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Neuropathological Disorders and Calcium Independent Forms of Phospholipase A_2 Activities in the Brain

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1. Introduction

Phospholipases A_2 (PLA_2s) constitute a large and diverse group of enzymes with broad biological functions, ranging from membrane synthesis and turnover to the generation of signaling molecules. So far, more than 20 isoforms of PLA_2 presenting diverse characteristics, including calcium requirement and subcellular localization, have been documented. Based on their nucleotide sequence and other properties, PLA_2 enzymes have been categorized into 15 groups (I-XV) − according to the classification of Dennis (Burke & Dennis, 2009a, 2009b). Released by cells, several groups of PLA_2s are relatively small proteins (~14 kDa) that require millimolar amounts of calcium for their optimal activation. These groups of enzymes have historically been called the secreted forms of PLA_2 (or $sPLA_2$). The remaining groups are larger proteins, localized in intracellular compartments, which are either dependent or not on calcium ions.

The first intracellular PLA_2 to be cloned was a 85-kD protein, classified as a group IV PLA_2 (Dennis, 1997; Leslie, 1997). This enzyme, now designated as cytosolic $PLA_2\alpha$ ($cPLA_2\alpha$), is known to be under the influence of extracellular signals likely to induce calcium mobilization and phosphorylation (Leslie, 1997). Another group of PLA_2 (group VI), which does not require calcium variations for its activity, has been cloned (Balboa et al., 1997; Ma et al., 1997; Tang et al., 1997). This PLA_2 isoform has been designated as calcium-independent PLA_2 ($iPLA_2$) (Balsinde & Dennis, 1997; Dennis, 1997) and, according to numerous lines of biochemical evidence, may account for most of the PLA_2 activity detected in resting cells. From a pharmacological perspective, $iPLA_2$ activity is markedly reduced by bromoenol lactone (BEL) suicide substrate, which is not an effective inhibitor of $sPLA_2$ or $cPLA_2$ enzymes at comparable concentrations (Balboa et al., 1997; Kudo & Murakami, 2002). Several interesting reviews have considered the functional and pathological implications of PLA_2 enzymes (Balsinde & Balboa, 2005; Bazan et al., 1993; Brown et al., 2003; Farooqui & Horrocks, 2004; Farooqui et al., 2004; Hooks & Cummings, 2008; Kolko et al., 2007; Kudo & Murakami, 2002; Leslie, 2004; Phillis & O'Regan, 2004; Sun et al., 2004; Sun et al., 2005). In this report, we will describe new and unique functional roles of $iPLA_2$ in the regulation of brain glutamate receptor functions, neuronal plasticity and neurodegenerative processes.

2. iPLA$_2$ isoforms and functions

Among PLA$_2$ enzymes, group IV (cPLA$_2$) and group VI (iPLA$_2$) families represent intracellular enzymes with a catalytic serine in their lipase consensus motif. Various studies, including gene targeting, have indicated that group IVA cPLA$_2$ (cPLA2α), which is regulated by calcium-dependent membrane translocation and mitogen-activated protein kinase (MAPK)-dependent phosphorylation, is central in stimulus-dependent eicosanoid biosynthesis (Bonventre et al., 1997; Uozumi et al., 1997). On the other hand, group VIA iPLA$_2$ (iPLA2β) and group VIB iPLA$_2$ (iPLA$_2$γ) isoforms mainly exhibit PLA$_2$ activity, whereas other iPLA$_2$ isoforms δ, ε, ξ and η display triglyceride lipase and transacylase activities (Table 1) in marked preference to PLA$_2$ activity (Jenkins et al., 2004; Quistad et al., 2003). Group VIA iPLA$_2$β, the most extensively studied iPLA$_2$ isoform, has been implicated in various cellular events, such as phospholipid remodelling (Balsinde et al., 1997; Balsinde & Dennis, 1997), eicosanoid formation (Tay & Melendez, 2004), cell proliferation (Herbert & Walker, 2006), apoptosis (Atsumi et al., 1998), and activation of store-operated channels and capacitative calcium influx (Smani et al., 2004). Disruption of the iPLA$_2$β gene causes impaired sperm motility (Bao et al., 2004), mitigated insulin secretion (Bao, Bohrer et al., 2006; Bao, Song et al., 2006) and neuronal disorders presenting iron dyshomeostasis (Morgan et al., 2006).

Group	Source	Molecular Mass (kDa)	Feature	Alternate names
VIA-1	Human/Murine	84-85	8 ankyrin repeats	iPLA$_2$
VIA-2	Human/Murine	88-90	7 ankyrin repeats	iPLA$_2$β
VIB	Human/Murine	88-91	Membrane-bound	iPLA$_2$γ
VIC	Human/Murine	146	Integral membrane protein	iPLA$_2$δ
VID	Human	53	Acylglycerol transacylase,triglycerol lipase	iPLA$_2$ε
VIE	Human	57	Acylglycerol transacylase,triglycerol lipase	iPLA$_2$ζ
VIF	Human	28	Acylglycerol transacylase,triglycerol lipase	iPLA$_2$η

Table 1. Calcium-independent group VI phospholipase A$_2$ (iPLA$_2$) (Adapted from (Schaloske & Dennis, 2006))

Group VIB iPLA$_2\gamma$ is a membrane-bound iPLA$_2$ enzyme with unique features, such as utilization of distinct translation initiation sites producing different sizes of enzymes with distinct subcellular localizations (Kinsey,McHowat,Beckett et al., 2007; Mancuso et al., 2000; Mancuso et al., 2004; Murakami et al., 2005; Tanaka et al., 2000; J. Yang et al., 2003) and phospholipid selectivity in terms of sn-1/sn-2 positional specificity that differs among substrates (Yan et al., 2005) iPLA$_2\gamma$ has a mitochondrial localization signal in the N-terminal region and a peroxisomal localization signal near the C-terminus, and the 88-kDa full-length and 63-kDa translation products of iPLA$_2\gamma$ are preferentially distributed in mitochondria and peroxisomes, respectively (Kinsey,McHowat,Beckett et al., 2007; Mancuso et al., 2004; Murakami et al., 2005). In the brain, iPLA$_2$ represents predominant phospholipase activity in cells under resting conditions (Wolf et al., 1995; H. C. Yang et al., 1999). Reverse transcription-polymerase chain reaction experiments have revealed that rat brains constitutively express messenger RNAs for at least 3 calcium-independent PLA$_2$ isoforms, iPLA$_2\beta$, iPLA$_2\gamma$ and cPLA2γ (Kinsey et al., 2005; Tang et al., 1997; Underwood et al., 1998). These isoforms are characterized by differential sensitivity to PLA$_2$ inhibitors and, by isolating each enantiomer of the iPLA$_2$ inhibitor BEL, Jenkins et al. (Jenkins et al., 2002) established that the (S)-enantiomer of BEL selectively reduces iPLA$_2\beta$ activity, while its (R)-enantiomer blocks the iPLA$_2\gamma$ isoform more efficiently.

Although little is known about iPLA$_2$ functions in neurons, a growing body of evidence suggests their involvement in hippocampal long-term potentiation (LTP) of excitatory synaptic transmission (Fujita et al., 2001; Wolf et al., 1995). Hippocampal LTP, first described by Bliss and Lomo in 1973, is commonly regarded as a functional model of synaptic adaptation (i.e. plasticity) that likely participates in learning and memory (Bliss & Collingridge, 1993). PLA$_2$ activities are increased in membranes of slices prepared from the dentate gyrus after LTP induction in anaesthetized rats (Clements et al., 1991) and could be involved in hippocampal LTP expression by elevating the production of arachidonic acid (AA) that retrogradely increases transmitter release at glutamatergic synapses (Drapeau et al., 1990; J. H. Williams et al., 1989). Facilitation of transmitter release by PLA$_2$s during LTP is also reinforced by the fact that iPLA$_2$ activity plays an important role in membrane fusion processes required for exocytosis (Brown et al., 2003; Takuma & Ichida, 1997).

The notion that iPLA$_2$ activity may facilitate LTP expression by increasing glutamate release is complicated, however, by an abundant number of reports demonstrating that synaptic potentiation, at least in area CA1 of the hippocampus, is not dependent on changes in transmitter release, but is rather mediated by mechanisms involving the up-regulation of postsynaptic responses mediated by alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors at glutamatergic synapses (Hayashi et al., 2000). Several alterations have been reported at postsynaptic sites during LTP, including faster kinetics of receptor-associated ion channels (Ambros-Ingerson & Lynch, 1993; Ambros-Ingerson et al., 1993), redistribution of existing receptors within the postsynaptic density (Xie et al., 1997) and insertion of new receptors at synapses (Lu et al., 2001; Pickard et al., 2001). Consistent with these observations, we recently demonstrated that pretreatment of hippocampal slices with the iPLA$_2$ inhibitor BEL completely abolishes AMPA receptor translocation in synaptic membranes and expression of CA1 hippocampal LTP (Martel et al., 2006). Interestingly, both LTP and AMPA receptor translocation display enantio-selective impairment by the iPLA$_2\gamma$ blocker (R)-BEL but not by the iPLA$_2\beta$ inhibitor (S)-BEL, suggesting that iPLA$_2\gamma$ represents the crucial isoform governing hippocampal synaptic strengthening.

$iPLA_2\gamma$ mRNAs and proteins are enriched in the endoplasmic reticulum (ER)-Golgi apparatus in several cell types (Kinsey et al., 2005), where they may be essential for diverse intracellular trafficking pathways, such as retrograde movement from the Golgi complex to the ER, transport of material from the trans-Golgi network to the plasma membrane or recycling of membrane and receptors through endocytic pathways (Brown et al., 2003). In this matter, Pechoux et al. (Pechoux et al., 2005) reported that $iPLA_2$ inhibition slowed down the transport of caseins from the ER to the Golgi apparatus and from the trans-Golgi network to the plasma membrane, indicating that $iPLA_2$ could participate in membrane trafficking events leading to the secretion of milk proteins. Interestingly, translocation of AMPA receptors originating from the ER-Golgi complex to postsynaptic membranes might be critically involved in LTP (Broutman & Baudry, 2001). Thus, the $iPLA_2\gamma$ isoform may be well-suited to favour AMPA receptor translocation from intracellular pools to synaptic membranes during LTP.

Interestingly, impairment in synaptic plasticity by PLA_2 inhibition is correlated with loss of animal abilities to perform on memory tasks. For instance, intracerebral injection of wide-spectrum PLA_2 inhibitors into the chick intermediate medial hyperstriatum ventrale curbs the learning of a passive avoidance task (Holscher & Rose, 1994), while intraperitoneal injections in rats impede spatial learning tested in the Morris water maze (Holscher et al., 1995). Additionally, intracerebroventricular injection of specific $iPLA_2$ inhibitors 30 min before a learning session impairs spatial working memory in rodents (Fujita et al., 2000). Acquisition of 1-trial step-down inhibitory avoidance in rats correlates with $iPLA_2$ activity in the hippocampus, and bilateral injection of $iPLA_2$ inhibitors in region CA1 of the dorsal hippocampus prior to training hinders both short-term and long-term memory (Schaeffer & Gattaz, 2005). Hence, intact $iPLA_2$ activity seems important for proper acquisition of new memories. In a modified protocol developed to test memory retrieval, the same group recently showed that injection of the dual $cPLA_2$ and $iPLA_2$ inhibitor palmitoyl trifluoromethylketone in region CA1 of the rat dorsal hippocampus before performance testing impaired trained behavior in the step-down inhibitory avoidance task (Schaeffer & Gattaz, 2007). Importantly, memory retrieval was re-established after recovery of PLA_2 activity, indicating that these PLA_2s are indeed necessary for memory retrieval. However, identification of $iPLA_2$ isoforms in memory acquisition and retrieval remains to be addressed.

3. $iPLA_2$ and neuronal cell death mechanisms

Recently, evidence from non-neuronal cells has suggested that $iPLA_2$ enzymes may have diverse effects on cell death. First, constitutive $iPLA_2$ activity may contribute to cell death since $iPLA_2\beta$ overexpression amplifies thapsigargin-induced apoptosis in INS-1 insulinoma cells (Ramanadham et al., 2004) and accelerates U937 cell death after long-term exposure to hydrogen peroxide (Perez et al., 2004). $iPLA_2$ has been shown to play a pivotal role in oxidant damage of astrocytes (Xu et al., 2003), and its blockade by BEL dampens oligomeric amyloid-beta (Aβ1-42-induced mitochondrial membrane potential loss and reactive oxygen species production in these cells (Zhu et al., 2006). Moreover, $iPLA_2$ inhibition reduces the size of infarcts produced by global ischemia (S. D. Williams & Gottlieb, 2002). On the other hand, $iPLA_2$ activity has also been shown to protect against cell death, as inhibition of $iPLA_2$ accentuates oxidant-induced cell death in renal proximal tubule cells and astrocytes (Cummings et al., 2002; Peterson et al., 2007). Likewise, $iPLA_2$ activity may also have

deleterious or beneficial effects on neurons. For instance, acute inhibition of $iPLA_2$ activity by racemic BEL has been found to be neuroprotective in organotypic hippocampal slices exposed to oxygen-glucose deprivation (Strokin et al., 2006). In contrast, immature cultures of primary cortical neurons exposed for several days to BEL show decreased neuritogenesis and cellular viability (Forlenza et al., 2007; Mendes et al., 2005). Moreover, $iPLA_2\beta$ knockout mice exhibit abnormal motor behaviors accompanied by the appearance of vacuoles and ubiquitin-positive axonal swelling (spheroids) in many brain regions (Malik et al., 2008; Shinzawa et al., 2008), suggesting that $iPLA_2\beta$ dysfunction leads to neuroaxonal dystrophy.

While the reported impact of $iPLA_2$ on cell viablility is mostly attributable to $iPLA_2\beta$, involvement of the $iPLA_2\gamma$ isoform is much less understood. A previous report demonstrated that $iPLA_2\gamma$ localized in mitochondria catalyzes AA liberation that mediates mitochondrial permeability transition, a key control point for apoptosis (Kinsey,McHowat,Patrick et al., 2007). On the other hand, $iPLA_2\gamma$ expression may exert cytoprotective effects during complement-mediated glomerular epithelial cell injury (Cohen et al., 2008). In addition, recent findings from our laboratory have revealed that constitutive $iPLA_2\gamma$ activity might represent an important neuroprotective system capable of limiting brain excitotoxic damage. We have shown that inhibition of $iPLA_2\gamma$ by the enantio-specific inhibitor (R)-BEL makes hippocampal slice cultures more vulnerable to AMPA-mediated excitotoxicity (Menard et al., 2007). Overactivation of N-methyl-D-aspartic acid (NMDA) or AMPA glutamatergic receptors, allowing the entry of high cation levels into cells, activates a number of enzymes, including ATPases, lipases, proteases and endonucleases that, in turn, deplete energy stores or damage cell membranes, cytoarchitecture or nucleus, respectively. Excitotoxicity has been reported to contribute to a variety of neuropathological disorders, including ischemic stroke, epilepsy, amyotrophic lateral sclerosis and Alzheimer's disease (AD) (Kwak & Weiss, 2006; Villmann & Becker, 2007).

Interestingly, the harmful effect of $iPLA_2\gamma$ inhibition on AMPA-mediated toxicity is associated with selective up-regulation of AMPA receptor GluR1 subunit (but not GluR2) phosphorylation with a subsequently increased level in synaptic membrane fractions (Menard et al., 2007; Menard et al., 2005; Villmann & Becker, 2007). In the hippocampus, AMPA receptors generally form heterodimers containing 2 copies of each of the GluR1 and GluR2 subunits. It is now well-recognized that GluR2 subunits render AMPA receptors impermeable to calcium. Consequently, its presence or absence plays a critical role in cellular calcium homeostasis and in determining susceptibility to excitotoxicity (Geiger et al., 1995; Sommer et al., 1991). Hence, the reduction of $iPLA_2\gamma$ activity, by promoting surface expression of the GluR1 subunit over the GluR2 subunit (which is reflected by a rise in the GluR1/GluR2 ratio in the membrane fraction), could exacerbate excitotoxic cell death through the formation of GluR2-lacking AMPA receptors that would allow adverse Ca2+ influx upon prolonged AMPA receptor activation. Consistent with this possibility, the greater cell death observed under $iPLA_2\gamma$ inhibition is prevented by GluR2-lacking AMPA receptor antagonists (Menard et al., 2007). How inhibition of $iPLA_2\gamma$ influences the expression of AMPA receptor subtypes in synaptic membranes remains an open question. As mentioned earlier, this may occur by the sorting of protein transport through intracellular secretory pathways (Pechoux et al., 2005). There are other circumstances in which GluR1 subunits are selectively up-regulated in hippocampal neurons, such as after activity deprivation elicited by prolonged blockade of AMPA receptors (Thiagarajan et al., 2005) or tumor necrosis factor-alpha receptor activation (Stellwagen et al., 2005). In the latter

case, it has been proposed that up-regulation of GluR1 homomeric receptors could derive from a reserve pool of non-GluR2-containing AMPA receptors existing near the membrane.

4. iPLA$_2$ dysfunction and neuropathological disorders

Whereas cPLA$_2$ and sPLA$_2$ are commonly believed to be preferentially involved in AA release, emerging evidence indicates that iPLA$_2$ activity can contribute to docosahexaenoic acid (DHA) release from brain phospholipids (J. T. Green et al., 2008). To our knowledge, the first suggestion that brain iPLA$_2$ activity may be crucial for DHA release came from a study by Strokin et al. (Strokin et al., 2003) who showed that racemic BEL inhibited DHA release from astrocytes. Later, using siRNA silencing procedures, the same group demonstrated that DHA release from phospholipids of astrocytes was mainly dependent on iPLA$_2\gamma$ activity (Strokin et al., 2007). DHA is one of the most abundant omega-3 polyunsaturated fatty acids (PUFA) present in phospholipids of the mammalian brain (Glomset, 2006), where it is recognized to be important for the maintenance of neural membranes and brain function integrity (Youdim et al., 2000). Deficient dietary intake of DHA has been associated with lower performance of learning abilities in rodents (Catalan et al., 2002; Fedorova & Salem, 2006; Takeuchi et al., 2002). On the other hand, DHA dietary supplementation could decrease the risk of developing AD (Calon & Cole, 2007; Calon et al., 2005; Calon et al., 2004) or exert neuroprotective actions in a mouse model presenting numerous aspects of Parkinson's disease (Bousquet et al., 2008), while high-fat consumption combined with low omega-3 PUFA intake promotes AD-like neuropathology (Julien et al., 2008).

Both iPLA$_2$ activity and DHA levels have been reported to be decreased in the plasma of AD patients (Conquer et al., 2000; Gattaz et al., 2004). iPLA$_2$ activity is also lower in AD brains (Ross et al., 1999; Talbot et al., 2000). Whether or not decreased iPLA$_2\gamma$ activity, through its capacity to alter DHA release from brain astrocytes, is a factor that contributes to AD pathology remains to be established. Numerous neurobiological studies have demonstrated that DHA may be acting at different fundamental levels to counteract the cellular manifestations of AD. There are, for instance, strong indications that DHA release in the brain may diminish oxidative stress (Wu et al., 2004; Yavin et al., 2002) and glutamate-induced toxicity (Wang et al., 2003). In this line, DHA-induced reduction of excitotoxic damage in the hippocampus might, in fact, be dependent on internalization of AMPA receptors (Menard et al., 2009). The potential ability of DHA to reduce caspase activation (Calon et al., 2005; Calon et al., 2004), Aβ peptide accumulation and tau hyperphosphorylation (K. N. Green et al., 2007; Oksman et al., 2006) also strongly supports the notion that DHA deficiency, through iPLA$_2$ down-regulation, could represent a precursor event that likely initiates the cellular manifestations of AD pathology.

This has been the premise of our recent investigation on the influence of iPLA$_2$ inhibition on microtubule-associated protein tau phosphorylation. We determined whether iPLA$_2$ blockade could contribute to the development of tau hyperphosphorylation in cultured hippocampal slices from transgenic P301L mice expressing human tau. In this experimental model, treatment for up to 12 h with the specific iPLA$_2\gamma$ inhibitor (R)-BEL resulted in significantly increased tau phosphorylation at Thr231, Ser199/202 and Ser404 sites, and in total tau levels. High-resolution imaging studies have demonstrated that hyperphosphorylation is primarily localized in cell bodies and dendrites of hippocampal pyramidal neurons (Fig. 1).

These changes appear to be associated with up-regulation of P25, an activator of cyclin-dependent kinase 5, and phosphorylation/activation of MAPK. These data provide strong evidence that constitutive iPLA$_2\gamma$ activity is important in the regulation of tau hyperphosphorylation in hippocampal pyramidal neurons, raising the possibility that iPLA$_2$ dysfunctions might contribute to the development of tauopathies in AD. In this line, a putative biochemical model that accounts for the potential influence of iPLA$_2\gamma$ on Tau pathology is represented in Figure 2

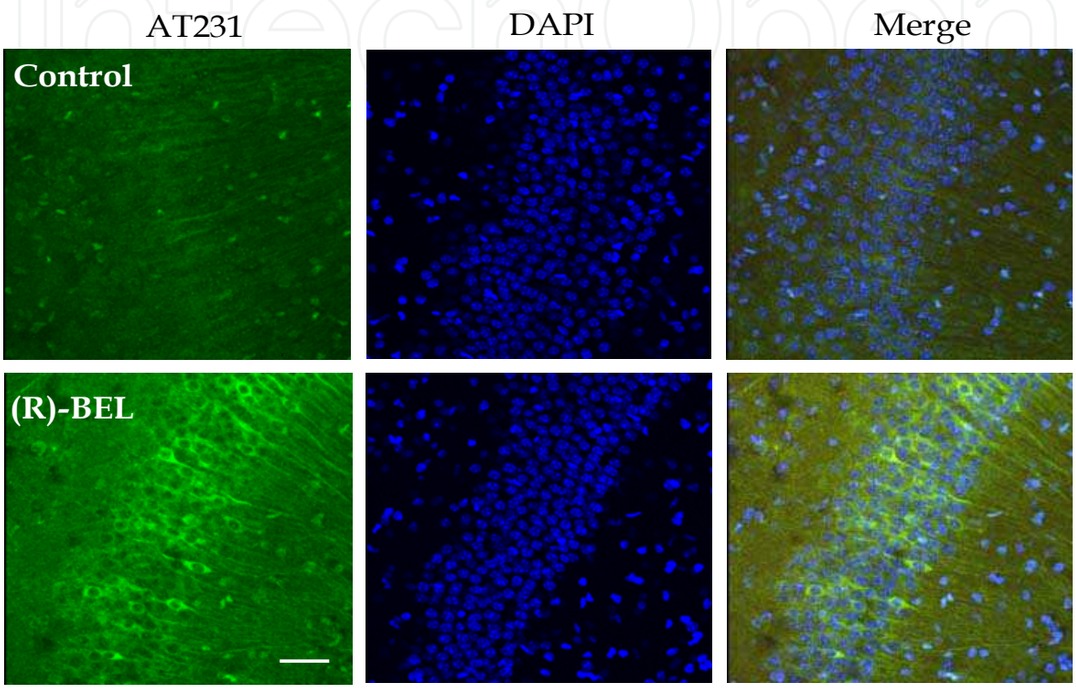

Fig. 1. Inhibition of iPLA$_2\gamma$ induces Tau phosphorylation in area CA1 of the hippocampus. Cultured hippocampal slices from P301L tau transgenic mice were pre-exposed to the iPLA$_2\gamma$ inhibitor R-BEL. Slices were then processed for confocal immunofluorescence microscopy with an antibody known to recognize the Thr-231 Tau epitope (AT231, in green). When compared to controls (upper panel), immunostaining revealed increased phosphorylation in the CA1 region of cultured hippocampal slices pre-exposed to 3 μM (R)-BEL for a period of 12 h (lower panel). DAPI (in blue) was included in the mounting medium to label nuclei. Scale bar = 25 μm

One of the central hypotheses underlying the pathophysiology of AD is the production of cytotoxic Aβ peptides that impairs neuronal activity and leads to a decline in memory and cognition (Palop et al., 2006). The exact mechanisms by which Aβ peptides contribute to AD pathogenesis remain uncertain. PLA$_2$ enzymes may be involved in this condition, as Aβ peptides accentuate cPLA$_2\alpha$ activity in neuronal cultures (Zhu et al., 2006) and primary cortical astrocytes (Sanchez-Mejia et al., 2008), while Aβ-induced learning and memory deficits in a transgenic mouse model of AD are prevented after genetic ablation of cPLA$_2\alpha$ activity in the brain (Sanchez-Mejia et al., 2008). Regarding the iPLA$_2$ system, it appears that its activity is essential for maintaining membrane phospholipid integrity by reducing peroxidative damage, especially injuries originating in the mitochondria. In this

regard, $iPLA_2$ expression prevents the loss of mitochondrial membrane potential and attenuates the release of cytochrome c as well as apoptotic proteins, and ultimately diminishes apoptosis in INS-1 cells exposed to staurosporine (Seleznev et al., 2006). Furthermore, Kinsey et al. (Kinsey et al., 2008; Kinsey,McHowat,Patrick et al., 2007) reported that prominent PLA_2 activity in the mitochondria of rabbit renal proximal tubular cells comes from $iPLA_2\gamma$ and is of capital importance for the prevention and repair of basal lipid peroxidation and the maintenance of mitochondrial viability. Based on recent studies, it has been proposed that Aβ-induced neurotoxicity might derive from mitochondrial defects. Indeed, in vitro experiments have shown that Aβ peptides can be internalized by cells, imported into mitochondria and ultimately elicit mitochondrial dysfunctions (Hansson Petersen et al., 2008). Given its localization, it is thus tempting to propose that $iPLA_2\gamma$ might represent an important cellular component that prevents mitochondrial dysfunctions. Experiments are required to determine whether $iPLA_2\gamma$ overexpression activity might exert protective effects against Aβ peptide-induced mitochondrial dysfunctions.

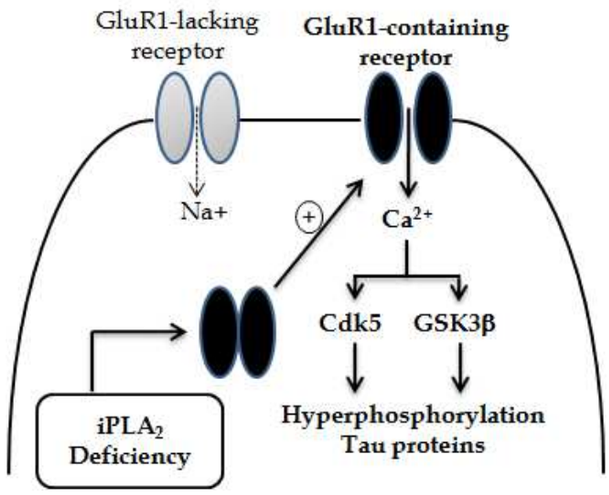

Fig. 2. A putative model illustrating the potential implication of $iPLA_2\gamma$ in Alzheimer's disease. In this simplified model, $iPLA_2$ dysfunction leads to delivery of new GluR1-containing receptors on neuronal membranes. These receptors are then inclined to induce calcium influx and, eventually, Tau phosphorylation by calcium-dependent protein kinases such as Cdk5 and GSK-3β

5. Conclusion

Besides AD, aberrant function of $iPLA_2$s has also been observed in several other neurological disorders. For instance, increased $iPLA_2$ activity might be an important factor that contributes to phospholipid abnormalities in schizophrenia or bipolar patients with a history of psychosis (Ross et al., 2006; Ross et al., 1999). However, the relationship between $iPLA_2$ up-regulation and cellular manifestations of schizophrenia requires further investigation. As mentioned earlier, because $iPLA_2\gamma$ regulates glutamate receptor subunit expression on cell membranes and functions, it will be interesting to examine whether the increase in $iPLA_2\gamma$ activity can lead to down-regulation of the AMPA receptor GluR1 subunit. This is of particular importance, since GluR1 down-regulation may evoke striatal

hyperdopaminergia (Wiedholz et al., 2008), a well-established biological defect involved in schizophrenia-related behaviours. Interestingly, the relationship between $iPLA_2$s and the dopaminergic system is reinforced by the fact that $iPLA_2$ inhibition or knockdown in the rat striatum, motor cortex and thalamus results in the apparition of Parkinson-related behaviours (Lee et al., 2007), which are also known to depend on dopamine dysfunction. Thus, given the growing evidence relating the importance of $iPLA_2$s in physiological and pathological conditions, targeting $iPLA_2$ activity may represent a potentially new therapeutic strategy against several neurological disorders.

6. References

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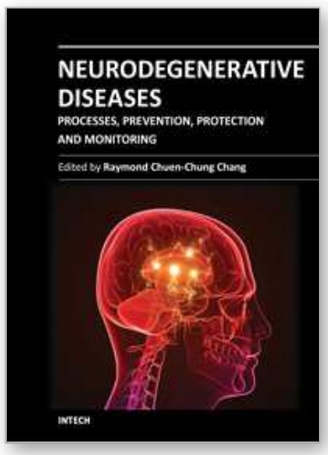

Neurodegenerative Diseases - Processes, Prevention, Protection and Monitoring

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Neurodegenerative Diseases - Processes, Prevention, Protection and Monitoring focuses on biological mechanisms, prevention, neuroprotection and even monitoring of disease progression. This book emphasizes the general biological processes of neurodegeneration in different neurodegenerative diseases. Although the primary etiology for different neurodegenerative diseases is different, there is a high level of similarity in the disease processes. The first three sections introduce how toxic proteins, intracellular calcium and oxidative stress affect different biological signaling pathways or molecular machineries to inform neurons to undergo degeneration. A section discusses how neighboring glial cells modulate or promote neurodegeneration. In the next section an evaluation is given of how hormonal and metabolic control modulate disease progression, which is followed by a section exploring some preventive methods using natural products and new pharmacological targets. We also explore how medical devices facilitate patient monitoring. This book is suitable for different readers: college students can use it as a textbook; researchers in academic institutions and pharmaceutical companies can take it as updated research information; health care professionals can take it as a reference book, even patients' families, relatives and friends can take it as a good basis to understand neurodegenerative diseases.

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