonin)

RyR, ryondine receptor

SERCA, sarco(endo)plasmic reticulum Ca^{2+} ATPase

sn-2 position, position 2 in a 3-carbon glycerol backbone

Acknowledgments

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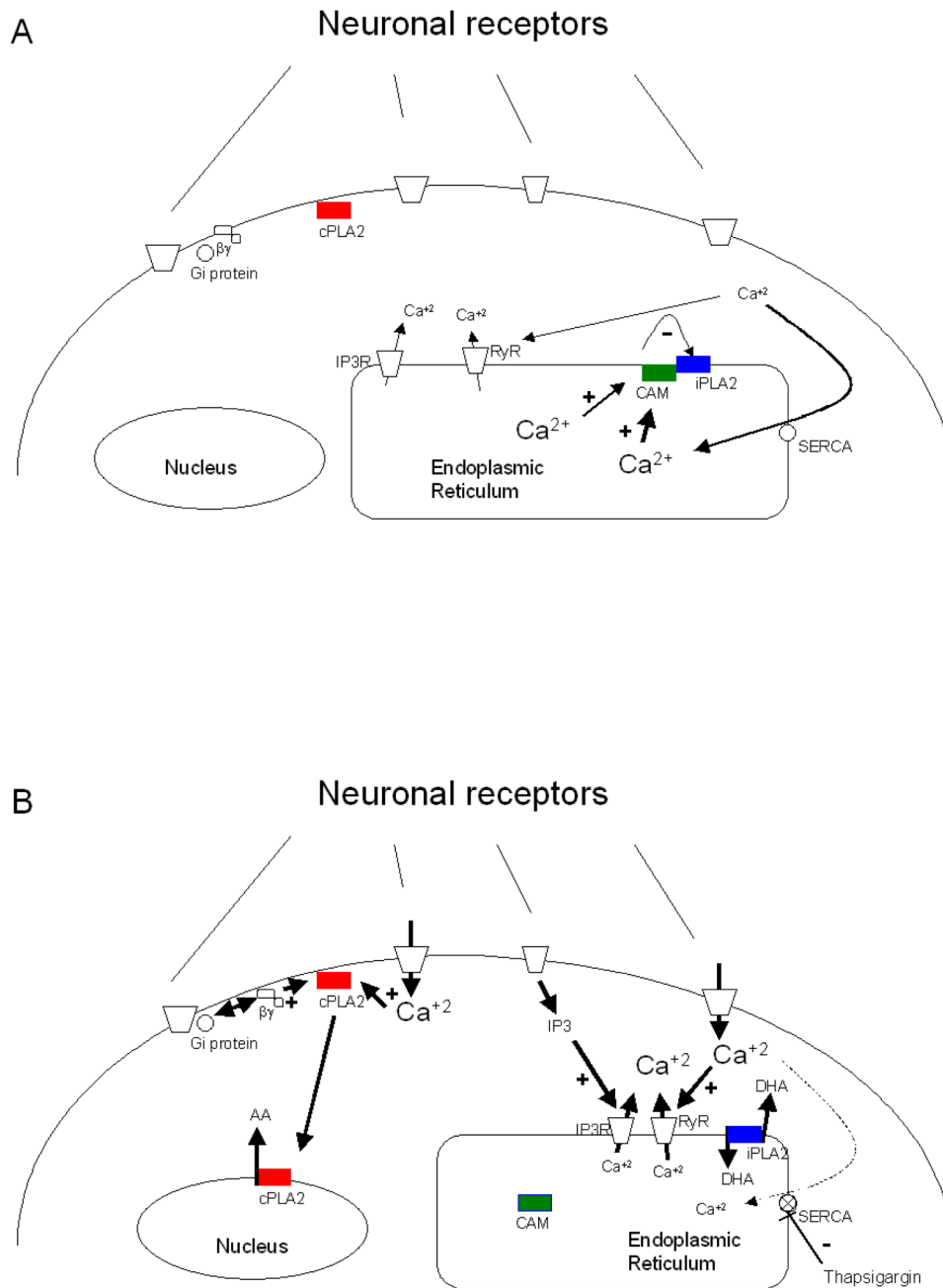
Figure 1.
Hypothetical regulation of $cPLA_2$ (red) and $iPLA_2$ (blue) activities by activation of neuronal receptors. Receptor activation can stimulate $cPLA_2$ though Ca^{2+} entry from extracellular space or via Gi protein coupling. $iPLA_2$ can be activated by Ca^{2+} release from intracellular stores through activation of $InsP_3$ or Ca^{2+} -induced Ca^{2+} release from the ER. (A) $cPLA_2$ is not stimulated by Ca^{2+} and do not release AA. SERCA works continuously to pump Ca^{2+} into the ER. In this circumstance, calmodulin inhibits $iPLA_2$ in a Ca^{2+} dependent manner. (B) Neuronal receptors are stimulated and permeate Ca^{2+} or stimulate the production of IP_3. $cPLA_2$ is translocated to the nucleus in presence of μM concentration of Ca^{2+} and release AA. When Ca^{2+} concentration is decreased inside ER, either by an increase in ER receptors stimulation

or by SERCA inhibition, probably calmodulin (green, represented as CAM) is not interacting with iPLA$_2$, allowing its activity. Differences in Ca^{2+} symbols size represent difference in concentrations of this ion, whereas small letters represents decreased calcium concentrations and big letters represents increased calcium concentrations.

Table 1

PLA$_2$ enzymes and their subcellular localization, and Ca^{2+}-dependence of their activity [1,8,16−23]

Enzyme	sPLA$_2$	cPLA$_2$	iPLA$_2$	Lysosomal-PLA$_2$	PAF-AH
Effect of Ca^{2+}	Stimulated (mM)	Translocation	No catalytic effect. Activated by Ca^{2+} release from ER [*]	No effect	No effect
Expression profile	Ubiquitous	Ubiquitous	Heart, brain, placenta, islets, testes, skeletal muscle	Heart, lung, liver, kidney, spleen, brain, thymus, inflammatory cells (macrophages)	Ubiquitous
Fatty acid preference	None	AA	DHA	oleate and linoleate are preferred relative to arachidonate	DHA and AA

[*] This effect may be achieved by Ca^{2+} release itself and not by Ca^{2+} from the ER binding the enzyme

Table 2

cPLA$_2$ and iPLA$_2$ enzymes found in brain [1,17,18,38,49–51]

	cPLA$_2$	iPLA$_2$
Localization	Cytosol	Cytosol, ER 80-kDa (iPLA$_2$β) rat
Mol. Mass	85-kDa (cPLA$_2$α) 114-kDa (cPLA$_2$β) 61 -kDa (cPLA$_2$γ)	85-kDa (subtype unknown) monkey 110-kDa (subtype unknown) bovine 30-kDa (subtype unknown) bovine