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Phospholipase A₂ and Arachidonic Acid in Alzheimer's Disease

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Abstract

Essential fatty acids (EFA) play a critical role in the brain and regulate many of the processes altered in Alzheimer's disease (AD). Technical advances are allowing for the dissection of complex lipid pathways in normal and diseased states. Arachidonic acid (AA) and specific isoforms of phospholipase A₂ (PLA₂) appear to play critical mediator roles in amyloid- β (A β) - induced pathogenesis, leading to learning, memory, and behavioral impairments in mouse models of AD. These findings and ongoing research into lipid biology in AD and related disorders promise to reveal new pharmacological targets that may lead to better treatments for these devastating conditions.

Essential Fatty Acids and Phospholipase A₂

Essential fatty acids comprise a subset of unsaturated fatty acids that play critical roles in normal neuronal and glial physiology by regulating intracellular signaling and membrane function. Humans rely on dietary intake of EFAs because they lack the necessary enzymes to synthesize them. EFAs are packaged into hepatic lipoproteins before transport to the brain where they are incorporated into phospholipids (PLs). EFAs can be released from the sn-2 position of PLs by phospholipase A₂. Liberated EFAs and their metabolic products modulate synaptic function, neuronal toxicity, cerebrovascular tone, neuroinflammation, amyloid precursor protein (APP) processing, and oxidative stress [1,2].

EFAs can be subdivided into omega-3 and omega-6 subgroups, depending on the distance between the end of the fatty acid chain and the nearest double bond. The principal omega-3 fatty acids are α -linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The principal omega-6 fatty acids are linoleic acid (LA) and AA (Figure 1). In the brain, AA and DHA appear to be the most important. DHA and AA are enriched in brain PLs, make up the majority of free fatty acids and appear to be the most biologically active [1,3].

PLA₂s make up a growing family of lipases that are categorized into 12 groups and vary by biological activity, substrate specificity, activating factors and localization [4,5]. In the CNS, Groups IIA, IVA, V and VI have been studied the most [6,7]. GIVA-PLA₂ has the strongest substrate specificity for AA [5], is expressed constitutively in neurons [3,8,9] and can be induced in glia [10]. PLA₂ activity is particularly high in the hippocampus, consistent with

the high levels of GIVA-PLA₂ protein in hippocampal neurons [3]. However, in the brain, GIVA-PLA₂ is also present in endothelial cells, vascular smooth muscle cells and hematopoietic cells [11,12]. GIVA-PLA₂ is primarily regulated by intracellular Ca²⁺ concentrations and by phosphorylation at several sites that control its translocation to and interaction with its PL substrate [5]. The phosphorylation sites are regulated primarily by mitogen-activated protein (MAP) kinases [5]. Free AA levels in the brain are probably determined mostly by GIVA-PLA₂ activity, although AA may also be generated as a byproduct of endocannabinoid hydrolysis by fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL)[13].

GVIA-PLA₂ is expressed in diverse cell types and brain regions [14] and, in contrast to GIVA-PLA₂, does not require Ca²⁺ for activation. Although it does not have a preference for any particular fatty acid substrate [4], it is the predominant PLA₂ responsible for DHA release in the brain [7]. Other isoforms, such as GIIA and GV, are also expressed in the brain, but less is known about their function [6].

Physiologic Roles of AA and PLA₂ in Regulation of Neuronal Activity

A number of findings suggest that PLA₂ and AA play important roles in synaptic signaling, long-term potentiation (LTP), learning and memory. Non-specific pharmacologic inhibition of PLA₂ activity in rats impaired performance during the probe trial portion of the Morris water maze [15]. Similarly, non-specific inhibition of PLA₂ activity diminished memory retrieval after avoidance training [16,17]. Inhibitors with a preference for GVIA-PLA₂ impaired performance on Y-maze testing [18]. In contrast, specific reduction of GIVA-PLA₂ by genetic modulation had no negative impact on learning and memory measured in the Morris water maze [3]. Further studies are required to determine what roles GIVA-, GVIA-, and other PLA₂ isoforms play in behavioral functions and the specific mechanisms involved.

The effect of PLA₂s on cognitive function may relate, at least in part, to the ability of AA to alter neuronal and synaptic activity. AA can increase neuronal firing [3,19] and enhance LTP in hippocampal neurons in anesthetized rats and hippocampal slices [20]. How AA enhances synaptic transmission and LTP is not completely understood. AA rapidly increases the level of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA) at the neuronal surface [3], which might increase neuronal activity by increasing currents through Ca²⁺-permeable AMPARs [21] and N-methyl-D-aspartic acid receptors (NMDARs) [22]. Therefore, AA may mediate changes in AMPAR surface levels. AMPA binding in hippocampal slices was increased by exogenous PLA₂, possibly by increasing AA-mediated increase in surface AMPAR levels [23]. The opposite was observed with PLA₂ inhibition [24]. By regulating surface levels of AMPARs [3] and NMDARs (Cisse and Mucke, unpublished data), PLA₂ and AA may potentiate LTP, learning and memory. Consistent with this idea, LTP can be blocked with PLA₂ inhibitors, and this blockade can be reversed by the addition of exogenous AA [25]. Notably, these findings do not preclude the possibility that excessive levels of PLA₂ and AA in disease states could have detrimental consequences (see below) [1,3,26].

Indeed, the ability of AA to increase neuronal activity could escalate to abnormal levels through several positive feedback mechanisms. Increasing neuronal activity by electrical stimulation in the dentate gyrus increases PLA₂ activity and AA liberation [27]. Similarly, neuronal activation with glutamate generates a Ca²⁺-dependent increase in PLA₂ activity and AA levels that depends on NMDARs and AMPARs [28]. NMDA treatment can increase AA production [29,30], and kainate can increase neuronal GIVA-PLA₂ protein levels in the hippocampus [8]. Lastly, neuronal activity increases the production and release of A β [31], which should increase GIVA-PLA₂ and AA [3,26].

AA may affect neuronal functions directly or indirectly through one of its many metabolites (Figure 1). Prostaglandins (PGs) are formed by cyclooxygenase (COX)-dependent metabolism of AA. COX, like GIVA-PLA₂, is concentrated in the hippocampus, particularly in dendritic spines [32]. COX inhibition diminishes LTP induction [33] as well as spatial learning in the water maze [34]. AA can also be metabolized by the lipoxygenase pathway to generate hydroxyeicosatetraenoic acid (HETE) and leukotrienes (LTs), which have also been shown to regulate synaptic function. Lipoxygenase inhibitors block hippocampal LTP [35], and 12-HPETE can induce long term depression (LTD) in CA1 pyramidal cells in hippocampal slices [36].

DHA is liberated in the brain predominantly by GVI-PLA₂ [7] and possibly plasmalogen-selective PLA₂ (PlsEtn-PLA₂) [12]. There is less evidence to support a direct link between DHA and synaptic function, but DHA is important for neuronal survival and development [37], promotes neurite outgrowth in the hippocampus [38], and may affect neural transmission by affecting membrane fluidity [37]. Further, DHA and AA compete for phospholipid binding sites and increases in dietary DHA intake decreases levels of phospholipid-bound AA that is available for release by PLA₂ [39]. Neuronal activity is tightly linked to the availability of oxygen and nutrients through the neurovascular unit [40–42]. Increase in neuronal activity must be matched by cerebrovascular dilation in order to calibrate blood flow to energy needs. GIVA-PLA₂ and AA metabolites play an important role in regulating cerebrovascular tone in response to neuronal activity [12]. PGs (PGD₂, PGE₂, PGI₂) and epoxyeicosatrienoic acids (EETs) mediate arterial vasodilation, increasing cerebral blood flow (CBF), whereas PGs (PGF_{2a} and TXA₂) and LTs (LTC₄, LTD₄, LTE₄) mediate vasoconstriction [11,12]. Therefore, AA metabolites can regulate not only neuronal activity, but also associated changes in cerebrovascular tone.

Altered AA Metabolism in hAPP mice

Fatty acid metabolism is a dynamic process determined by the availability of substrate, enzymatic activity, and access of the enzyme to the substrate (Figure 1). Alterations in the levels of individual fatty acids or enzymatic activities can affect the concentration of multiple other metabolites. Therefore information on multiple metabolites in a pathway is more informative than data on select mediators. However, measurement of multiple fatty acids simultaneously was not practical until the recent introduction of multiple chromatography and mass spectrometry techniques [43]. These new techniques allow for a snapshot of fatty acid metabolism in an unbiased manner to assess the consequences of experimental perturbations and disease states [3,44–46]. We recently used liquid chromatography coupled with tandem mass spectrometry to analyze fatty acid metabolism in human amyloid precursor protein (hAPP) transgenic mice (line J20), which simulate key aspects of Alzheimer's disease (AD). This analysis revealed an increase in free fatty acid liberation in the hippocampus of these mice, as compared with nontransgenic (NTG) controls [3]. The increase was largely due to a specific elevation in the production and metabolism of AA [3]. Because this alteration was not seen in transgenic mice overexpressing wildtype hAPP, it was probably caused by increased A β levels or another consequence of the FAD mutations expressed in the hAPP-J20 line [3].

In addition to elevations in AA, hAPP-J20 mice showed an increase in COX-dependent metabolites such as PGs [3]. This increase in PGs may be due to an increased supply of AA to COX or to increases in the activity of the inducible isoform of COX, COX-2. AA released by GIVA-PLA₂ can increase COX-2 transcription leading to increased protein levels [47]. This causal chain may also explain the elevated levels of COX-2 seen in response to A β *in vitro* [2,48], in AD patients [49–51] and in hAPP mice [52]. The increase in AA and PGE₂

in hAPP mice could increase neuronal activity and lead to excitotoxicity, which may play an important role in the pathogenesis of AD [53–56].

The increase in PGD₂, PGE₂ and EETs in hAPP mice could also promote cerebrovascular dilation, which may represent a physiological response to increased neuronal activity or a compensatory response to the vasoconstrictive effects of A β [57–60]. How A β causes vasoconstriction is unknown [57].

Some of the fatty acid metabolites that are increased in hAPP mice (e.g., AA, PGE₂, and LTB₄) have proinflammatory activities and could be related to neuroinflammatory processes seen in AD [61–63]. Elevations in AA might also contribute to oxidative stress, because AA metabolism generates reactive oxygen species as a byproduct [64]. Indeed, markers of oxidative stress are increased in AD brains and in some lines of hAPP mice [65–67]. Isoprostanes, non-enzymatic oxidation products of AA, are released from PLs by PLA₂. Therefore, the increased activity of PLA₂ would be expected to result in increased release of isoprostanes, whose levels are elevated in AD patients and hAPP mice [65,68]. Another non-enzymatic product of AA oxidation, 4-hydroxynonenal (4-HNE), is also elevated in AD [69]. An increase in AA release from PLs should decrease levels of PL-bound AA, and this alteration is indeed seen in AD patients as compared to non-demented controls [70].

Increased Activation of GIVA-PLA₂ in hAPP mice and AD

Consistent with the selective increase in AA and its metabolites in the hippocampus of hAPP mice, these mice had increased levels of activated GIVA-PLA₂ in the hippocampus, where GIVA-PLA₂ immunoreactivity was highest in neurons of CA1-3 regions and dentate gyrus [3]. GIVA-PLA₂ is activated by phosphorylation at several sites. ERK and p38 MAPK phosphorylate Ser505, whereas Ca²⁺/calmodulin-dependent kinase (CaMK)II phosphorylates Ser515 and MAPK interacting kinase (MNK)1 phosphorylates Ser727 [5,6]. GIVA-PLA₂ can also be phosphorylated by protein kinase C (PKC)-dependent kinases [71]. Phosphorylation of Ser505 appears to be most important for regulating GIVA-PLA₂ activity [5], and A β increased phosphorylation of this residue in both neuronal culture and hAPP mice [3]. Phosphorylation of Ser505 was also increased in the hippocampus of AD patients, as compared to non-demented controls and patients with frontotemporal dementia [3]. Increased phosphorylation of this residue suggests increased activation of MAPK. Indeed, inhibition of MAPK blocked A β -mediated GIVA-PLA₂ phosphorylation in neuronal cultures [3], establishing a new role for the MAPK pathway in AD [72,73].

GIVA-PLA₂ activity is also regulated directly by intracellular Ca²⁺ concentrations. The C2 domain of GIVA-PLA₂ binds Ca²⁺ allowing GIVA-PLA₂ to translocate to the Golgi apparatus, endoplasmic reticulum and nuclear envelope, where it gains access to PL-bound AA [5,6]. Several processes may increase intracellular Ca²⁺ levels in AD [55], which would be expected to increase GIVA-PLA₂ activity. GIVA-PLA₂ activity can also be increased by transforming growth factor (TGF)- β [74], whose production by cultured primary cortical neurons is increased by A β and whose levels are elevated in brains of AD patients and hAPP mice [75–77].

GIVA-PLA₂ activity was not increased in mice overexpressing wildtype hAPP, which have much lower levels of A β than hAPP mice expressing FAD-mutant hAPP[3]. In cultured neurons, A β treatment increased GIVA-PLA₂ activation in a dose-dependent manner[3]. These findings suggest that A β causes GIVA-PLA₂ activation in hAPP mice and in AD. Elevations in GIVA-PLA₂ activation and AA metabolism are also seen in other neurological conditions where A β is elevated such as stroke and traumatic brain injury[1,78–82].

AA May Mediate A β -Induced Excitotoxicity

A β can increase neuronal activity and cause excitotoxic injury [55,83–85]. Because A β increases the activation of GIVA-PLA₂, which liberates AA from PLs, AA may be a key mediator of these effects [3,85–88]. Indeed, AA itself is excitotoxic [1,3,89] and pharmacological inhibition of GIVA-PLA₂ prevented A β from increasing neuronal activity in cortical slices and from eliciting neuronal degeneration in cell culture [3]. Interestingly, A β and AA acutely and transiently increased the level of AMPARs on the neuronal surface [3]. This effect could account, at least in part, for their detrimental effects, as excesses in AMPAR-mediated neuronal activation can lead to excitotoxicity [55,83–85,90].

A transient elevation in surface AMPARs would enhance NMDAR activation, Ca²⁺ influx and membrane depolarization. The transient increase in intracellular Ca²⁺ would also be expected to further activate GIVA-PLA₂ and increase AA release. AA and its metabolites are diffusible and, thus, could affect the function of surrounding neurons. This scenario is particularly interesting in light of evidence for epileptiform activity in hAPP mice and patients with AD [53,91,92].

GIVA-PLA₂ Mediates A β -induced Behavioral Deficits in hAPP Mice

Like humans with AD, hAPP mice develop a range of behavioral alterations, including deficits in learning and memory. Interestingly, behavioral deficits in hAPP-J20 mice depend, at least in part, on GIVA-PLA₂ [3]. On the GIVA-PLA₂ wildtype background, hAPP-J20 mice show deficits in hippocampus-dependent learning and memory. These mice also have increased hippocampal levels of GIVA-PLA₂ activation, as do patients with AD [3]. What is more, genetic ablation of GIVA-PLA₂ in hAPP mice reduced their learning and memory deficits [3].

hAPP mice also have other behavioral alterations such as disinhibition and hyperactivity that may be related to problems with encoding new information [93]. Reduction or removal of GIVA-PLA₂ also improved these behavioral deficits. Furthermore, hAPP mice suffer from premature mortality, which may be due to epileptic activity [54,91,92]. Decreasing GIVA-PLA₂ in hAPP mice would be expected to decrease A β -induced neuronal excitation and raise the seizure threshold, thereby lowering mortality. Indeed, reduction or removal of GIVA-PLA₂ reduced premature mortality in these mice [3].

Learning and memory deficits in hAPP-J20 mice correlate with depletions in specific synaptic activity-related markers, such as calbindin [94,95]. Interestingly, removal of GIVA-PLA₂ in hAPP-J20 mice restores normal calbindin levels. GIVA-PLA₂ inhibition therefore ameliorates both behavioral and biochemical A β -induced deficits in hAPP-J20 mice. Most likely, GIVA-PLA₂ mediates these effects through previously unknown mechanisms that affect neuronal excitation and network activity.

The striking effects of GIVA-PLA₂ modulation in hAPP mice raise the possibility that it may play an important role in the pathogenesis of AD-related cognitive and behavioral abnormalities and call attention to its potential value as a therapeutic target in this disease.

Therapeutic Targets and Drug Development

As outlined above, PLA₂s fulfill important physiological functions, but some of them are also involved in pathogenic pathways, making the development of isoform-specific inhibitors an important therapeutic objective. In relation to AD, specific inhibition of GIVA-PLA₂ may be desirable based on the data reviewed here. However, it has been difficult to develop selective inhibitors for specific PLA₂ isoforms. Many inhibitors initially thought to

be specific were later shown to inhibit also other isoforms. For example, AA-trifluoromethylketone (AACOCF₃) has a strong preference for GIVA-PLA₂ over other PLA₂ isoforms but also inhibits GVIA-PLA₂, thromboxane synthase and FAAH. Therefore, studies evaluating the *in vivo* role of GIVA-PLA₂ have used genetic ablation instead of pharmacologic inhibition [3].

New GIVA-PLA₂ inhibitors are being introduced, although it is unclear if further scrutiny will confirm their reported specificities [96]. Wyeth (now Pfizer) has developed indole-based inhibitors that are reported to be highly specific for GIVA-PLA₂. One of these inhibitors, WAT0196025, blocks GIVA-PLA₂ but not the GIVB or GIVC isoforms. This inhibitor prevented the development of experimental autoimmune encephalomyelitis (EAE) [97]. Merck has introduced heteroaryl-substituted acetone derivatives that inhibit GIV-PLA₂s at micromolar concentrations [96]. Others have developed similar compounds that inhibit GIVA-PLA₂ at nanomolar concentrations [96]. 2-oxoamide inhibitors of GIVA-PLA₂ based on γ -amino acids have also been developed and are undergoing testing [96].

Another strategy to decrease GIVA-PLA₂-dependent AA production is to decrease the availability of PL-bound AA by displacing AA with DHA [37,98]. Indeed, observational studies suggest the beneficial effects of increasing omega-3 dietary intake in mild cognitive impairment (MCI) and AD patients are due to increasing DHA and lowering AA [37]. The MIDAS [99] and ADCS DHA [100] trials did not show a benefit of DHA treatment in mild to moderate AD patients but improved cognitive performance in individuals without AD who presented with memory complaints, suggesting the potential need for earlier intervention. Other studies have related a high omega-3 to omega-6 fatty acid ratio in the blood to a lower incidence of AD or cognitive decline independent of AD [37]. Other potential benefits of DHA include its abilities to block the A β -induced loss of NMDARs [98], decrease A β production, inhibit apoptosis, increase brain-derived neurotrophic factor (BDNF), serve as an anti-oxidant, increase neuroprotectin D1, and improve coupling of blood flow to glucose utilization [37].

Lastly, specific downstream effects of AA may be blocked by inhibiting distal AA processing enzymes. Epidemiological studies have linked the intake of non-steroidal anti-inflammatory drugs (NSAIDs) to decreased risk of developing AD [101]. Although animal studies support this notion [102], a prospective, randomized clinical trial did not show benefits of COX inhibition in AD [101,103]. However, the trial evaluated only one year of treatment with rofecoxib or naproxen in patients with established mild to moderate AD [103]. It is noteworthy in this context that inhibition of distal enzymes in the AA pathway can divert proximal substrates to other enzymes. For example, in some patients, COX inhibition can lead to shunting of AA into the lipoxygenase pathway with secondary bronchospasm or allergic skin reactions [104]. In AD, COX inhibition could exacerbate the increase in AA levels that results from A β -induced GIVA-PLA₂ activation, which in turn might offset downstream benefits of COX inhibition. Inhibitors of GIVA-PLA₂ could avoid this problem.

Conclusions

The role of essential fatty acids in the pathogenesis of AD is intriguing. While studies have so far failed to demonstrate a clear benefit of DHA and of inhibiting COX, AA and GIVA-PLA₂ represent new targets that appear to play important roles in mediating biochemical and cognitive abnormalities caused by A β . AA and its metabolites regulate many of pathways that are altered in AD, further underlining the potential importance of developing specific inhibitors for GIVA-PLA₂ that can penetrate the blood-brain barrier.

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Figure 1.

PLA₂-dependent fatty acid metabolism. PLA₂ mediates the release of fatty acids from membrane phospholipids (PL), including linoleic acid (LA), α -linolenic acid (ALA), arachidonic acid (AA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA). These metabolites can be metabolized further by lipoxygenase (LO), cyclooxygenase (COX), or p450 enzymes. LA is metabolized into hydroxyperoxyoctadecadienoic acids (HPODE), hydroxyoctadecadienoic acid (HODE), epoxy-hydroxy-octadecenoic acids (EpOME), epoxyperoxyoctadecadienoic acids (EpODE), dihydroxy-octadecenoic acids (DHOMe), and oxo-octadecadienoic acids (oxo-ODE). ALA is metabolized by 15-LO to 15-hydroxyeicosatrienoic acid (HETrE). AA is metabolized into PGs, LTs, EETs, and HETEs. EPA can be metabolized into 12- and 15-hydroxyeicosapentaenoic acid (HEPE). sEH, soluble epoxide hydrolase; LTC₄S, LTC₄ synthase; LTA₄H, LTA₄ hydrolase; PGES, PGE₂ synthase; PGDS, PGD₂ synthase.

Figure 2.

PLA₂ may mediate excitotoxicity, cerebrovascular dysfunction and oxidative stress in AD. Aβ leads to increases in intracellular Ca²⁺ and activation of kinases in the ERK/MAPK pathway. GIVA-PLA₂ activity and access to its phospholipid substrate is increased by Ca²⁺ binding to its C2 domain and phosphorylation by ERK/MAPK kinases. Increased GIVA-PLA₂ activity increases AA release from membrane phospholipids. AA can increase neuronal excitability, presumably by elevating surface levels of AMPARs and NMDARs. AA and its metabolites are diffusible and can affect neighboring neurons to increase network excitability and blood vessels to cause cerebrovascular dysfunction. They can also lead to excessive production of reactive oxygen species leading to oxidative stress.

Figure 3.

Potential role for GIVA-PLA₂ in network dysfunction and behavioral abnormalities in AD. Aβ activates GIVA-PLA₂, leading to the generation of AA and its metabolites. AA can increase neuronal excitation and synchronization, partly by elevating surface AMPAR levels. When excessive, neuronal excitation can cause neurotoxicity or aberrant neural network activity. Together, aberrant neuronal activity, excitotoxicity, and compensatory mechanisms can decrease AMPAR and cause synaptic deficits, network dysfunction, and behavioral deficits that are ameliorated by removal or reduction of GIVA PLA₂.