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Role of Cytosolic Calcium-Dependent Phospholipase A2 in Alzheimer's Disease Pathogenesis

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Abstract Phospholipases (PLA2s) are a superfamily of enzymes characterized by the ability to specifically hydrolyze the sn-2 ester bond of phospholipids generating arachidonic acid, utilized in inflammatory responses, and lysophospholipids involved in the control of cell membrane remodeling and fluidity. PLA2s have been so far considered a crucial element in the etiopathogenesis of several neurological diseases such as cerebral ischemia, multiple sclerosis, Parkinson's disease, and Alzheimer's disease (AD). In AD, the role of beta-amyloid (Aβ) fragments is well established although still more elusive are the molecular events of the cascade that from the Aβ accumulation leads to neurodegeneration with its clinical manifestations. However, it is well known that inflammation and alteration of lipid metabolism are common features of AD brains. Findings obtained from in vitro studies, animal models, and human brain imaging analysis point towards cPLA2 as a key molecule in the onset and maintenance of the neurodegenerative mechanism(s) of AD. In this review, we have focused on the molecular and biological evidence of the involvement of cPLA2s in the pathogenesis of AD. An insight into the molecular mechanism(s) underlying the action and the regulation of cPLA2 is of tremendous interest in the pharmaceutical and biotechnology industry in developing selective and potent inhibitors able to modulate the onset and/or the outcome of AD.

Keywords Alzheimer's disease · β-Amyloid · Neurodegeneration · Inflammation · PhospholipaseA2

Abbreviations

AA	Arachidonic acid
AD	Alzheimer's disease
APP	Amyloid precursor protein
BBB	Blood brain barrier
CNS	Central nervous system
COX	Cyclooxygenase
IP3	Inositol trisphosphate
LTD	Long-term depression
LTP	Long-term potentiation

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NFT Neurofibrillary tangles
PDE Phosphodiesters
PG Prostaglandins
PLA2 Phospholipase A2
PME Phosphomonoesters
SP Senile plaques

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative and age-related disorder that accounts for 50–60 % of all dementia cases. AD is characterized by irreversible cognitive deterioration manifesting as memory loss, language difficulties, visuospatial deficit, and impairment in judgment and decision making. Neuropathological hallmarks of AD, in post-mortem brains, are senile plaques (SP) and neurofibrillary tangles (NFTs). SP are composed mainly of fibrillar amyloid β-peptides (Aβ) generated from the abnormal proteolitic cleavage of the amyloid precursor protein (APP), a ubiquitously expressed transmembrane glycoprotein. Amyloid β-peptides are composed of 40 and/or 42 amino acids (Aβ1-40 and Aβ1-42), precipitate in insoluble form, and aggregate in brain tissues causing neuronal death [1, 2]. NFTs are aggregates of hyperphosphorylated Tau protein. Tau is a phosphoprotein with stabilizing properties that was detected in neuronal microtubules and nuclei. It is hypothesized that Tau induces neurodegeneration through the formation of filamentous deposits (NFTs) composed of hyperphosphorylated Tau [3]. Moreover, it has been recently shown that APP overexpression may influence Tau phosphorylation and its subcellular compartmentalization both in AD brain samples and in vitro, thus indicating a pathogenetic link between APP alteration and Tau abnormal phosphorylation and suggesting that the two typical hallmarks of AD may not be independent events [4].

A large bulk of genetic evidence suggests that an increased level of Aβ, especially the more aggregatory Aβ1-42 form, may be causal in AD, generating SP. If the pathogenic role of Aβ in the familial form of AD (that represents less than 5 %) is not questioned, then still debated are the pathogenic mechanisms in the sporadic forms. AD has to be regarded as the result of the overproduction of Aβ and/or of impairment of the only partially known mechanisms of its clearance [5, 6]. Still more elusive are the molecular events of the cascade that from the Aβ accumulation leads to neurodegeneration with its clinical manifestations. The presence of the marker of inflammation in AD brains is well established [7–10]. Elevated cytokines, IL-6 in particular, and chemokines as well as the accumulation of activated microglia and reactive astrocytes are found in or near the pathologic lesions of AD [11]. However, it remains unclear whether neuroinflammation may be the cause of AD neuropathology, the result of a neurodegenerative process, or may represent a secondary reaction to Aβ deposition.

Phospholipases A2 (PLA2s) are a superfamily of enzymes characterized by the ability to specifically hydrolyze the sn-2 ester bond of phospholipids [12]. PLA2s are also involved in the response to inflammatory stimuli by regulating the release of arachidonic acid (AA), a precursor of eicosanoid synthesis [13, 14]. PLA2 products are important for lipid metabolism, signal transduction processes, and host defense and have been implicated in intracellular membrane trafficking, differentiation, proliferation, and apoptotic processes [15, 16]. PLA2s have been so far considered a crucial element in the etiopathogenesis of several diseases such as cerebral ischemia [17], multiple sclerosis [18], Parkinson's disease [19], and AD [20]. In this review, we will focus on the pathogenic link between the cytoplasmic calcium-dependent isoform of PLA2 and AD.

Molecular and Cellular Biology of PLA2 in the Central Nervous System

PLA2: Nomenclature, Structure, and Biochemical Function

To date, in humans, 17 genes and 25 PLA2 isoforms have been identified. PLA2s can be distinct in five main groups on the basis of their specific features such as sequence, molecular weight, disulfide bonding patterns, and Ca^{2+} dependency. They are: (1) the secreted small molecular weight PLA2s (sPLA2s), (2) the Ca^{2+}-independent PLA2s (iPLA2s), (3) the larger cytosolic Ca^{2+}-dependent PLA2s (cPLA2s), (4) the platelet activating factor-acetylhydrolases (PAF-AH), and (5) the lysosomal PLA2s (Table 1). Only members of the first three superfamilies have been detected in the human brain [21].

sPLA2s are small secreted proteins (14–18 kDa) usually containing five to eight disulfide bonds. The members of this group use a histidine as active site, require millimolar levels of Ca^{2+} for catalysis, and do not share specificity for determined fatty acid [15, 30]. Moreover, it has been recently demonstrated that sPLA2, in the presence of lipopolysaccharide (LPS), is a potent activator of macrophages. It stimulates iNOS expression and nitrite production by a mechanism that requires the activation of NF-kB [31]. Moreover, it has been described that sPLA2 activity can be measured in cerebrospinal fluid and was found increased in patients with AD. For this reason, sPLA2 has been proposed as a valuable biomarker of neuroinflammation in AD [32].

iPLA2s (80 kDa) present in the brain are Ca^{2+}-independent enzymes, utilize a serine for catalysis, and

Table 1 CNS distribution and function of isoenzymes

Isoenzyme	CNS distribution	Function
sPLA2 [22, 23]	Ubiquitously expressed in the brain	Modulate the degranulation process leading to the release of neurotransmitters, activated by neuroinflammation
iPLA2 [24, 25]	Ubiquitously expressed in the brain	Control of the long-term potentiation (LTP) and long-term depression (LTD), induces DHA release
cPLA2 [26]	Hippocampus, amygdale, substantia nigra, thalamus, subthalamic nucleus, corpus callosum	Neuroinflammation, LTP, membrane homeostasis and fluidity, regulation of gene expression
PAF-AH [27]	Not in CNS	Immunological response, inflammation
Lysosomal PLA2 [28, 29]	Not in CNS	Expressed in alveolar macrophages, may play a role in the catabolism of pulmonary surfactant

preferentially produce linoleonyl acid [15]. Both sPLA2s and iPLA2s are ubiquitously expressed in the brain.

The three cPLA2 isoforms present in the brain (cPLA2-IVA, cPLA2-IVB, and cPLA2-IVC) have specific and well-characterized expression sites. All of them are expressed in the hippocampus, amygdale, substantia nigra, thalamus, subthalamic nucleus, and corpus callosum. cPLA2-IVB and cPLA2-IVC are also expressed in the caudate nucleus; moreover, cPLA2-IVB has been detected in the temporal, frontal, and occipital lobes [15, 20, 33]. The major products of the cPLA2-catalyzed reaction are AA and lysocompounds. In particular, AA is converted in inflammatory mediators such as prostaglandins (PG) and leukotrienes. However, it can also directly modulate cellular function by altering membrane fluidity, activating protein kinases, and regulating gene transcription. On the other hand, lysophospholipids are involved in the control of phospholipid remodeling and membrane perturbation. Thus, cPLA2 activity is tightly regulated in order to maintain levels of AA and lysophospholipids necessary for the correct cellular homeostasis [20, 23, 34]. Each of these types of PLA2s has been implicated in pathogenic mechanisms of several diseases so that there has been a tremendous interest in the pharmaceutical and biotechnology industry in developing selective and potent inhibitors of each of these types.

PLA2 Signaling and Mechanisms of Regulation

In the central nervous system (CNS), among PLA2s, sPLA2 and cPLA2 have been mostly studied. In particular, it has been reported that the sPLA2 is present in all regions of the mammalian brain and is mainly associated with synaptosomes and synaptic vesicle fractions [35]. It is synthesized in the cytoplasm and secreted in its mature form in the extracellular space. Two different types of sPLA2 cell surface receptors are known: the N type, identified in neurons, and the M type in skeletal muscle [36]. sPLA2 contains a secretion peptide and needs millimolar concentration of Ca^{2+} for its enzymatic activity. Poor is the knowledge about its physiological function. Rat brain synaptosomes and PC12 cells release sPLA2 via acetylcholine stimulation or depolarization. Based on pharmacological studies, the sPLA2 released from neuronal cells may modulate the degranulation process leading to the release of neurotransmitters [37]. Moreover, several studies reported that mitochondrial fraction from rat brain, PC12, and astrocytoma cell cultures contain significant sPLA2 activities. In PC12 cells, sPLA2 induces neurite outgrowth. Mutants with reduced sPLA2 activity exhibit a comparable reduction in neurite-inducing activity, indicating that sPLA2 plays a neurotrophin-like role in the CNS [15, 38]. Among the brain's PLA2s, iPLA2s are the less known. They are present in all brain regions with the highest activity in the striatum, hypothalamus, and hippocampus. Its proposed role in phospholipid remodeling, mitochondrial activity, and apoptosis is based on the analysis of the iPLA2β KO mice which show partial membrane loss at axon terminals accompanied by degenerative membranes in the same areas. In these mice, imaging mass spectrometry showed a prominent increase of docosahexaenoic acid-containing phosphatidylcholine in the gray matter, suggesting insufficient membrane remodeling in the presence of iPLA(2)β deficiency [39].

Differently from other PLA2 isoforms, considerable information is available about cPLA2 structure, function, and mechanisms of regulation. In particular, it is well known that it is constitutively expressed in neurons and can be induced in glia [40]. Immunolabeling and in situ hybridization studies indicate that cPLA2 is located in somata and dendrites of Purkinje cells, in astrocytes of the gray matter, as well as in hippocampal neurons. Its activity is particularly evident in the hippocampus in which, in physiological conditions, may be involved in LTP, an important mechanism for memory storage [20]. Moreover, cPLA2 is also present in endothelial cells of the cerebral microvessels [41].

cPLA2 has both lysophospholipase and transacetylase activity; however, the lysophospholipase activity is insensitive to calcium concentration. This form of enzyme must be sequestered to a phospholipid interface to be active. The binding of cPLA2 to the membrane is mediated through a

mechanism involving three steps: (1) binding of a secondary lipid messenger, (2) phosphorylation, and (3) Ca^{2+}-mediated translocation. Submicromolar calcium concentration is needed for the protein translocation from the cytosol to the membrane and for its binding to the latter [12, 15]. The cPLA2 is also activated by binding many lipid second messengers. It has been demonstrated that phosphatidylinositol 4,5 bisphosphate significantly activates the enzyme in a Ca^{2+}-independent manner. Finally, cPLA2 phosphorylation at several serine (Ser) residues is crucial in mediating the interaction of the enzyme with the membrane phospholipids. In particular, phosphorylation at the Ser-505, Ser-515, and Ser-727 is operated by mitogen-activated protein kinase (MAPK), mitogen-activated protein kinase interacting kinase (MNK1), and calmodulin kinase II (CamKII). Recent studies have demonstrated that phosphorylation at Ser 505 induces a conformation change that causes a tighter binding to the lipid surface. Finally, Ser 515 phosphorylation likely increases the activity of the enzyme through conformational changes [15] (Fig. 1).

The development of cPLA2-deficient mice helped to understand the role of cPLA2 in CNS both in normal and pathological conditions. Under basal condition, cPLA2−/− mice show significantly reduced brain AA levels, even if total phosphatidylcholine levels are not different as compared to wild-type mice. They also show reduced cyclooxygenase-2 (COX-2) mRNA and enzymatic activity, both in basal conditions and after LPS administration, without any changes in COX-1, 5-lypooxygenase, and cytochrome P450 epoxygenase activity indicating that cPLA2 and COX-2 are functionally coupled for the biosynthesis of PG [42]. Moreover, cPLA2 knockout mice do not show any alteration in other PLA2 expression and activity, suggesting that sPLA2 and iPLA2 do not compensate the loss of cPLA2 [43].

Cytosolic Calcium-Dependent PLA2 in AD

Two main hypotheses are addressed about the origin of Aβ-peptides which, in turn, generate amyloid plaques. The first postulates that the peptides originate within the CNS where they impair neuronal activities leading to the decline in cognition, mainly in memory. According to this hypothesis, in the brain, soluble Aβ oligomers are able to interfere with synaptic transmission and to initiate inflammatory processes that produce reactive oxygen species [44]. Moreover, several studies report that Aβ-peptides open channels in the cell membranes, permitting calcium ions to enter the cell and triggering several processes leading to mitochondrial

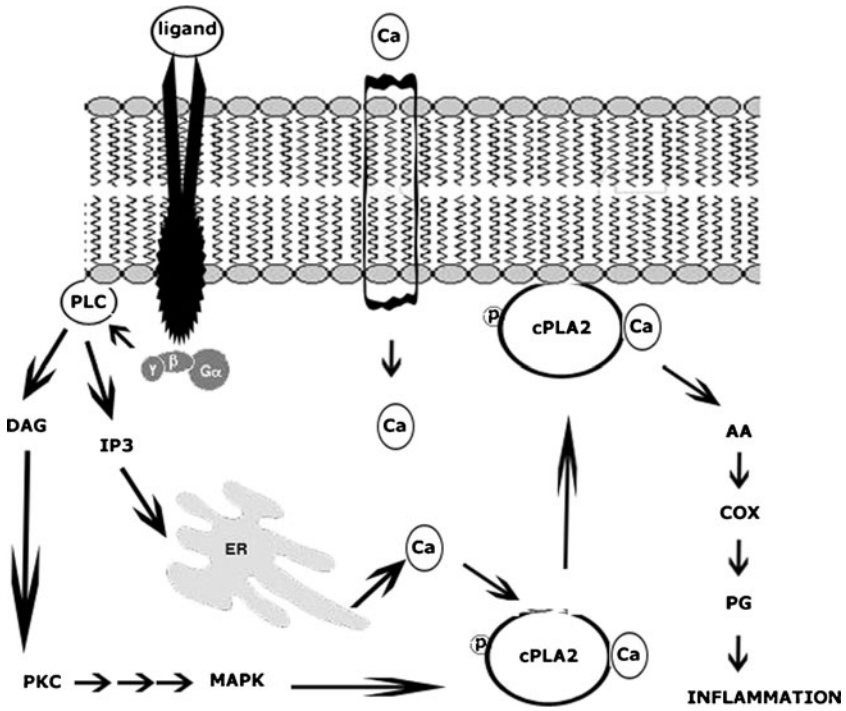

Fig. 1 cPLA2 mechanisms of regulation. PLA2 has lysophospholipase and transacetylase activity and to be active must be sequestered to a phospholipid interface. The binding of cPLA2 to the membrane is mediated through a mechanism originated by a ligand-mediated receptor activation. This mechanism triggers the binding of a secondary lipid messenger such as IP3 and diacylglycerol (*DAG*) that induce calcium release from endoplasmic reticulum and membrane channels, and cPLA2 phosphorylation at several serine (Ser) residues operated by MAPK, MNK1, and CamKII (Ca C2) crucial in mediating the interaction of the enzyme with the membrane phospholipids. Once bound to the membrane, cPLA2 activates AA cascade that leads to inflammation via COX and PG

dysfunction, inflammation, and cell death [45, 46]. This mechanism can be addressed as the central hypothesis of Aβ.

On the other hand, according to the so-called peripheral hypothesis, Aβ fragments are released continuously during cellular metabolism and circulate in soluble globular form in the bloodstream [47]. In particular, recent findings suggest that the liver may be the origin of the brain Aβ deposit [48, 49]. In normal conditions, the blood brain barrier (BBB) does not allow free bidirectional exchange of polar solutes such as Aβ between blood and brain. However, in conditions of altered BBB permeability, the influx of atypical blood-borne substances in the brain tissues could determine a number of mechanisms of brain damage that could favor Aβ production and/or accumulation in the brain [50, 51]. On this issue, it has been demonstrated that, in animal models of acute and chronic hypertension, vascular dysfunctions, altering BBB permeability, are able to induce brain damage through the increase of oxidative stress, activation of proinflammatory cytokines such as IL-6 and TNF-alpha, marked reactive astrogliosis [52], and Aβ deposition in the cortex and hippocampus [53].

In both cases, inflammation and production of reactive oxygen species play a crucial role in the pathogenesis of AD. cPLA2 may represent a pathogenetic link between the generation of Aβ fragments and the production of inflammatory molecules.

Several studies have been performed to investigate the role of cPLA2 in the onset of AD [54]. Different experimental approaches support the hypothesis that abnormalities in lipid metabolism in AD are induced by Aβ fragments [55–58]. In fact, using in vivo ^{31}P-NMR spectroscopy, increased phosphomonoester (PME) content was observed in AD brain in the early stages of the disease. Moreover, at later stages, an elevation in the amount of phosphodiesters (PDE), like glycerophosphorylethanolamine and glycerophosphorylcholine, is the most frequently reported observation [59]. It is well known that PMEs are intermediate products of phospholipid metabolism, while PDEs represent products of their breakdown. Furthermore, in vitro studies point towards an involvement of lipid metabolism in the pathogenic mechanism(s) induced by Aβ. In fact, Aβ(25–35) is able to activate cPLA2, PLC, and PLD in a human cholinergic neuroblastoma cell line, LAN-2. In particular, cPLA2 activation by Aβ(25–35) is dependent on the release of Ca^{2+} from a ryanodine-sensitive intracellular storage site, whereas it was independent of Ca^{2+} released from stores activated by inositol trisphosphate (IP3) [60]. Further support to the role of cPLA2 in mediating the effects of Aβ is suggested by experiments carried out in retinal primary cultures. In these experiments, MAPK (ERK1/2) inhibition blocked Aβ(25–35)-mediated cPLA2 phosphorylation, suggesting a role for the MAPK pathway in the AD pathogenesis [61]. Moreover, the treatment of rat cortical neurons with low concentrations of soluble Aβ(1–40) or Aβ(1–42) peptide resulted in an early calcium-dependent release of AA associated with a transient relocalization of cPLA2. Both cPLA2 antisense oligonucleotides and a selective inhibitor of cPLA2 activity abolished the release of AA from neurons and also protected cells against apoptosis induced by Aβ(1–42). Furthermore, inhibitors of the PKC, p38, and MEK/ERK pathways, which are involved in cPLA2 phosphorylation and activation, reduced Aβ oligomer-induced cell death [62]. Furthermore, in other cell types, such as endothelial cells and fibroblasts, Aβ is able to induce intracellular Ca^{2+} increase and PKC activation, thus corroborating the finding that Aβ(1–40) can activate cPLA2 also by enhancing its translocation to the plasma membrane [63]. On the other hand, several recent studies demonstrated that oligomeric Aβ(1–42) could induce cPLA2 activation also in a calcium independent manner. In fact, it has been reported that Aβ(1–42) is able to induce reactive oxygen species (ROS) production from cortical neurons through activation of NADPH oxidase. ROS derived from NADPH oxidase led to activation of ERK 1/2, phosphorylation of cPLA2a, and AA release [64, 65]. It is worth noting that in all cases, activation of ERK is involved. Actually, ERK inappropriate phosphorylation/activation has been regarded as a common molecular event in the neurodegenerative processes induced by different noxious stimuli [66].

Moreover, data obtained from analysis of human amyloid precursor protein (hAPP) transgenic mice (line J20) strongly corroborate alteration of lipid metabolism and cPLA2 involvement. Actually, the hAPP transgenic mice show elevation in AA as well as in COX-dependent metabolites as PG. This increase in PGs could be due to an increased supply of AA to inducible COX-2. AA released by cPLA2 can increase COX-2 transcription leading to increased protein levels and PG production. This causal chain could explain the increased neuronal activity and excitotoxicity which may be important in the pathogenesis of AD [67]. Moreover, elevations in AA levels may also contribute to oxidative stress since AA metabolism generates reactive oxygen species as a bio-product. Consistent with the increase in AA and its metabolites, in the hippocampus of hAPP mice, an increased activation of cPLA2 has been observed [68, 69].

Studies in humans further support the involvement of cPLA2 in AD pathogenesis. Analysis of AD brain tissues showed an increase of PMEs and PDEs as compared to nondemented control brains [70]. In addition, cPLA2 phosphorylation of Ser 505 was also increased in the hippocampus of AD patients as compared to nondemented controls and to patients with frontotemporal dementia [68].

It is consistent with previous findings that the increased content of PMEs and PDEs found in AD brain tissue is the result of increased cPLA2 activity that in turn might be

caused by Aβ [70]. A consequence of the sustained activation of cPLA2s by Aβ is the enhanced membrane phospholipid destruction. During early stages of the disease, it is likely that the cell can readily replenish these membrane components. As the disease progresses and the Aβ accumulation increases, there would be a progressive increased rate of phospholipid breakdown to replace them. This continual drainage of energy supply would compromise other cellular functions including Na^+/K^+ ATPase, ion pumps, and axoplasmic transport [71]. Eventually, the cell would succumb to these excessive demands for phospholipid replenishment. Another consequence of sustained, aberrant cPLA2 activation would be the continued formation of the lipid second messengers AA and lysophospholipids. These messengers would elicit a stereotypic cellular response to an unnecessary physiological stimulation by Aβ. The bulk of data that we reported suggest that an increase of phospholipid breakdown could represent one of the mechanisms of Aβ neurotoxicity in AD. Thus, the observed PME and PDE increase, respectively at the early and late stage of the disease, might be its expression.

According to the crucial role played by cPLA2 in AD pathogenesis, there is a recent observation that in an AD transgenic mouse, cPLA2 reduction ameliorates cognitive deficits [68]. However, some studies in laboratory animals have shown that the inhibition of cPLA2, as well as the blockade of AA production, impairs learning and memory simulating deficits that are found in the earliest phases of AD. For instance, Schaeffer et al. showed that infusion of cPLA2 inhibitors into rat hippocampal CA1 field impaired the acquisition of short- and long-term memory [72]. Furthermore, Smesny and colleagues described a reduced cPLA2 activity in cerebrospinal fluid (CSF) in AD, vascular dementia (VD), and mixed AD/vascular dementia (MD). In particular, they analyzed intracellular cPLA2 activity in CSF of 16 AD, 12 VD, and 15 MD patients, and 19 healthy control subjects using the cPLA2-specific substrate NBDC6-HPC [73]. Significantly reduced cPLA2 activity was not only found in AD, but also in VD and MD [74].

Nevertheless, the bulk of the literature points towards cPLA2 as a key player in the regulation of cognitive functions and may be regarded as a possible therapeutic target amenable to be manipulated by pharmacological and nonpharmacological approaches (Fig. 2).

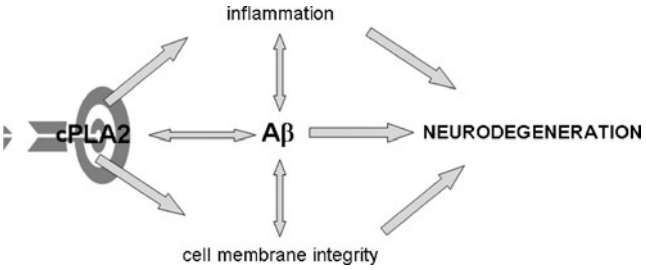

Fig. 2 cPLA2 may represent a key molecule in the pathogenesis of AD. PLA2s are a superfamily of enzymes able to generate arachidonic acid, utilized in inflammatory responses and lysophospholipids involved in the control of cell membrane remodeling and fluidity. Both these mechanisms are involved in the origin and/or accumulation of Aβ into the brain tissue with the consequent onset of the irreversible neurodegenerative cascade. Thus, cPLA2 may represent an intriguing research target amenable to be manipulated by pharmacological and nonpharmacological approach

Future Perspectives: cPLA2 as Therapeutic Target

cPLA2s and their inhibitors represent attractive and intriguing targets for the pharmaceutical researcher because of their wide range of effects and activities in the CNS and in part because they are found widely in nature. Indeed, natural cPLA2 inhibitors extracted from the ashwaganda plant (*Withania somnifera*) are used in Ayurvedic medicine for immune support. Moreover, the aqueous extracts of this plant have been reported to neutralize venom of the Indian speckled cobra (*Naja naja*) which induces neurotoxicity, myotoxicity, and inflammation [75]. Finally, it has been reported that a naturally isolated polypeptide with cPLA2 inhibitory activity blocked the inflammatory response to injury and prevented neural degeneration when administrated to rats with traumatic brain injury [76].

Several phospholipase A2 synthetic inhibitors have been developed and used for the treatment of ischemia and other neurological diseases in cell culture. In particular, in kainic acid-mediated neurotoxicity, the activities of phospholipase A2 isoforms and their immunoreactivities are markedly increased, and phospholipase A2 inhibitors such as arachidonyl trifluoromethyl ketone (AACOCF3), bromoenol lactone, and vitamin E inhibit phospholipase A2 activity and immunoreactivity [20]. However, although AACOCF3 is a 500-fold more potent inhibitor of cPLA2 than sPLA2 [77], it also blocks cyclooxygenase activity [78]. Moreover, bromoenol lactone that is considered an iPLA2 inhibitor also inhibits, even though at higher concentration, cPLA2 and sPLA2 [20]. Finally, in contrast to cell culture studies, in vivo studies showed that vitamin E has only symptomatic effects on AD and ischemia animal models, but there is no evidence about its influence on PLA2 expression or activity in brain tissues [20]. Thus, the development of synthetic chemical inhibitors of cPLA2s found, up to date, some problems associated with the specificity because of the wide number of isoforms and similarity of action. Moreover, at this time, very little is known about in vivo neurochemical effects, mechanism of action, or toxicity of phospholipase A2 inhibitors in human or animal models of neurological disorders [20].

Thus, the development of specific inhibitors for different cPLA2 isoforms should be an important goal for future

research on brain cPLA2 activities. The chemical approach together with molecular biological procedures may provide the important information needed to develop specific cPLA2 inhibitors that can be used to retard oxidative stress and inflammatory reactions during neurodegeneration. In fact, in recent years, advanced molecular biology procedures have been used in a number of studies to overcome some of the problems associated with the specificity of chemical inhibitors of cPLA2. In particular, antisense oligonucleotide and RNAi have been developed to selectively inhibit the different PLA2 isoforms [79].

Literature reporting that nonpharmacological interventions with dietary lipid compounds are recognized as important protective measures against the development of AD-related pathology in animal models cannot be ignored. In fact, animal studies have shown that long-term intake of dietary compounds enriched with AA preserves hippocampal synaptic plasticity and neuronal membrane fluidity and enhances spatial memory performance in aged rats [80–83]. Moreover, Kotani and colleagues investigated the effects of supplementation with AA in human amnesic patients and demonstrated that subjects with mild cognitive impairment treated with the supplementation showed a significant improvement of the immediate memory and attention score, and subjects with organic brain lesions showed a significant improvement of immediate and delayed memories [84].

However, as extensively demonstrated, cPLA2 activation is a deleterious event for its role in promoting intracellular accumulation of AA, which is a proinflammatory mechanism being the precursor of PG and COX2. The accumulation of AA at the cell membrane is extremely detrimental for its strong peroxidation potential. In fact, the peroxidated cell membrane determines peroxidation of other compartments of the cell, with a strong domino effect on cellular DNA and protein oxidation, thus accumulating huge amounts of ROS [85].

In conclusion, in the light of the pathogenetic role of cPLA2 in AD, a deep insight into the molecular and cellular mechanism(s) of its regulation may be instrumental in finding new inhibitors to manage this devastating neurodegenerative disease.

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