

Cerebral Arachidonate Cascade in Dementia: Alzheimer's Disease and Vascular Dementia

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Abstract: Phospholipase A₂ (PLA₂), cyclooxygenase (COX) and prostaglandin (PG) synthase are enzymes involved in arachidonate cascade. PLA₂ liberates arachidonic acid (AA) from cell membrane lipids. COX oxidizes AA to PGG₂ followed by an endoperoxidase reaction that converts PGG₂ into PGH₂. PGs are generated from astrocytes, microglial cell and neurons in the central nervous system, and are altered in the brain of demented patients. Dementia is principally diagnosed into Alzheimer's disease (AD) and vascular dementia (VaD). In older patients, the brain lesions associated with each pathological process often occur together. Regional brain microvascular abnormalities appear before cognitive decline and neurodegeneration. The coexistence of AD and VaD pathology is often termed mixed dementia. AD and VaD brain lesions interact in important ways to decline cognition, suggesting common pathways of the two neurological diseases. Arachidonate cascade is one of the converged intracellular signal transductions between AD and VaD. PLA₂ from mammalian sources are classified as secreted (sPLA₂), Ca²⁺-dependent, cytosolic (cPLA₂) and Ca²⁺-independent cytosolic PLA₂ (iPLA₂). PLA₂ activity can be regulated by calcium, by phosphorylation, and by agonists binding to G-protein-coupled receptors. cPLA₂ is upregulated in AD, but iPLA₂ is downregulated. On the other hand, sPLA₂ is increased in animal models for VaD. COX-2 is induced and PGD₂ are elevated in both AD and VaD. This review presents evidences for central roles of PLA₂s, COXs and PGs in the dementia.

Key Words: Alzheimer's disease, arachidonic acid, cyclooxygenase, mixed dementia, phospholipase A₂, prostaglandin, vascular dementia, PGD₂, 15d-Δ^{12,14}-PGJ₂.

INTRODUCTION

Dementia is currently defined by DSM-IV [3] as a loss of intellectual abilities of sufficient severity to interfere with social or occupational functioning, always accompanied by memory impairment and at least one of the following: impairment of abstract thinking, judgment or other disturbance of higher cortical function in the absence of delirium. Alzheimer's type is the commonest form of dementia, the other forms being vascular dementia (VaD) and mixed dementia. For more than 30 years, Alzheimer's disease (AD) has been classified and managed as a neurodegenerative disease characterized by extracellular amyloid plaques and intracellular neurofibrillary tangles (NFTs) [8] (Table 1). On the other hand, VaD is caused by vascular lesions, cerebral infarctions, multiple lacunar infarctions and ischemic periventricular leukoencephalopathy (Table 1).

AD is the major form of dementia affecting older people and accounts for 60% to 65% of dementia cases. Autopsy series from dementia clinics report that coexisting vascular pathology occurs in 24% to 28% of AD cases [75]. There is emerging evidence that the cascade of events leading to the development of AD brain plaques and tangles may be due to ischemia resulting from cerebrovascular disease (CVD) [22]. The association of the apolipoprotein E (APOE) ε4 genotype

with an increased risk for both AD and CVD further suggests a potential link between CVD and AD [39] (Table 1). Conversely, amyloid deposition in cerebral blood vessels due to AD increases the risk for hemorrhagic strokes and subsequent VaD [12]. These common pathways leading from CVD to both AD and VaD support the notion that when there is evidence of both CVD and a gradual progressive dementia, the illness should be conceptualized as the coexistence of interacting pathological processes resulting in mixed dementia.

Stroke or symptoms of transient brain ischemia have long been viewed as the hallmark expression of CVD (Table 1). A considerable number of cerebral infarcts are clinically silent although they share the same risk factors as clinically apparent stroke [10]. The fact that white matter hyperintensities (WMH) significantly predict future stroke [83] and mortality [131] and are associated with evidence of disease to the carotids [76] and other organ systems [20] lends further support to the notion that WMH are part of a spectrum of vascular related brain injury [20]. Finally, vascular risk factors are also significantly associated with cerebral atrophy in humans [118] and animal models [35], and at least one hypothesis suggests that atrophy results from an ischemic process [81]. In conclusion, it appears that vascular factors lead to a spectrum of a symptomatic brain injury. These various forms of brain injury also affect behavior in a variety of ways, further expanding the clinical relevance of vascular factors and the potential interaction between AD and VaD. In this review, arachidonate cascade in the central nervous system (CNS) is focused as one of the common pathological processes in AD and VaD.

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Table 1. Symptoms, Lesions and Risk Factors of Alzheimer’s Disease and Vascular Dementia

	Alzheimer's dementia	Vascular dementia
Symptoms	Cognitive decline Extrapyramidal motor dysfunction	Impairment of short-term memory, Visual disturbances Brain stem abnormalities, Sensory or motor symptoms
Lesions	Extracellular amyloid plaques Intracellular neurofibrillary tangles	Cerebral infarction, Multiple lacunar infarctions Ischemic periventricular leukoencephalopathy
Risk factors	Aging, Stroke, Hypertension, Diabetes, Smoking High serum homocystein, Apolipoprotein E4 Amyloid precursor protein, Presenilin 1, Presenilin 2	Aging, Stroke, Hypertension, Diabetes, Smoking Coronary artery disease, Hyperlipidemia

1. CLASSIFICATION OF DEMENTIA

1.1. Alzheimer’s Disease

AD is the fourth largest cause of death for people over 65 years of age. AD is a neurodegenerative disease characterized primarily by cognitive impairment and secondarily by motor dysfunction (Table 1). AD is the most common cause of late-life dementia [152]. AD can be divided into an early-onset form (onset <60 years) and the more common late-onset (>60 years) form. Although most cases of AD are thought to be sporadic, the risk factors for AD include stroke [11], hypertension [11], diabetes [104], smoking [105] and high serum homocysteine [58]. All these conditions have a vascular involvement and are known to reduce cerebral perfusion. ApoE ε4 is associated with the late-onset AD [17]. Three genes are linked to early-onset AD including the β-amyloid precursor protein (APP) on chromosome 21 [68], presenilin-1 (PS1) on chromosome 14 [124], and presenilin-2 (PS2) on chromosome 1 [69]. AD is defined pathologically by extracellular neuritic plaques comprised of fibrillar deposits of a 4 kDa hydrophobic polypeptide known as β-

amyloid (Aβ) and (NFTs) consisting of paired helical filaments (PHF) of hyperphosphorylated tau (HP-Tau) (Table 1). Other pathologic hallmarks of AD activated microglia, reactive astrocytes, and neuronal cell loss [126].

Aβ deposition is an invariant feature of AD, and there is a strong correlation between the amyloid burden in the cortex and the degree of cognitive impairment in the patient [127]. In most AD cases, Aβ peptides also form some deposits in the cerebrovasculature, leading to cerebral amyloid angiopathy and hemorrhagic stroke. Plaques consist of aggregated Aβ peptides that are produced by proteolytic cleavages of the amyloid precursor protein (APP) by the action of proteases called β- and γ-secretases (Fig. 1). As a result of APP processing, neurons produce Aβ peptides of different sizes, the most prominent being 40 and 42 amino acids long (Aβ40 and Aβ42, respectively). The majority of all Aβ isoforms produced is Aβ40, but about 10% is Aβ42 [172]. Cleavage of the APP may occur via two pathways: (1) the normal pathway involves α-secretase and does not lead to formation of Aβ and (2) an alternative pathway, which involves β- and γ-secretases and liberates Aβ, a peptide

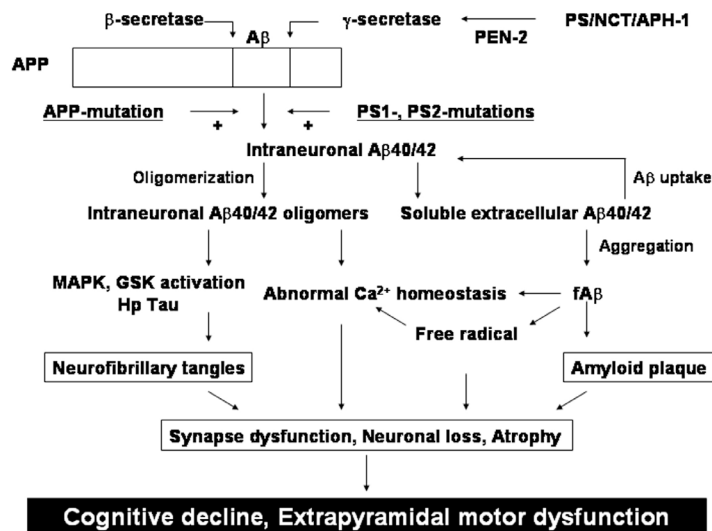


Fig. (1). The amyloid β protein cascade in AD. Scheme showing the Aβ hypothesis in AD, which is based on biochemical, neuropathological, molecular-biological and genetic evidences. Aβ: amyloid β protein, APP: amyloid precursor protein, fAβ: fibrillar amyloid β protein, GSK: glycogen synthase kinase, HP-Tau: hyperphosphorylated tau, MAPK: mitogen-activated protein kinase, PHF: paired helical filaments, NCT: nicastrin, PS: presenilin.

associated with the neurodegeneration seen in AD [99]. γ -Secretase is a membrane protease complex that possesses presenilin as a catalytic subunit. Nicastrin (NCT) [71] and APH-1 [67] initially form a subcomplex to bind and stabilize presenilin. Then, Pen-2 confers the γ -secretase activity [67] and facilitates endoproteolysis of presenilin. There are both secretory and intracellular pools of A β . Soluble extracellular A β 40/42 forms aggregated A β 40/42 or is uptaken. A β produced intraneuronally and reuptaken contributes to the intracellular A β accumulation.

The intracellular A β staining is most evident in AD-vulnerable brain regions, pyramidal neurons of the hippocampus and entorhinal cortex [37]. Intracellular A β deposition is detected prior to the appearance of PHF-positive structures, indicating that it precedes both NFT and A β plaque deposition [26] (Fig. 1). Furthermore, A β 42 oligomers are observed within abnormal processes and synaptic compartments in human AD brains [134]. A β 42 oligomers turn out to be potent neurotoxins in neuronal organotypic cultures at nanomolar concentrations and can inhibit hippocampal long-term potentiation (LTP) and disrupt synaptic plasticity [64]. The activity-dependent synaptic plasticity such as LTP is a critical component of the neural mechanisms underlying learning and memory [86].

Transgenic (Tg) mice are used as animal models for AD amyloidosis. For example, Tg2576 mice develop characteristic AD-like A β brain deposits because of overexpression of a human APP transgene with a double mutation found in a Swedish family with early onset AD [48]. Urine, plasma, and CNS levels of lipid peroxidation are increased as early as 8 months of age in Tg2576 mice compared with WT mice,

preceding the onset of A β deposition and a surge in CNS A β 40/42 in the Tg2576 mice. On the other hand, the development of extrapyramidal motor dysfunction in AD has been associated with coexistent Parkinson's disease [23] and the Lewy body variant of AD [41], and is related to concomitant synucleinopathy (Fig. 1).

The primary genetic risk factor for AD is the inherited complement of alleles for ApoE (Table 1). In comparison to the risk level of the most common ϵ 3/ ϵ 3 genotype, the ϵ 4 and ϵ 2 alleles of the human ApoE gene, respectively, increase and decrease sporadic AD risk with 65 % of AD attributable to the presence of ϵ 4 and an additional 23 % attributable to the absence of an ϵ 2 [17]. Using hippocampal slices from ApoE knockout (ApoE-KO) and human ApoE2, E3, and E4 targeted replacement (ApoE-TR) mice, we found that oligomeric A β 42 inhibited LTP with a hierarchy of susceptibility mirroring clinical AD risk (ApoE4-TR > ApoE3-TR = ApoE-KO > ApoE2-TR), and that comparable doses of unaggregated A β 42 did not affect LTP. These data provide a novel link among ApoE isoform, A β 42, and a functional cellular model of memory. In this model, ApoE4 confers again of negative function synergistic with A β 42, ApoE2 is protective, and the ApoE A β interaction is specific to oligomeric A β 42 [139].

Fig. 2 shows one of mechanisms involved in the neurotoxicity of A β . Although soluble A β exhibits low toxicity, fibrillar A β (fA β), an A β conformation similar to that found in the AD brain, greatly increase A β toxicity in neuronal cultures [140]. fA β generates reactive oxygen species (ROS) [142], which cause membrane lipid peroxidation and disturb the integrity of neuronal membranes.

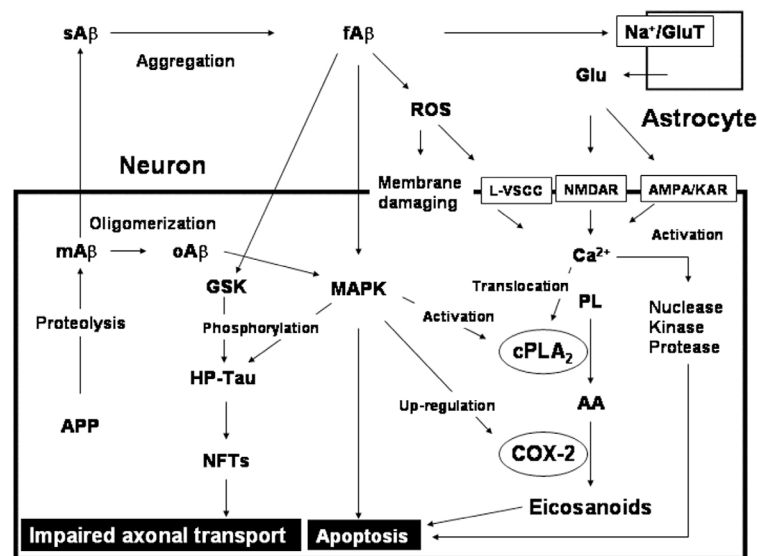


Fig. (2). Steps involved in neurodegeneration of AD. Scheme showing the A β hypothesis in AD, which is based on novel findings on the role of arachidonate cascade. AA: arachidonic acid, AMPA/KAR: α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid/ kainate receptor, APP: amyloid precursor protein, COX-2: cyclooxygenase-2, cPLA₂, cytosolic phospholipase A₂, fA β : fibrillar amyloid β protein, GSK: glycogen synthase kinase, HP-Tau: hyperphosphorylated tau, MAPK: mitogen activated protein kinase, mA β : amyloid β protein monomer, Na⁺/GluT: Na⁺-dependent glutamate transporter, NFTs: neurofibrillary tangles, NMDAR: N-methyl-D-aspartate receptor, oA β : amyloid β protein oligomers, PL: phospholipids, ROS: reactive oxygen species, sA β : soluble amyloid β protein, Glu: glutamate, L-VSCC: L-type voltage-sensitive Ca²⁺ channel.

These free radicals stimulate L-type voltage-sensitive Ca^{2+} channel (L-VSCC), and potentiate the influx of Ca^{2+} into neurons [142]. Increased oxidative stress is an early event in AD that decreases with disease progression and formation of characteristic lesions [100]. Products of lipid peroxidation show a significant increase of intracellular $\text{A}\beta$ production [107].

Glutamate transporters on the glial membrane are Na^+ -dependent and transmembrane gradient of Na^+ and K^+ is the driving force for the transport (Fig. 2). $\text{A}\beta$ -induced elevation of $[\text{Ca}^{2+}]_i$ causes further Ca^{2+} release from endoplasmic reticulum by IP_3 -signalling. These changes in glial membrane conductance reduces glial glutamate uptake by blockade of Na^+ -dependent glutamate transporters (Na^+/Glu transporter) [43]. Glutamate acts at three types of ionotropic receptors on post-synaptic membrane. These receptors have been named after their agonists as *N*-methyl-D-aspartate (NMDA), α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and kainate (KA) receptors. NMDA receptors are present mainly in neurons and their activation results into Ca^{2+} influx [45], whereas AMPA and KA receptors are present in neurons as well as in glia and cause Na^+ -influx and K^+ -efflux on activation [80]. This increases glutamate concentration in synaptic cleft beyond physiological levels [130], causing calcium excitotoxicity-induced neuronal death by activating NMDA receptors on post-synaptic neuronal membrane.

The increment in intracellular Ca^{2+} concentration ($[\text{Ca}^{2+}]_i$) affects Ca^{2+} -dependent enzymes including cytosolic phospholipases A_2 (cPLA₂s), nucleases, kinases and proteases (Fig. 2). These enzymes are involved in $\text{fA}\beta$ -induced neuronal cell death, which is typified by several features characteristic of apoptosis [141, 157-161]. Besides Ca^{2+} -dependent protein kinases, $\text{fA}\beta$ stimulates various kinases including mitogen-activated protein kinase (MAPK) and glycogen synthase kinase (GSK) [136]. MAPK phosphorylates and activates cPLA₂ [73], up-regulates cyclooxygenase-2 (COX-2) via NF- κ B [56]. cPLA₂ mediates apoptosis by $\text{A}\beta$ [63]. Tau protein is phosphorylated by MAPK [114] and GSK [109]. The hyperphosphorylated tau (HP-Tau) protein form NFTs resulting in the impaired axonal transport (Fig. 2). The NFTs of microtubules and HP-Tau proteins are the major pathological lesions in AD brains [8].

1.2. Vascular Dementia

There are several features of VaD distinguished from AD (Table 1). In the initial stages of VaD, major impairments of short-term memory are not always observed unlike in AD. The cholinergic system is involved in VaD similar to that seen in AD, however. Stroke-prone spontaneously hypertensive rats, an animal model of VaD, have impaired cholinergic function that appears to correlate with deficits in learning and memory function [60]. VaD is the second most common form of dementia, ranking after AD, and is likely to have an increasing impact in an aging population [29, 103]. In the Rotterdam study [103], investigators found that 6.3% of study participants aged 55 to 106 years met the criteria for dementia, but the frequency increased exponentially with age to 43.2% at age 95 years and greater. While AD is the predominant diagnosis in that oldest population (AD: 72%,

vascular dementia: 16%), [103] studies of eastern populations, such as those in Japan, China, and Russia, have suggested that vascular dementia may be more common in these populations than AD [29]. In other surveys, prevalence of dementia varied from 0.3% to 1% in persons aged 60 to 64 years and doubled every 5 years, to about 50% in persons older than 95 years [78].

VaD can result from ischemic or hemorrhagic brain damage. The three most common mechanisms causing this disease are single, strategically placed infarcts; multiple cortical infarcts; and subcortical small-vessel disease [7]. These may occur individually or in combination and result in neuropathology that comprises combinations of multiple large infarcts, single strategic infarcts, lacunes, and white-matter lesions. Single strategic infarcts are of particular note because damage in critical locations such as the anteromedial thalamus can cause significant disability in the absence of sensory and motor problems. Because of the variety of pathogenic mechanisms involved in vascular dementia, clinical manifestations can be heterogeneous. Clinical deficits are determined by the size, location, and type of cerebral damage. Common focal neurologic signs include hemiparesis, visual field defects, pseudobulbar palsy, and hemisensory loss. Neurologic symptoms include visual disturbances, brainstem abnormalities, and sensory or motor symptoms (Table 1). The degree of loss of cognition and other function is the sum of various single deficits caused by individual infarcts and hemorrhages. Cognitive and behavioral abnormalities may progress in a stepwise or fluctuating manner and are often accompanied by motor and sensory abnormalities.

Stroke is the potent risk factor for VaD identified in epidemiologic data [54] (Table 1). Stroke is caused by a critical alteration of blood flow to a region of the brain. An acute obstruction of an artery results in ischemia *i.e.*, insufficient blood flow to the tissue [122]. The ischemic brain suffers a mismatch between its cellular energy demands and the ability of the vascular system to supply substrate, most importantly oxygen. Subsequently, neurologic malfunctions and neuronal cell death are caused by increased intracellular calcium, excessive extracellular glutamate, free radicals, and inflammation (Fig. 3). At the beginning of the stroke, there is a definite gradation of injury—a central area or core, with low blood flow already showing signs of massive cell death, and an outer area, the penumbra, that is still alive, but will malfunction after several days. A rat with the middle cerebral artery (MCA) occlusion has been established as an animal model for stroke [144]. MCA occlusion causes irreversible necrosis and infarction in the core [40]. On the other hand, cell death is induced not only via necrosis, but also via apoptosis, and cells remain viable for several hours in the penumbra [70]. Therefore, interventions designed to terminate the reversible proapoptotic state are expected to reduce the ischemic damage and lead to successful treatment of stroke.

2. PHOSPHOLIPASE A_2

PLA₂ (EC3.1.1.4.) belongs to a family of enzymes that catalyze the cleavage of fatty acids from the *sn*-2 position of glycerophospholipids to produce free fatty acids and

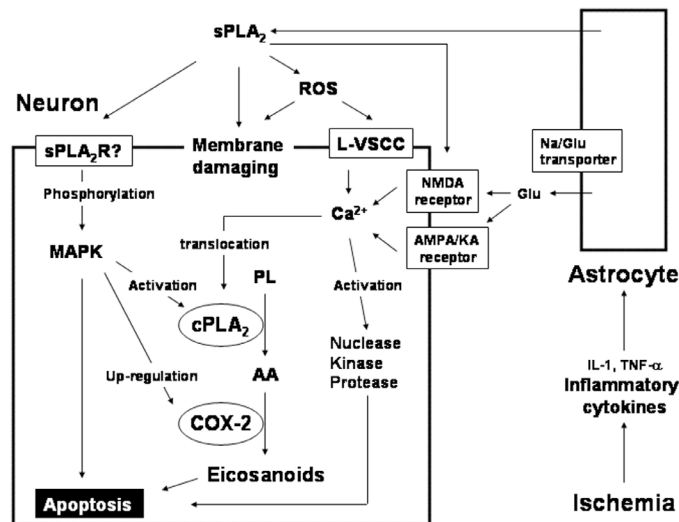


Fig. (3). Steps involved in neurodegeneration of stroke. Scheme showing the sPLA₂ hypothesis in ischemia, which is based on novel findings on the role of arachidonate cascade. AA: arachidonic acid, AMPA/KAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid/ kainate receptor, COX-2: cyclooxygenase-2, cPLA₂, cytosolic phospholipase A₂, Glu: glutamate, IL-1: interleukin-1, MAPK: mitogen activated protein kinase, Na⁺/GluT: Na⁺-dependent glutamate transporter, NMDAR: N-methyl-D-aspartate receptor, PL: phospholipids, ROS: reactive oxygen species, sPLA₂: secretory phospholipase A₂, sPLA₂R: secretory phospholipase A₂ receptor, TNF-α: tumor necrosis factor-α L-VSCC: L-type voltage-sensitive Ca²⁺ channel.

lysophospholipids [5,145]. PLA₂s participate in a wide variety of physiological processes, including phospholipid digestion, remodeling of cell membranes and host defense. They also take part in other processes by producing precursors of various types of biologically active lipid mediators (Fig. 4), such as prostaglandins (PGs), leukotrienes (LTs), thromboxanes (TXs) and platelet-activating factor (PAF) [5]. In the mammalian system, more than 19 different isoforms of PLA₂ have been identified, and different PLA₂s have been shown to participate in pathophysiological events

related to cell injury, inflammation, and apoptosis [87,110]. According to their biochemical features such as cellular localization, requirement of Ca²⁺, substrate specificity and the primary structure, these PLA₂s are classified into several families, including low molecular weight secretory PLA₂ (sPLA₂), Ca²⁺-sensitive arachidonoyl-specific 85-kDa cytosolic PLA₂ (cPLA₂), Ca²⁺-independent PLA₂ (iPLA₂), and PAF-acetylhydrolase [129]. In the mammalian CNS, five sPLA₂ (IIA, IIC, IIF, V and XII), cPLA₂ (IV) and iPLA₂ (VI) have been detected [32, 84, 146] (Table 2).

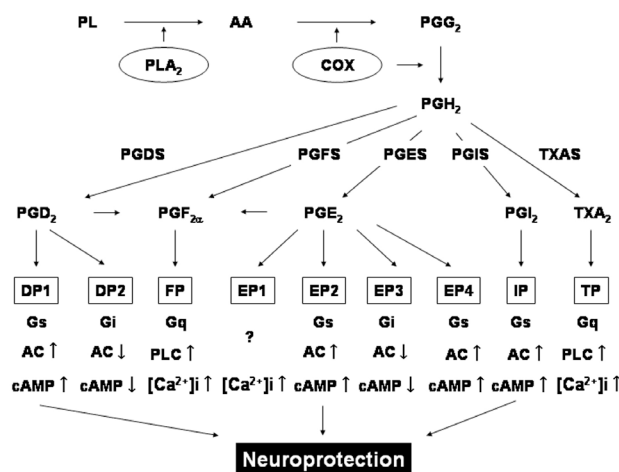


Fig. (4). Schematic pathway of prostanoids formation and actions. PGs protect neurons via receptors coupled to Gs in a cAMP-dependent manner. AA: arachidonic acid, AC: adenylate cyclase, COX: cyclooxygenase, DP: PGD₂ receptor, EP: PGE₂ receptor, FP: PGF_{2α} receptor, Gi: inhibitory GTP-binding protein, Gq: GTP-binding protein stimulating PLC, Gs: stimulatory GTP-binding protein, IP: PGI₂ receptor, PG: prostaglandin, PGDS: PGD₂ synthase, PGES: PGE₂ synthase, PGFS: PGF_{2α} synthase, PGIS: PGI₂ synthase, PL: phospholipid, PLA₂: phospholipase A₂, PLC: phospholipase C, TP: TXA₂ receptor, TXA₂: thromboxane A₂, TXAS: TXA₂ synthase.

Table 2. Physiochemical Properties OF Brain PLA₂

	sPLA ₂	cPLA ₂	iPLA ₂
Brain	IIA, IIC, IIF, XII	IVA, IVB, IVC	VIA-1, VIA-2, VIB
Molecular mass	14kDa	85kDa	80kDa
localization	Extracellular	Cytosol	Cytosol
Calcium	Stimulated	Translocation	None
Substrate	Phosphatidylcholine	Phosphatidylcholine	Phosphatidylcholine
Fatty acid	None	Arachidonic acid	Linoleic acid

2.1. Secretory Phospholipase A₂

PLA₂s IIA, IIC, IV and VI mRNA appear to be ubiquitously expressed in rat brain, with relatively similar levels in all brain regions (Table 2). PLA₂-IIF is induced in brains of mice injected with lipopolysaccharide intraperitoneally, to stimulate an inflammatory reaction [88]. PLA₂-V mRNA is found at high levels in the hippocampus and at low levels in most other areas. Measurement of PLA₂s activity levels demonstrates that PLA₂-VI constitutes the dominant form of activity in adult rat brain, with the highest levels in the hippocampus and striatum.

Mammalian sPLA₂s possess a consensus domain structure consisting of a Ca²⁺-binding loop and an active center including the His-Asp pair, and are classified into different groups according to the number and positions of cysteine residues as well as their characteristic domain structures. sPLA₂-IIA possesses an intramolecular disulfide bond between Cys50 and Cys137, as well as an amino acid C-terminal extension, and sPLA₂-IIA does not have a propeptide. sPLA₂-IIA is found in many cells and tissues and its expression is modulated by various inflammatory cytokines, such as interleukin 1 β (IL-1 β) and tumor necrosis factor- α (TNF- α) in astrocytes [55] (Fig. 3). These inflammatory cytokines are increased by cerebral ischemia, leading to the expression of sPLA₂-IIA in the ischemic brain [102]. The cortical sPLA₂ activity is significantly elevated in response to focal cerebral ischemia [102]. sPLA₂-IIA is induced in the cortex, in which the ischemic core and the penumbra coexist [74]. The sPLA₂ inhibitor, indoxam, reduces the elevated PLA₂ activity completely and the infarct volume significantly in the cortex [102]. Indoxam ameliorated occlusion-induced inflammation and neurodegeneration in the penumbra, suggesting that sPLA₂ might play an important role in apoptosis in the penumbra [102]. As shown in Fig. 3, sPLA₂-IIA potentiates Ca²⁺ influx through L-VSCC [163] and glutamate receptors [62], and induces neuronal cell death via apoptosis [74]. Although sPLA₂-IB has not yet been detected in the brain, high-affinity binding sites of sPLA₂-IB exist on the plasma membrane of cortical neurons [164]. sPLA₂-IB also induces the excess influx of Ca²⁺ into neurons via L-VSCC [165], and subsequently neuronal cell death via apoptosis [166]. It is unclear whether the high-affinity binding sites of sPLA₂-IB are sPLA₂ receptor or not (Fig. 3).

2.2. Cytosolic Phospholipase A₂

cPLA₂ belongs to the group IV PLA₂s (Table 2). Although four isoforms, i.e., cPLA₂ α , - β , - γ and - δ , have been identified, the 85 kDa cPLA₂ α has been studied most extensively. cPLA₂ requires micromolar Ca²⁺ for activity; however unlike sPLA₂, calcium is necessary for binding cPLA₂ to membrane or phospholipids vesicles rather than for catalysis. An increase in intracellular Ca²⁺ concentration promotes binding of Ca²⁺ ions to the C2 domain and then allows cPLA₂ α to translocate from the cytosol to the perinuclear region including the Golgi apparatus, endoplasmic reticulum and nuclear envelope [36,123]. Activation of cPLA₂ proceeds primarily through phosphorylation [73,91]. This protein is comprised of a C2 domain and multiple phosphorylation sites, including two consensus sites (Ser505 and Ser727) for phosphorylation by mitogen-activated protein kinases (MAPKs) [73] and a Ser515 site for Ca²⁺/calmodulin-dependent protein kinase [91].

In neurons, cPLA₂ is known to control fundamental processes, including neurotransmitter release and long-term potentiation. Both functions are altered in the early stages of AD [24]. Using hippocampal organotypic cultures, a study has shown that cPLA₂ mediates apoptosis induced by ischemic insults [4]. Following a transient ischemic episode, cPLA₂ immunostaining has been observed in astrocytes or reactive glial cells of the rat brain [16], and an increased expression of the gene for cPLA₂ was observed in neurons of the hippocampus [106]. cPLA₂ immunoreactive astrocytes are detected in regions of the cortex that contained numerous amyloid β deposits [132].

2.3. Ca²⁺-independent Phospholipase A₂

The iPLA₂ family is comprised of group VIA and VIB (Table 2). Group VIA enzyme has at least five splice variants, all with ankyrin repeats, whereas group VIB iPLA₂ lacks ankyrin repeats but consists of a signal motif for peroxisome localization [89]. In normal rat brain, >70% of PLA₂ activity can be attributed to iPLA₂s. iPLA₂ is the dominant PLA₂ in the cytosolic fraction, and generally regarded as house keeping enzymes for the maintenance of membrane phospholipids [169]. iPLA₂ display a substrate preference toward the fatty acid chain in the *sn*-2 position of phosphatidylcholine of linoleyl > palmitoyl > oleoyl > arachidonyl, and a head group preference for choline >=

ethanolamine \gg inositol. iPLA₂ activity is significantly decreased in the dorsolateral prefrontal, but not the lateral temporal cortex of the frontal AD case, a variant of AD [137]. The frontal cortex is not typically the most damaged brain in AD. In typical AD cases, the density of NFTs is greatest in the entorhinal cortex and adjoining hippocampal formation [6]. In frontal AD, however, the density of NFTs in the prefrontal cortex is as high as or higher than in the entorhinal cortex [57].

3. CYCLOOXYGENASE

COX is classified into three forms, a constitutive form, COX-1, a mitogen-inducible form, COX-2 and a variant of COX-1, COX-3 [25]. COX-1 is expressed intensely in microglia in rat brain and in control human brains as well as in hippocampal and cerebral cortical neurons [21]. A COX-3 mRNA is abundant in the human cerebral cortex. In contrast, COX-2 is absent in the control human brains but is induced robustly in neuronal cell bodies and dendrites in peri-infarct regions during the acute phase of focal ischemic injury [138]. The COX-2 gene is expressed throughout the rat forebrain, with higher levels in the cerebral cortex and hippocampus in discrete populations of neurons, but not in glia [170]. COX-2 is localized in neuronal dendritic spines where active synapses are present [59]. In the brain, basal expression of COX-2 has been shown to be regulated by synaptic activity, and its expression is upregulated by a high frequency stimulation that is associated with LTP [170]. COX-2 inhibitors significantly reduce postsynaptic membrane excitability, back-propagating dendritic action potential-associated Ca²⁺ influx and LTP induction in hippocampus dentate granule neurons, while a COX-1 inhibitor is ineffective [15]. These studies suggest that COX-2 participates in synaptic modification.

Epidemiology has pointed to nonsteroidal anti-inflammatory drugs (NSAIDs) reducing the risk of developing AD [65]. The beneficial actions of NSAIDs are linked to inhibition of the inducible COX-2 activity at inflammatory sites. On the other hand, their side effects (*e.g.*, gastric damage) are ascribed to suppression of the constitutive COX-1 activity. Clinical trials of AD patients with a COX inhibitor, indomethacin, indicated a beneficial effect [79,115]. COX-2 is up-regulated in the brain of AD patients [108] and transgenic mouse models [86,87]. COX-2 is induced in A β -treated SH-SY5Y neuroblastoma cells [108]. COX-2 selective inhibitors, *e.g.* S-2474, prevent cerebral cortical neurons from undergoing A β -induced apoptosis [157]. Slowing of cognitive decline in patients with mild to moderate AD over 12 months have not yet been detected in the trial of COX-2 inhibitors, rofecoxib and naproxen, however [49]. COX-3 is elevated in AD and in the primary culture of IL-1 β /A β 1-42-treated human neural (HN) cells [19]. The inflammation in AD and in stressed HN cells, COX-3 may play ancillary roles in membrane-based COX signaling or when basal levels of COX-1 or COX-2 expression persist.

Infarcts in the MCA up-regulate COX-2 in the brain of stroke patients [50,117]. In the animal model, gene expression of COX-2 is induced in the ischemic brain [98]. Resting cerebral blood flow is decreased [97], and brain

ischemia/reperfusion injury is increased [51] in COX-1-deficient mice. In contrast, COX-2 deficient mice display reduced susceptibility to ischemic injury and NMDA neurotoxicity [52]. The COX-2 selective inhibitors reduce infarct size following focal ischemia in rats [98] and effectively limit hippocampal damage following forebrain ischemia in the gerbil [14]. In the primary culture, another COX-2 selective inhibitor, S-2474, rescues cortical neurons from undergoing sPLA₂-IIA-induced apoptosis [157]. Thus, the pathway through PLA₂ and COX-2 plays an important role in neurodegeneration after ischemia.

4. PROSTAGLANDIN

Eicosanoids are divided into two groups according to their mechanism of action: the conventional eicosanoids, *e.g.*, PGD₂ and PGE₂, the cyclopentenone-type PGs (Fig. 4), *e.g.*, PGJ₂ and PGA₂ (Fig. 5). PGD₂ and PGE₂ are further dehydrated to produce PGJ₂ and PGA₂, respectively [101] (Fig. 5). Once AA has been supplied, both isoforms of COX form PGG₂ and PGH₂ via identical enzymatic processes (Fig. 4). Following these steps, PGH₂ can be metabolized by different enzyme pathways to a range of products with potent biological effects. The profile of products made by cells expressing COX-1/COX-3 or COX-2 is therefore determined by the presence of different downstream enzymes. Eicosanoids modulate cellular function during a variety of physiologic and pathologic processes [94].

4.1. Prostaglandin E₂

Earlier it appeared that when cells expressed large amounts of COX-2, the PGH₂ formed could be saturating for the PG synthase enzymes resulting in the formation of proportionately larger amounts of PGE₂ [82], possibly by non-enzymatic conversion (Fig. 4). In addition to the cytosolic PGE synthase, there is an inducible microsomal or membrane-associated perinuclear PGE synthase (mPGES) regulated, for instance, by proinflammatory cytokines and glucocorticoids. While the cytosolic PGE synthase is principally coupled with COX-1, this inducible mPGES appears coupled with COX-2 [90]. PGES is induced by A β in astrocytes [121]. PGE₂ is elevated in the cerebrospinal fluids of living AD patients [85] and in the postischemic brain [171]. PGE₂ synthesis is reduced in the postmortem cerebral cortices of AD patients [153]. In *in vitro* models for AD, PGE₂ rescues neurons from the toxicity of A β [160] and TNF α [66]. Intracerebroventricular injection of naturally secreted human A β inhibited LTP [148], a correlate of learning and memory [86]. PGE₂ reverses COX-2 inhibitor-induced suppression of postsynaptic membrane excitability, back-propagating dendritic action potential-associated Ca²⁺ influx and LTP in hippocampal dentate granule neurons [15], indicating that PGE₂ also participates in synaptic modification.

Four PGE₂ receptor subtypes, *i.e.*, EP1, EP2, EP3, and EP4, have been identified [92]. Activation of EP1 produces phosphatidylinositol and increases intracellular Ca²⁺ concentration ([Ca²⁺]_i) [96]. EP2 and EP4 are coupled to G_s, adenylate cyclase (AC) activation and cAMP generation [96]. There are at least three variants of EP3, and these variants can cause increased [Ca²⁺]_i or the activation or

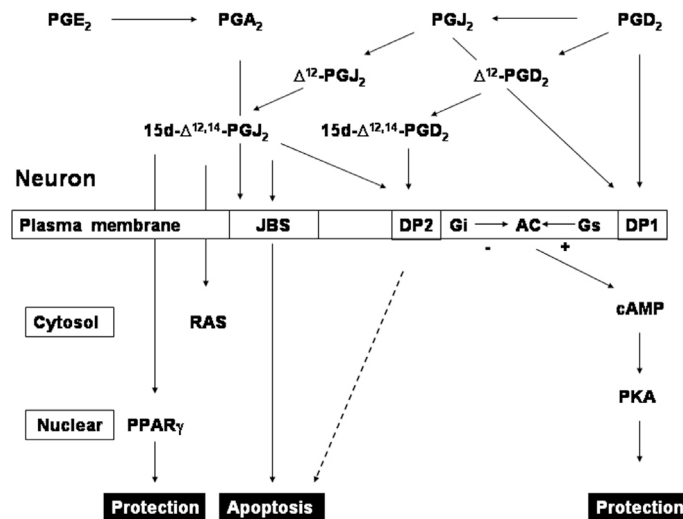


Fig. (5). Actions of PGD_2 and PGE_2 metabolites to neurons. $15\text{d-}\Delta^{12,14}\text{-PGJ}_2$ mediates the neurotoxicity of PGD_2 independently from $\text{PPAR}\gamma$, probably via the binding sites of $15\text{d-}\Delta^{12,14}\text{-PGJ}_2$ on plasma membranes. AC: adenylate cyclase, DP1: PGD_2 receptor coupled to Gs, DP2: CRTH2 receptors, Gi: inhibitory GTP-binding protein, Gs: stimulatory GTP-binding protein, PG: prostaglandin, PKA: cAMP-dependent protein kinase, $15\text{d-}\Delta^{12,14}\text{-PGJ}_2$: 15-deoxy- $\Delta^{12,14}\text{-PGJ}_2$, $\text{PPAR}\gamma$: peroxisome proliferator-activated receptor γ , JBS: binding site of 15-deoxy- $\Delta^{12,14}\text{-PGJ}_2$ on plasma membranes.

inhibition of AC [92]. PGE_2 is suggested to be involved in the NMDA-mediated component of oxygen-glucose deprivation toxicity via the activation of the prostanoids EP1 and/or EP3 [34]. In rodent *in vivo* and *in vitro* models for stroke, PGE_2 exhibits neuroprotective function against cerebral ischemia via its receptor, EP2 [77] and glutamate toxicity [2]. In addition to neurons and astrocytes, EP2 is expressed in the microglia [13]. The role of microglial cells in the AD brain is controversial, as it remains unclear if the microglial cells form the amyloid fibrils of plaques or react to them in a macrophage-phagocytic role. Although activated microglia can secrete neurotoxic factors to surrounding neurons, PGE_2 reduces microglial-induced neurotoxicity via EP2 [13]. On the other hand, microglial cells specifically lacking EP2 increases $\text{A}\beta$ phagocytosis and decrease $\text{A}\beta$ -induced damage to neurons [127]. Thus, microglia play dual roles in secretion of neurotoxins and phagocytosis of amyloid.

4.2. Prostaglandin $\text{F}_{2\alpha}$

$\text{PGF}_{2\alpha}$ is synthesized via three pathways from PGE_2 , PGD_2 , or PGH_2 by PGE 9-ketoreductase, PGD 11-ketoreductase, or PGH 9-, 11-endoperoxide reductase, respectively [149] (Fig. 4). Although there are no reports of PGF synthase being inducible, its levels in the uterus may increase during pregnancy associated with the peak of $\text{PGF}_{2\alpha}$ production that accompanies parturition [151]. Oxidative damage to the CNS predominantly manifests as lipid peroxidation (LPO) because of the high content of polyunsaturated fatty acids that are particularly susceptible to oxidation. 8-*iso*- $\text{PGF}_{2\alpha}$, is an isoprostane (iP). Isoprostanes are specific and sensitive markers of *in vivo* LPO [111]. Levels of a major isoprostane, 8, 12-*iso*-iPF $_{2\alpha}$ -V I, are increased not only in specific AD brain regions [112] but also in the urine, plasma, and CSF of patients with a clinical diagnosis of AD [113]. Plasma levels of isoprostanes were

significantly higher among stroke patients than control [119]. $\text{PGF}_{2\alpha}$ receptor FP is coupled with Gq, stimulates phospholipase C (PLC), and increases $[\text{Ca}^{2+}]_i$ [93]. Although $\text{PGF}_{2\alpha}$ exhibits no neurotoxicity in the primary culture of rat cortical neurons [74], it is unclear whether $\text{PGF}_{2\alpha}$ is a neurotoxic or neuroprotective factor.

4.3. Prostaglandin I_2

PGI_2 is produced from PGH_2 by the action of PGI synthase, a member of the P450 superfamily [42] (Fig. 4). Plasma levels of PGI_2 were significantly higher among stroke patients than control [119]. PGI_2 receptor (IP) is coupled to AC via Gs [43]. PGI_2 is a potent vasodilator, and has an antithrombotic effect *via* IP1. PGI_2 exhibits protective effects for ischemic neuronal damage because it improves cerebral circulation [38]. Another type of PGI_2 receptor, IP2, is in the CNS [135]. In the rat brain, IP2 receptor is expressed in the hippocampus, cerebral cortex, thalamus, striatum, and septum, and the IP1 receptor is expressed in the caudal medulla such as the nucleus of the solitary tract. IP receptor ligands prevent the death of hippocampal neurons *in vitro* and protect CA1 pyramidal neurons against ischemic damage *in vivo* [120].

4.4. Thromboxane A_2

TXA_2 is metabolized from PGH_2 by thromboxane synthase [95] (Fig. 4). An elevated level of TXA_2 has been found in the postmortem brains of AD patients [55]. TXA_2 is suggested to be involved in the extrapyramidal motor dysfunction of patients with AD [167]. Patients with poststroke dementia more often show increased thromboxane biosynthesis than nondemented stroke patients [147]. In the brain, TXA_2 receptors (TP) are expressed in both neuronal cells and glial cells [30]. TP stimulates PLC via Gq, and elevates $[\text{Ca}^{2+}]_i$ [93]. Neurotoxicity of TXA_2 has not yet been detected in *in vitro* [162] and *in vivo* [167] models.

4.5. Prostaglandin D₂

PGD synthase (PGDS) exists in both lipocalin-type and hematopoietic forms [143]. The lipocalin type is a major constituent of the human cerebrospinal fluid (CSF), representing 3% of total CSF protein [156]. The hematopoietic form produces PGD₂ in cells such as mast cells, basophils, and Th2 cells. PGD₂ is increased significantly in the postmortem cerebral cortex of Alzheimer-type dementia patients [55] and an animal model for stroke, gerbil brain during reperfusion after bilateral common carotid artery occlusion [31]. PGD₂ elicits its downstream effects by activating two G protein-coupled receptors, the DP and chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2) receptors (hereafter termed DP1 and DP2) [1,46,47]. The DP1 and DP2 receptors have divergent effects on cAMP production, and are coupled to G_s and G_i respectively [18,44]. At physiological concentrations from 1 nM to 1 μM, PGD₂ protects hippocampal neurons from glutamate toxicity via DP1 in a cAMP-dependent manner [72]. The shared neuroprotection of the DP1, EP2 and IP2 receptors, which are coupled to cAMP, would suggest that other prostaglandin receptors similarly positively coupled to cAMP production, such as the PGE₂, EP4 receptor, may also promote neuroprotection.

In contrast, at high concentrations (> 1 μM), PGD₂ itself causes apoptosis in the primary culture of cortical neurons [168]. BWA868C, a selective DP1 antagonist, does not prevent neurons from PGD₂-induced apoptosis. mRNA of DP2 receptor is detected in the forebrain such as cortex and hippocampus [72]. 15-deoxy-Δ^{12,14}-prostaglandin J₂ (15d-Δ^{12,14}-PGJ₂), a selective agonist for DP2 receptor, is neurotoxic [116], suggesting a possible involvement of DP2 in the neurotoxicity of PGD₂. However, several evidences do not support the possibility. First, few specific binding sites of [³H]PGD₂ are detected in plasma membranes from rat cortices [168]. Second, the extent of specific [³H]PGD₂ in total binding is very low (30-40%), although binding sites of PGD₂ have been reported in synaptosomes of rat [128] and human brains [150]. Third, another selective agonist for DP2 receptor, 15d-Δ^{12,14}-PGD₂, exhibits no neurotoxicity [168]. Fourth, PGD₂ requires a latent time to cause neuronal apoptosis [168]. Finally, the ED₅₀ value (8.2 μM) of PGD₂ is much higher than the affinity for DP2 receptor (binding affinities (K_i) = 24 nM) [94]. These discrepancies suggest that the neurotoxicity of PGD₂ is mediated by other pathways besides DPs.

4.6. Prostaglandin J₂ and Prostaglandin A₂

PGD₂ is non-enzymatically dehydrated to produce PGJ₂, Δ¹²-PGJ₂, and 15d-Δ^{12,14}-PGJ₂ [27,168] (Fig. 5). As well as PGD₂, 15d-Δ^{12,14}-PGJ₂ induced neuronal cell death via apoptosis [116,168]. 15d-Δ^{12,14}-PGJ₂ is a ligand for the nuclear receptor, peroxysome proliferators-activated receptor (PPARγ) [28,61]. Activation of PPARγ protects the brain from cerebral ischemia [133] and Aβ-dependent neurodegeneration [53]. Thus, 15d-Δ^{12,14}-PGJ₂ causes neuronal cell death via the pathway independent from PPARγ. Novel binding sites of 15d-Δ^{12,14}-PGJ₂ are found in the neuronal plasma membranes of the cerebral cortex [168], and are tentatively termed JBS, here (Fig. 5). The specific binding

sites of [³H]15d-Δ^{12,14}-PGJ₂ (>80%) in total binding is much higher than that of [³H]PGD₂ (30-40%). The affinity for JBS is 15d-Δ^{12,14}-PGJ₂ > Δ¹²-PGJ₂ > PGJ₂ >> PGD₂, in the same sequence as the neurotoxic potency. Another neurotoxic cyclopentenone PG, PGA₂, is metabolized from PGE₂, and also binds JBS [168]. None of the other eicosanoids, PPAR-agonists, or PGD₂ receptor blocker exhibits any affinity for the binding site and the neurotoxicity. There are close correlation between the affinity of eicosanoids for JBS and their neurotoxicity, indicating the involvement of JBS in neuronal apoptosis.

CONCLUSION

Dementia is principally diagnosed to AD, VaD and the mixed dementia, suggesting common causative mechanisms (Fig. 6). In these diseases, free radicals and glutamate are released and stimulate L-VSCCs and glutamate receptors, respectively. Excess influx of Ca²⁺ disrupts intracellular calcium homeostasis. Arachidonate cascade is one of the downstreams of the second messenger, calcium ion, and is the important pathway in common with AD and VaD. Among various enzymes in the cerebral arachidonate cascade, cPLA₂, COX-2 and PGDS are the key enzymes involved in the development of the two neurologic diseases. Among PGs, conventional types, PGD₂ and PGE₂, mediate neuronal protection via their receptors coupled to G_s in a cAMP-dependent manner. On the other hand, PGD₂ and PGE₂ are metabolized to neurotoxic cyclopentenone types, PGJ₂ and PGA₂, respectively. 15d-Δ^{12,14}-PGJ₂ mediates the COX-2 neurotoxicity independent from PPARγ, probably via the binding sites of 15d-Δ^{12,14}-PGJ₂ on the plasma membrane. Thus, one of causative mechanisms of AD and VaD are merged into cerebral arachidonate cascade. Further studies are required to clear the mechanism in which 15d-Δ^{12,14}-PGJ₂ induces neuronal apoptosis. The present review sheds light on the agonists and antagonists for enzymes and receptors in the arachidonate cascade as targets for therapy in AD and VaD.

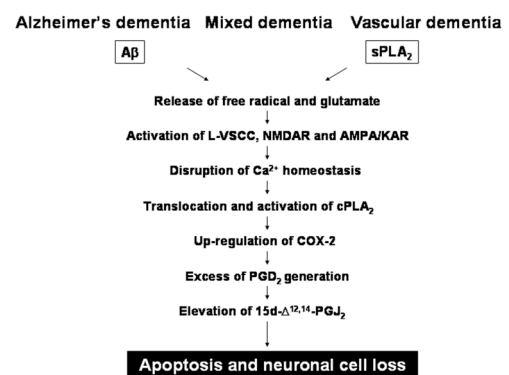


Fig. (6). Common causative mechanisms of AD and VaD. Scheme showing Aβ and sPLA₂ hypothesis in AD and VaD, respectively, which is based on novel findings on the role of arachidonate cascade. Aβ: amyloid β protein, AMPA/KAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid/ kainate receptor, COX-2: cyclooxygenase-2, cPLA₂, cytosolic phospholipase A₂, 15d-Δ^{12,14}-PGJ₂: 15deoxy-Δ^{12,14}-prostaglandin J₂, L-VSCC: L-type voltage-sensitive Ca²⁺ channel, NMDAR: N-methyl-D-aspartate receptor, PGD₂: prostaglandin D₂, sPLA₂: secretory phospholipase A₂.

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