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REVIEW

Differential regulation of $cPLA_2$ and $iPLA_2$ expression in the brain

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Abstract **The phospholipase A_2 (PLA_2) family members are critical regulators of membrane structure and lipid composition and have been implicated in neuroinflammation, oxidative stress and neurodegeneration. Here, we review the published data describing regulation of $cPLA_2$ and $iPLA_2$ gene expression. Based on promoter sequence, $cPLA_2$ expression can be regulated by glucocorticoid and pro-inflammatory cytokines, whereas transcription of $iPLA_2$ can be controlled in response to sterol level. RNA degradation in 3′ UTR and epigenetic mechanisms may be involved in the regulation of $cPLA_2$ and $iPLA_2$ expression, respectively. MicroRNA target sequences lie within $cPLA_2$ and $iPLA_2$ mRNAs. Together, these findings indicate differential regulation of $cPLA_2$ and $iPLA_2$ expression. It is hoped that determination of diverse regulatory mechanisms of the PLA_2 family may open new doors for development of novel therapeutic compounds that modulate PLA_2 expression and function in the treatment of brain diseases.**

Keywords phospholipase A_2, transcriptional regulation, single nucleotide polymorphism, miRNA

Introduction

The phospholipase A_2 (PLA_2) superfamily of enzymes catalyzes the hydrolysis of unsaturated fatty acids from the *sn*-2 position of glycerol moiety of neural membrane phospholipids. The PLA_2 superfamily is classified into cytosolic PLA_2 ($cPLA_2$), calcium-independent PLA_2 ($iPLA_2$), plasmalogen-selective PLA_2 (PlsEtn-PLA_2) and secretory PLA_2 ($sPLA_2$). The occurrence of multiple forms of PLA_2 and their differential gene expression in brain provides diversity in their function, and specificity for regulation of enzymatic activity in response to a wide range of extracellular and intracellular signals. The isoforms of PLA_2 do not function interchangeably but act in parallel to transduce signals. They act on different pools of phospholipids located in neural cells, and are regulated not only through gene expression as reviewed in this article, but also by different coupling mechanisms to generate lipid mediators. This process provides brain tissue with great versatility in ensuring that neural cells efficiently utilize fatty acids and its metabolites (Farooqui et al., 1997).

It is proposed that under pathological conditions, increased activity of Ca^{2+}-independent PlsEtn-PLA_2 may initiate neural injury by decreasing plasmalogens (a unique vinyl ether containing phospholipid), altering membrane fluidity, and increasing neural membrane permeability (Farooqui, 2010) (Fig.1). This leads to increased intracellular Ca^{2+} which facilitates the translocation of various paralogs of $cPLA_2$ from the cytosol to the plasma membrane, endoplasmic reticulum or nuclear membrane. $cPLA_2$ activity results in hydrolysis of neural membrane phosphatidylcholine. As the concentration of Ca^{2+} reaches the mM range, $sPLA_2$ is activated, leading to neuronal injury and death (Farooqui, 2010).

PLA_2 isoforms in the brain

$cPLA_2$

There are at least six $cPLA_2$ isoforms, namely $cPLA_2\alpha$, β, γ, δ, ε, and ζ, identified in mammals (Murakami et al., 2011a). Among them, $cPLA_2\alpha$, β and γ are present in the brain (Farooqui et al., 2000, 2006). $cPLA_2\alpha$ is an 85 kDa protein

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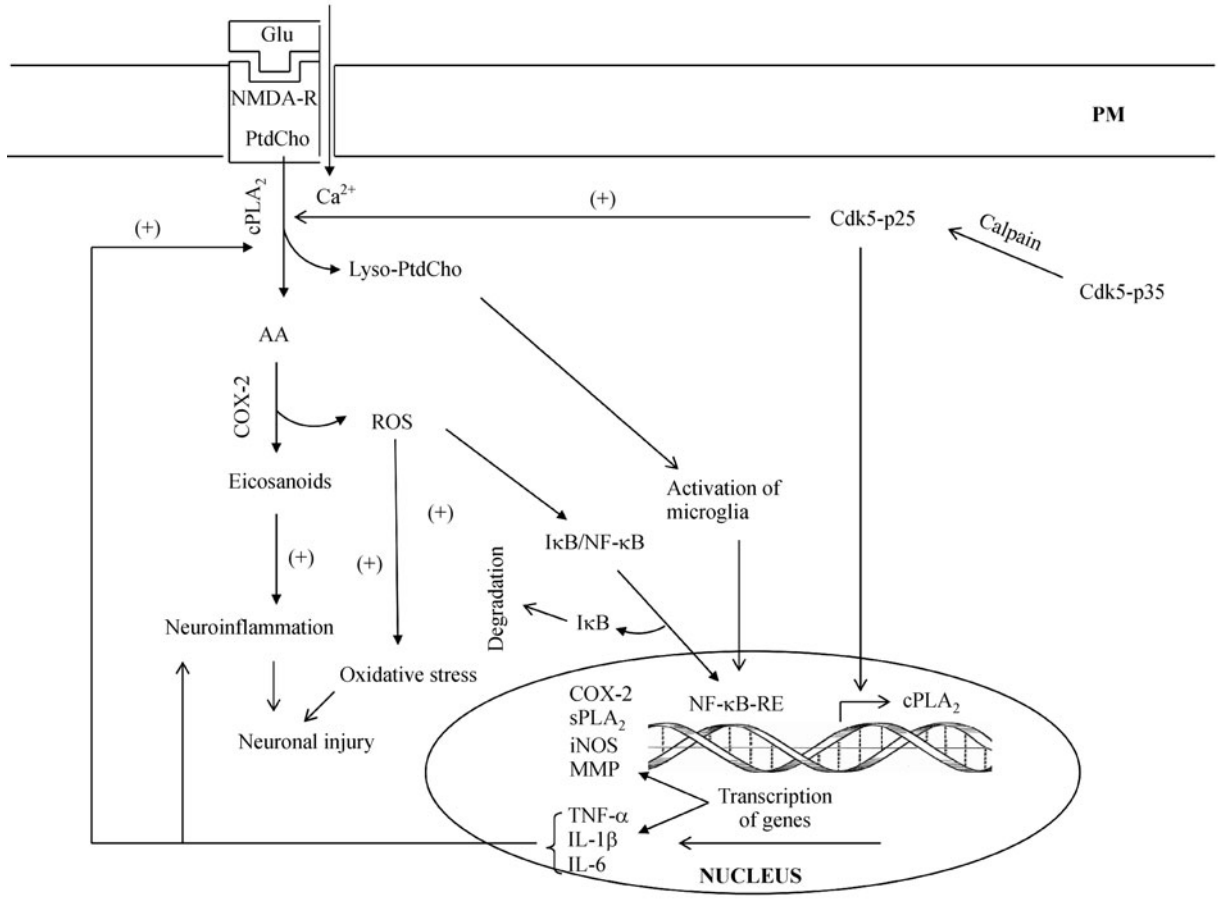

Figure 1 Hypothetical model showing expression of $cPLA_2$ and proinflammatory cytokines. Plasma membrane (PM); *N*-methyl-D-aspartate receptor (NMDA-R); glutamate (Glu); phosphatidylcholine (PtdCho); lyso-phosphatidylcholine (lyso-PtdCho); cytosolic phospholipase A_2 ($cPLA_2$); secretory phospholipase A_2 ($sPLA_2$); cyclooxygenase (COX-2); arachidonic acid (AA); reactive oxygen species (ROS); cyclin-dependent kinase 5 (Cdk5); a component of cyclin-dependent kinase 5 (p35); a calpain cleavage product of p35 (p25); nuclear factor kappaB (NF-κB); nuclear factor kappaB response element (NF-κB-RE); inhibitory subunit of NF-κB (IκB); tumor necrosis factor-α (TNF-α); interleukin-1β (IL-1β); interleukin-6 (IL-6); matrix metalloproteinases (MMPs); positive sign (+) represents upregulation.

comprising of a calcium binding domain and a catalytic domain. $cPLA_2\beta$, a 114 kDa protein, also has a calcium binding domain, but $cPLA_2\gamma$, a 61 kDa protein, does not contain a calcium binding domain and has a prenyl group. All three isoforms are detected in human brain and expressed in the hippocampus, amygdala, substantia nigra, thalamus, subthalamic nucleus and corpus callosum (Schaeffer et al., 2010). The major products of the $cPLA_2$-catalyzed reaction are arachidonic acid (AA) and lysophospholipids. AA directly modulates cellular function by altering membrane fluidity, activating protein kinases, and regulating gene transcription. AA can also be converted to inflammatory mediators such as prostaglandins, leukotrienes and thromboxanes. Lysophospholipids are involved in phospholipid remodeling and membrane perturbation. Thus, $cPLA_2$ activity is tightly regulated to maintain levels of AA and lysophospholipids necessary for cellular homeostasis.

$cPLA_2$ has been implicated in pathogenic mechanisms of several brain diseases. PLA_2 inhibitors reduce the release of excitatory amino acids from the cortex following ischemia in rats (Phillis and O'Regan, 1996). Low constitutive expression of $cPLA_2$ is present in the cerebral cortex and hippocampus (Ong et al., 1999), but $cPLA_2$ mRNA and protein are rapidly induced after excitotoxic injury (Sandhya et al., 1998; Ong et al., 2003) or transient forebrain ischemia (Owada et al., 1994; Clemens et al., 1996). The increased $cPLA_2$ expression is associated with elevated levels of the toxic lipid peroxidation product, 4-hydroxynonenal. $cPLA_2$ but not $iPLA_2$ inhibitors, have been shown to reduce the level of this metabolite, and have a neuroprotective effect on hippocampal neurons after excitotoxic injury (Lu et al., 2001). Likewise, $cPLA_2$ inhibitors significantly protect cultured hippocampal pyramidal neurons from oxygen-glucose deprivation (Arai et al., 2001), and improve functional recovery in a mouse model of

spinal cord injury (Huang et al., 2009). Together, the results indicate that $cPLA_2$ inhibition may be an attractive approach in designing novel drugs for treatment of brain injury.

$iPLA_2$

$iPLA_2$ hydrolyzes *sn*-2 fatty acids from phosphatidylcholine with preferences linoleoyl > palmitoyl > oleoyl > arachidonyl group (Farooqui et al., 2006). Major $iPLA_2$ activity is found in two isoforms ($iPLA_2\beta$ and $iPLA_2\gamma$), although minor $iPLA_2$ isoforms δ, ε, ξ, and η which display triglyceride lipase and transacylase activities are aslo present (Quistad et al., 2003; Jenkins et al., 2004). $iPLA_2\beta$ has unique structural features, including eight N-terminal ankyrin repeats, caspase-3 cleavage sites, an ATP binding domain, a serine lipase consensus sequence (GXSXG), a bipartite nuclear localization sequence, and a C-terminal calmodulin binding domain (Tang et al., 1997; Ma and Turk, 2001). The human $iPLA_2$ gene *PLA2G6*, maps to chromosome 22q13.1 and encodes several isoforms (Ma et al., 1999). Higher constitutive mRNA expression of $iPLA_2$ than $cPLA_2$ is present in the normal rat brain (Ong et al., 2010). $iPLA_2$ immunoreactivity is observed in the cerebral cortex, hippocampus, striatum and brainstem. The enzyme is detected on the nuclear envelope of neurons, and dendrites and axon terminals at electron microscopy (Ong et al., 2005). $iPLA_2$ may play an important role in long-term potentiation and long-term depression, believed to underlie learning and memory in the hippocampus (Fitzpatrick and Baudry, 1994; Wolf et al., 1995; Fujita et al., 2001), and in neural cell proliferation, apoptosis, and differentiation (Farooqui et al., 2004). A frontal variant of Alzheimer's disease exhibits decreased calcium-independent phospholipase A_2 activity in the prefrontal cortex (Talbot et al., 2000). $iPLA_2$ has also been found to play an important role in effect of the antidepressant, maprotiline. Positive effects of the drug on climbing behavior in the forced swim test are abolished after injection of $iPLA_2$ antisense oligonucleotide to the prefrontal cortex (Lee et al., 2009a; 2012). Moreover, $iPLA_2$ antisense injection to the striatum of rats results in decreased pre-pulse inhibition of the auditory startle reflex (Lee et al., 2009b), a common finding in human schizophrenic patients. It is therefore possible that $iPLA_2$ activation may be a novel approach for new drugs to treat cognitive deficits and neurodegeneration.

$sPLA_2$

The mammalian $sPLA_2$ enzymes include groups IB, IIA, IIC, IID, IIE, IIF, III, V, X, XIIA and XIIB $sPLA_2$ and many of these subtypes are present in the brain. Their biological functions have received in-depth treatment in an excellent article by Murakami et al. (2011b). The regulation of $sPLA_2$ isoforms however, needs further investigation and is not included in this review.

Regulation of $cPLA_2$ and $iPLA_2$ expression by transcription factors

$cPLA_2\alpha$

mRNA transcription of $cPLA_2$ may play a role in the amount of expressed enzyme in a cell, and thus affect total phospholipase A_2 activity and AA release. Expression of $cPLA_2$ through changes in gene transcription is mediated by a number of endogenous agonists including cytokines, thrombin and growth factors (Cowan et al., 2004; Tsou et al., 2008). In addition, overexpression of p25, a component of the cytoarchitecture regulating enzyme, cyclin-dependent kinase 5 (Cdk5), causes upregulation of $cPLA_2$ expression activity, and increases the levels of lysophosphatidylcholine (Sundaram et al., 2012). It is proposed that overexpression of p25 mediates this response via the transcriptional regulation of $cPLA_2$ gene expression. The human $cPLA_2\alpha$ promoter is characterized by lack of TATA or described downstream promoter elements. The minimal basal promoter of human $cPLA_2\alpha$ is located within 73 bp of sequence proximal to the transcription start site, and an element between 31 and 73 is critical for basal transcriptional activity (Cowan et al., 2004). A number of putative binding sites for possible regulatory elements have been identified within the promoter, including nuclear factor κB (NF-κB), glucocorticoid response element (GRE), interferon-γ-responsive element (γ-IRE) and interferon γ-activated sequence (GAS) sites (Morri et al., 1994; Wu et al., 1994a; Cowan et al., 2004). In addition, the $cPLA_2$ promoter has a distal cluster of hypoxia-inducible factor-1 (HIF-1)-DNA binding sites (Alexandrov et al., 2006).

Two Sp1 binding sites on the $cPLA_2\alpha$ promoter are required for response to phorbol ester (PMA) and c-Jun overexpression (Tsou et al., 2008). Upregulation of $cPLA_2\alpha$ by glucocorticoids requires the cAMP/protein kinase A/CREB-1 pathway, and phosphorylated CREB-1 interacts with GR at the GRE on the promoter (Guo et al., 2010). IL-1β-induced upregulation of $cPLA_2$ is mediated by a myeloid differentiation factor 88/c-Src-dependent matrix metalloproteinase/heparin binding epidermal growth factor cascade linking to activation of epidermal growth factor (EGF) receptor/phosphatidylinositol 3-kinase (PtdIns 3K)/Akt, p300, and NF-κB p65 pathways (Lee et al., 2010; Chi et al., 2011). Activation of Akt leads to enhanced histone acetyltransferase activity on NF-κB elements of the $cPLA_2$ promoter (Chi et al., 2011). TNF-α-induced upregulation of $cPLA_2$ in human tracheal smooth muscle cells is mediated by activation of MAPKs, translocation of NF-κB, and association of p300 and histone H4 (Lee et al., 2011). Blocking the p38 MAPK signaling pathway with SB203580 abolishes the effect of IL-1β-induced $cPLA_2\alpha$ gene expression. ATP-induced upregulation of $cPLA_2$ is mediated through activation of PKCδ/c-Src/EGF receptor/PI3K/Akt pathway (Lin et al., 2012).

cPLA$_2$γ

cPLA$_2$γ mRNA is induced by TNFα in lung epithelial cells (Bickford et al., 2012). A TNFα-responsive element in the proximal cPLA$_2$γ promoter region resides within 114 bp upstream of the transcription start site. CRE, NF-κB and E-box promoter elements are identified as functional transcription factor binding sites within the proximal cPLA$_2$γ enhancer/promoter, and interact with ATF-2–c-Jun, p65–p65 and USF1–USF2 respectively (Bickford et al., 2012).

iPLA$_2$

The promoter of human iPLA$_2$ gene has been partially characterized, and shown to contain a CpG island but lack a TATA box, suggesting that iPLA$_2$ is a housekeeping gene (Larsson Forsell et al., 1999). The 5′ flanking region of iPLA$_2$ contains a putative sterol-regulatory element (SRE) with a canonical E-box near a putative binding site for NF-Y, a potential cofactor for transcriptional regulation by sterol regulatory element binding proteins (SREBPs). Expression of iPLA$_2$ mRNA and protein is induced under sterol-depleted conditions (Seashols et al., 2004). Electrophoretic mobility shift assay (EMSA) analysis shows that mature SREBP-2 forms a complex with a 30-mer EMSA probe corresponding to the iPLA$_2$ promoter regions. In contrast, only modest association is found when a mutant EMSA probe is used. Luciferase reporter assay indicates that sterol depletion induces transcription of iPLA$_2$, and cells with constitutive expression of mature SREBP proteins show increased iPLA$_2$ activity and expression (Seashols et al., 2004).

Regulation of cPLA$_2$ and iPLA$_2$ expression by epigenetic mechanisms

The result of CpG island search shows no CpG island in the cPLA$_2$ promoter (Takai and Jones, 2003), whereas the iPLA$_2$ gene has a CpG island on its promoter (Larsson Forsell et al., 1999). Hypermethylation typically occurs at CpG islands in the promoter region and is associated with gene inactivation; hence, epigenetic mechanisms may be involved in regulation of iPLA$_2$ expression.

Regulation of cPLA$_2$ and iPLA$_2$ expression by miRNAs

cPLA$_2$α

MicroRNAs (miRNA) are small non-coding RNAs that negatively regulate gene expression in a sequence-specific manner. miRNA binds to the 3′ UTRs on target mRNA sequences, resulting in inhibition of translation, mRNA degradation or DNA methylation (Kusenda et al., 2006). miRanda from the Sanger miR Database predicts several miRNA targeting cPLA$_2$α mRNA sequence, including hsa-miR-374a, hsa-miR-374b, hsa-miR-448, hsa-miR-543 and hsa-miR-144.

iPLA$_2$

Based on miRanda, iPLA$_2$ mRNA sequence also has several miRNA target sites. Deletion/insertion polymorphism in the 3′ UTR region of the iPLA$_2$ gene with a frequency higher than 0.10 on putative miRNA binding sites may affect the expression of this enzyme.

Effect of human mutations on cPLA$_2$ and iPLA$_2$

cPLA$_2$α

Heterozygosity for a 331T-C transition and a 1454G-A transition in cPLA$_2$α, resulting in a ser111-to-pro (S111P) and arg485-to-his (R485H) substitutions, respectively, was reported in a patient with ulcers of the small intestine, platelet dysfunction, and globally decreased eicosanoid production (Adler et al., 2008). The S111P mutation hampers calcium binding and membrane translocation without affecting catalytic activity of the enzyme. In contrast, the R485H mutation does not affect membrane translocation, but blocks its catalytic activity (Reed et al., 2011). Another mutation, D43N, abrogates the Ca^{2+} binding capacity and translocation of cPLA$_2$ to membranes but does not affect enzyme activation or formation of lipid droplets, whereas a S505A mutation does not affect membrane relocation of the enzyme in response to Ca^{2+}, but prevents its phosphorylation, activation, and the appearance of lipid droplets (Gubern et al., 2009). The rs3820185 C, Rs12749354 C and rs127446200 GG genotypes are frequently found in patients with familial adenomatous polyposis (Umeno et al., 2010).

iPLA$_2$

Infantile neuroaxonal dystrophy (INAD) is an autosomal recessive disorder with early onset and rapid progression of hypotonia, hyperreflexia and tetraparesis. A locus for INAD and neurodegeneration with brain iron accumulation (NBIA) has been mapped to chromosome 22q12-13, and identified mutations in iPLA$_2$ in NBIA, INAD and the related Karak syndrome (Morgan et al., 2006; Gregory et al., 2008; Kurian et al., 2008). Moreover, iPLA$_2$ has been reported to be the causative gene for PARK14 linked autosomal recessive early-onset dystonia-parkinsonism (Tomiyama et al., 2011). All reported risk variants are located in protein coding regions, and it is suggested that they affect catalytic- instead of transcription activity, or result in shorter enzymatically inactive isoforms that act as dominant-negative inhibitors (Morgan et al., 2006).

Disruption of the $iPLA_2\beta$ gene leads to decreased insulin secretion (Bao et al., 2006a). The fasting and fed blood glucose concentrations of iPLA2β null and wild-type mice are essentially identical, but $iPLA_2\beta$ null mice develop more severe hyperglycemia than wild-type mice after administration of multiple low doses of the β-cell toxin, streptozotocin (Bao et al., 2006a).

In contrast to $iPLA_2\beta$ null mice, $iPLA_2\gamma$ null mice exhibit remarkable resistance to obesity and metabolic abnormalities after consumption of western diet, indicating that $iPLA_2\gamma$ plays an important role in insulin secretion and metabolic regulation (Bao et al., 2006b).

Small molecules affecting $cPLA_2$ and $iPLA_2$ expression

$cPLA_2\alpha$

Induction of $cPLA_2\alpha$ by cortisol occurs in cultured human amnion fibroblasts, which requires Gαs induction and interaction of phosphorylated CREB-1 with GR at the GRE on the $cPLA_2\alpha$ promoter (Guo et al., 2010). In contrast, the GR antagonist RU486 blocks cortisol-induced $cPLA_2\alpha$ expression. Interferon-γ is a pro-inflammatory cytokine, and stimulates $cPLA_2$ gene transcription as well as AA release (Wu et al., 1994b). The 5′ flanking DNA of the $cPLA_2\alpha$ gene contain γ-IRE and GAS sites that are involved in the interferon induced gene expression (Wu et al., 1994a). EGF, platelet-derived growth factor (PDGF), fetal bovine serum (FBS) and PMA increase the steady-state level of $cPLA_2$ mRNA in cultured mesangial cells (Maxwell et al., 1993). These findings suggest that GR, interferon-γ, EGF, PDGF and PMA may be potential therapeutic targets for regulation of $cPLA_2\alpha$ enzyme expression.

$cPLA_2\alpha$ mRNA turnover plays a role in determining the level of enzyme expression. Treatment of cells with cycloheximide results in induction of gene expression, suggesting possible involvement of a labile mRNA-degrading protein in regulation of transcript abundance (Maxwell et al., 1993). Studies using chimeric 3′ UTR constructs support the view that adenosine-uridine rich element (ARE) in the 3′ UTR of the rat $cPLA_2$ gene may be responsible for instability of $cPLA_2$ transcripts (Liao et al., 2011). Further studies on functional domains at the 3′ UTR of the $cPLA_2$ gene should help to clarify the molecular mechanisms that affect turnover of $cPLA_2$ mRNA (Tay et al., 1994).

$iPLA_2$

$iPLA_2$ transcription is regulated through sterols and SREBP-2. Depletion of sterols induces $iPLA_2$ mRNA and protein expression. Conversely, cells expressing SREBP-2 show increased $iPLA_2$ expression (Seashols et al., 2004). Since statins increase the activation of SREBP-2 (Mascaró et al., 2000; Roglans et al., 2002), this suggests that these drugs may be inducers of $iPLA_2$ transcription.

Regulation of PLA_2 expression by reactive oxygen species (ROS)

Non-enzymatic oxidation of arachidonic acid produces ROS. Under physiological conditions, ROS are neutralized by antioxidant enzymes, but under pathological conditions, high level of ROS is able to modulate transcription factors such as NF-κB, HIF, CREB, AP-1, ATF2, A-1, CHOP-1, and E2F. The molecular mechanisms underlying ROS-mediated modulation of transcription factors are not fully understood, but it is increasingly evident that activation of protein kinases and regulation of stress responsive proteins by ROS may be closely associated with the above alterations (Adler et al., 1999). The activation of NF-κB appears to be a central event-ROS facilitates the migration of NF-κB from the cytosol to the nucleus, where it binds to the κB domain of the target gene promoter, leading to transcriptional activation of many proinflammatory cytokines (TNF-α, IL-1β, and IL-10), chemokines, immune receptors, and cell surface adhesion molecules (Li and Stark, 2002). They lead to activation of PLA_2 isoforms, and initiation of inflammatory responses through the participation of cyclooxygenase-2 (Farooqui et al., 2010).

Conclusion

Significant progress has been made on identification and regulation of brain PLA_2s during the past 15 years. These enzymes constitute a large family of distinct proteins involved in hydrolysis of neural membrane phospholipids. Their reaction products (free fatty acids including AA, and lysophospholipids) not only act as intracellular second messengers, but can also be converted into eicosanoids and platelet activating factor. Tight regulation of PLA_2 isozymes is necessary for maintaining physiologic levels of fatty acids and their metabolites in neural cells. Future studies should elucidate cell-type specific regulation and association of PLA_2 isoforms with human diseases. It is hoped that determination of diverse regulatory mechanisms of the PLA_2 family may open new doors for development of novel therapeutic compounds, that modulate PLA_2 expression and function in the treatment of brain diseases.

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