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

Tatsurou Yagami*

Faculty of Health Care Sciences, Himeji Dokkyo University, 2-1, Kami-ohno 7-Chome, Himeji, Hyogo, 670-8524, Japan

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 cells 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.

*Address correspondence to this author at Faculty of Health Care Sciences, Himeji Dokkyo University, 2-1, Kami-ohno 7-Chome, Himeji, Hyogo, 670-8524, Japan; Tel: +81-792-23-2211; Fax: +81-792-85-0352; E-mail: VZX00556@nifty.com

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 ϵ 4 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 ($A\beta$) 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].

$A\beta$ 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, $A\beta$ peptides also form some deposits in the cerebrovasculature, leading to cerebral amyloid angiopathy and hemorrhagic stroke. Plaques consist of aggregated $A\beta$ 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 $A\beta$ peptides of different sizes, the most prominent being 40 and 42 amino acids long ($A\beta$ 40 and $A\beta$ 42, respectively). The majority of all $A\beta$ isoforms produced is $A\beta$ 40, but about 10% is $A\beta$ 42 [172]. Cleavage of the APP may occur via two pathways: (1) the normal pathway involves α -secretase and does not lead to formation of $A\beta$ and (2) an alternative pathway, which involves β - and γ -secretases and liberates $A\beta$, a peptide

Fig. (1). The amyloid β protein cascade in AD. Scheme showing the $A\beta$ hypothesis in AD, which is based on biochemical, neuropathological, molecular-biological and genetic evidences. $A\beta$: amyloid β protein, APP: amyloid precursor protein, fA β : 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, mAb: amyloid β protein monomer, Na⁺/GluT: Na⁺-dependent glutamate transporter, NFTs: neurofibrillary tangles, NMDAR: N-methyl-D-aspartate receptor, oAb: 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 A β 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). A β -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 (cPLA $_2$ s), nucleases, kinases and proteases (Fig. 2). These enzymes are involved in fA β -induced neuronal cell death, which is typified by several features characteristic of apoptosis [141, 157-161]. Besides Ca^{2+} -dependent protein kinases, fA β stimulates various kinases including mitogen-activated protein kinase (MAPK) and glycogen synthase kinase (GSK) [136]. MAPK phosphorylates and activates cPLA $_2$ [73], up-regulates cyclooxygenase-2 (COX-2) via NF- κ B [56]. cPLA $_2$ mediates apoptosis by A β [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

PLA $_2$ (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	Stimulation	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 >> 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. $15d\text{-}\Delta^{12,14}\text{-PGJ}_2$ mediates the neurotoxicity of PGD_2 independently from $PPAR\gamma$, probably *via* the binding sites of $15d\text{-}\Delta^{12,14}\text{-PGJ}_2$ 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, $15d\text{-}\Delta^{12,14}\text{-PGJ}_2$: 15-deoxy- $\Delta^{12,14}\text{-PGJ}_2$, $PPAR\gamma$: 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 $A\beta$ phagocytosis and decrease $A\beta$ -induced damage to neurons [127]. Thus, microglia play dual roles in secretion of neurotoxins and phagocytosis of amyloid.

4.2. Prostaglandin $F_{2\alpha}$

$PGF_{2\alpha}$ 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 $PGF_{2\alpha}$ 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*- $PGF_{2\alpha}$, 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]. $PGF_{2\alpha}$ receptor FP is coupled with Gq , stimulates phospholipase C (PLC), and increases $[Ca^{2+}]_i$ [93]. Although $PGF_{2\alpha}$ exhibits no neurotoxicity in the primary culture of rat cortical neurons [74], it is unclear whether $PGF_{2\alpha}$ 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 $[Ca^{2+}]_i$ [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 μ M, 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 μ M), 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- $\Delta^{12,14}$ -prostaglandin J₂ (15d- $\Delta^{12,14}$ -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- $\Delta^{12,14}$ -PGD₂, exhibits no neurotoxicity [168]. Fourth, PGD₂ requires a latent time to cause neuronal apoptosis [168]. Finally, the ED₅₀ value (8.2 μ M) 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, Δ^{12} -PGJ₂, and 15d- $\Delta^{12,14}$ -PGJ₂ [27,168] (Fig. 5). As well as PGD₂, 15d- $\Delta^{12,14}$ -PGJ₂ induced neuronal cell death via apoptosis [116,168]. 15d- $\Delta^{12,14}$ -PGJ₂ is a ligand for the nuclear receptor, peroxysome proliferators-activated receptor γ (PPAR γ) [28,61]. Activation of PPAR γ protects the brain from cerebral ischemia [133] and A β -dependent neurodegeneration [53]. Thus, 15d- $\Delta^{12,14}$ -PGJ₂ causes neuronal cell death *via* the pathway independent from PPAR γ . Novel binding sites of 15d- $\Delta^{12,14}$ -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- $\Delta^{12,14}$ -PGJ₂ (>80%) in total binding is much higher than that of [³H]PGD₂ (30-40%). The affinity for JBS is 15d- $\Delta^{12,14}$ -PGJ₂ > Δ^{12} -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 a 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- $\Delta^{12,14}$ -PGJ₂ mediates the COX-2 neurotoxicity independent from PPAR γ , probably *via* the binding sites of 15d- $\Delta^{12,14}$ -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- $\Delta^{12,14}$ -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 A β and sPLA₂ hypothesis in AD and VaD, respectively, which is based on novel findings on the role of arachidonate cascade. A β : 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- $\Delta^{12,14}$ -PGJ₂: 15deoxy- $\Delta^{12,14}$ -prostaglandin J₂, L-VSCC: L-type voltage-sensitive Ca²⁺ channel, NMDAR: N-methyl-D-aspartate receptor, PGD₂: prostaglandin D₂, sPLA₂: secretory phospholipase A₂.

REFERENCES

- [1] Abe, H., Takeshita, T., Nagata, K., Arita, T., Endo, Y., Fujita, T., Takayama, H., Kubo, M., Sugamura, K. (1999) Molecular cloning, chromosome mapping and characterization of the mouse CRTH2 gene, a putative member of the leukocyte chemoattractant receptor family. *Gene* **227**, 71-77.
- [2] Akaike, A., Kaneko, S., Tamura, Y., Nakata, N., Shiomi, H., Ushikubi, F., Narumiya, S. (1994) Prostaglandin E₂ protects cultured cortical neurons against N-methyl-D-aspartate receptor-mediated glutamate cytotoxicity. *Brain Res.*, **663**, 237-243.
- [3] American Psychiatric Association. (1994) Diagnostic and statistical manual of mental disorders, fourth edition. American Psychiatric Association (Washington D.C.), 138-142.
- [4] Arai, K., Ikegaya, Y., Nakatani, Y., Kudo, I., Nishiyama, N., and Matsuki, N. (2001) Phospholipase A₂ mediates ischemic injury in the hippocampus: a regional difference of neuronal vulnerability. *Eur. J. Neurosci.*, **13**, 2319-2323.
- [5] Arita, H., Nakano, T., Hanasaki, K. (1989) Thromboxane A₂: its generation and role in platelet activation. *Prog. Lipid Res.* **28**, 273-301.
- [6] Arnold, S. E., Hyman, B. T., Flory, J., Damasio, A. R., Van Hoesen, G. W. (1991) The topographical and neuroanatomical distribution of neurofibrillary tangles and neuritic plaques in the cerebral cortex of patients with Alzheimer's disease. *Cereb. Cortex* **1**, 103-116.
- [7] Black, S. E. (2005) Vascular dementia. *Postgrad. Med.* **117**, 15-24.
- [8] Blessed, G., Tomlinson, B. E., Roth, M. (1968) The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. *Br. J. Psychiatry* **114**, 797-811.
- [9] Boie, Y., Sawyer, N., Slipetz, D. M., Metters, K. M., Abramovitz, M. (1995) Molecular cloning and characterization of the human prostanoid DP receptor. *J. Biol. Chem.* **270**, 18910-18916.
- [10] Boon, A., Lodder, J., Heuts-van Raak, L., Kessels, F. (1994) Silent brain infarcts in 755 consecutive patients with a first-ever supratentorial ischemic stroke. Relationship with index-stroke subtype, vascular risk factors, and mortality. *Stroke* **25**, 2384-2390.
- [11] Breteler, M. M. (2000) Vascular risk factors for Alzheimer's disease: an epidemiologic perspective. *Neurobiol. Aging* **21**, 153-160.
- [12] Bugiani, O. (2004) A β -related cerebral amyloid angiopathy. *Neurol. Sci.* **25** Suppl. 1, S1-2.
- [13] Caggiano, A.O., Kraig, R. P. (1999) Prostaglandin E receptor subtypes in cultured rat microglia and their role in reducing lipopolysaccharide-induced interleukin-1 β production. *J. Neurochem.* **72**, 565-575.
- [14] Candelario-Jalil, E., Alvarez, D., Gonzalez-Falcon, A., Garcia-Cabrera, M., Martinez-Sanchez, G., Merino, N., Giuliani, A., Leon, O. S. (2002) Neuroprotective efficacy of nimesulide against hippocampal neuronal damage following transient ischemia. *Eur. J. Pharmacol.* **453**, 189-195.
- [15] Chen, C., Bazan, N.G. (2005) Lipid signaling: Sleep, synaptic plasticity, and neuroprotection. *Prostaglandins Other Lipid Med.* **77**, 65-76.
- [16] Clements, J.A., Stephenson, D.T., Smalstig, E.B., Roberts, E.F., Johnstone, E.M., Sharp, J.D. (1996) Reactive glia express cytosolic phospholipase A₂ after transient global forebrain ischemia in the rat. *Stroke* **27**, 527-535.
- [17] Corder, E. H., Saunders, A. M., Strittmatter, W. J., Schmechel, D. E., Gaskell, P. C., Small, G. W., Roses, A. D., Haines, J. L., Pericak-Vance, M. A. (1993) Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* **261**, 921-923.
- [18] Crider, J. Y., Griffin, B. W., Sharif, N. A. (1999) Prostaglandin DP receptors positively coupled to adenylyl cyclase in embryonic bovine tracheal (EBTr) cells: pharmacological characterization using agonists and antagonists. *Br. J. Pharmacol.* **127**, 204-210.
- [19] Cui, J.G., Kuroda, H., Chandrasekharan, N.V., Pelaez, R.P., Simmons, D.L., Bazan, N.G., Lukiw, W.J. (2004) Cyclooxygenase-3 gene expression in Alzheimer hippocampus and in stressed human neural cells. *Neurochem. Res.* **29**, 1731-1737.
- [20] DeCarli, C., Miller, B. L., Swan, G. E., Reed, T., Wolf, P. A., Garner, J., Jack, L., Carmelli, D. (1999) Predictors of brain morphology for the men of the NHLBI twins study. *Stroke* **30**, 529-536.
- [21] Deininger, M.H., Schluesener, H.J. (1999) Cyclooxygenase-1 and -2 are differentially localized to microglia and endothelium in rat EAE and glioma. *J. Neuroimmunol.* **95**, 202-208.
- [22] de la Torre, J.C. (2002) Vascular basis of Alzheimer's pathogenesis. *Ann. N. Y. Acad. Sci.* **977**, 196-215.
- [23] Ditter, S. M., Mirra, S. S. (1987) Neuropathologic and clinical features of Parkinson's disease in Alzheimer's disease patients. *Neurology* **37**, 754-760.
- [24] Farooqui, A. H., Yang, H. C. and Horrocks, L. (1997) Involvement of phospholipase A₂ in neurodegeneration. *Neurochem. Int.* **30**, 517-522.
- [25] Feng, L., Sun, W., Xia, Y., Tang, W.W., Channugam, P., Soyoola, E., Wilson, C. B., Hwang, D. (1993) Cloning two isoforms of rat cyclooxygenase: differential regulation of their expression. *Arch. Biochem. Biophys.* **307**, 361-368.
- [26] Fernandez-Vizarra, P., Fernandez, A. P., Castro-Blanco, S., Serrano, J., Bentura, M. L., Martinez-Murillo, R., Martinez, A., Rodrigo, J. (2004) Intra- and extracellular A β and PHF in clinically evaluated cases of Alzheimer's disease. *Histol. Histopathol.* **19**, 823-844.
- [27] Fitzpatrick, F. A., Wynalda, M. A. (1983) Albumin-catalyzed metabolism of prostaglandin D₂. *J. Biol. Chem.* **258**, 11713-11718.
- [28] Forman, B. M., Tontonoz, P., Chen, J., Brun, R. P., Spiegelman, B. M., and Evans R. M. (1995) 15-deoxy- $\Delta^{12,14}$ -prostaglandin J₂ is a ligand for the adipocyte determination factor PPAR γ . *Cell* **83**, 803-812.
- [29] Fratiglioni, L., De Ronchi, D., Aguero-Torres, H. (1999) Worldwide prevalence and incidence of dementia. *Drugs Aging* **5**, 365-375.
- [30] Gao, H., Peng, B., Welch, W. J., Wilcox, C. (1997) Central thromboxane receptors: mRNA expression and mediation of pressor responses. *Am. J. Physiol.*, **272**, R1493-R1500.
- [31] Gaudet, R. J., Alam, I., Levine, L. (1980) Accumulation of cyclooxygenase products of arachidonic acid metabolism in gerbil brain during reperfusion after bilateral common carotid artery occlusion. *J. Neurochem.* **35**, 653-658.
- [32] Gelb, M. H., Valentin, E., Ghomashchi, F., Lazdunski, M., Lambeau, G. (2000) Cloning and recombinant expression of a structurally novel human secreted phospholipase A₂. *J. Biol. Chem.* **275**, 39823-39826.
- [33] Gerashchenko, D., Beuckmann, C. T., Kanaoka, Y., Eguchi, N., Gordon, W. C., Urade, Y., Bazan, N. G., Hayaishi, O. (1998) Dominant expression of rat prostanoid DP receptor mRNA in leptomeninges, inner segments of photoreceptor cells, iris epithelium, and ciliary processes. *J. Neurochem.* **71**, 937-945.
- [34] Gendron, T. F., Brunette, E., Tauskela, J. S., Morley, P. (2005) The dual role of prostaglandin E₂ in excitotoxicity and preconditioning-induced neuroprotection. *Eur. J. Pharmacol.* **517**, 17-27.
- [35] Gesztelyi, G., Finnegan, W., DeMaro, J. A., Wang, J. Y., Chen, J. L., Fenstermacher, J. (1993) Parenchymal microvascular systems and cerebral atrophy in spontaneously hypertensive rats. *Brain Res.* **611**, 249-257.
- [36] Glover, S., de Carvalho M, S., Bayburt T., Jonas, M., Chi E., Leslie C.C., Gelb, M.H. (1995) Translocation of the 85-kDa phospholipase A₂ from cytosol to the nuclear envelope in rat basophilic leukemia cells stimulated with calcium ionophore or IgE/antigen. *J. Biol. Chem.* **270**, 15359-15367.
- [37] Gouras, G. K., Tsai, J., Naslund, J., Vincent, B., Edgar, M., Checler, F., Greenfield, J. P., Haroutunian, V., Buxbaum, J. D., Xu, H., Greengard, P., Relkin, N. R. (2000) Intraneuronal A β 42 accumulation in human brain. *Am. J. Pathol.*, **156**, 15-20.
- [38] Gryglewski, R.J. (1979) Prostacyclin as a circulatory hormone. *Biochem. Pharmacol.* **28**, 3161-3166.
- [39] Haan, M. N., Shemanski, L., Jagust, W. J., Manolio, T. A., Kuller, L. (1999) The role of APOE ϵ 4 in modulating effects of other risk factors for cognitive decline in elderly persons. *J. Am. Med. Assoc.* **282**, 40-46.
- [40] Hallenbeck, J. M. (1994) Blood-damaged tissue interaction in experimental brain ischemia. *Acta Neurochir.* **60**, 233-237.
- [41] Hansen, L., Salmon, D., Galasko, D., Masliah, E., Katzman, R., DeTeresa, R., Thal, L., Pay, M. M., Hofstetter, R., Klauber, M., (1990) The Lewy body variant of Alzheimer's disease: a clinical and pathologic entity. *Neurology* **40**, 1-8.

- [42] Hara, S., Miyata, A., Yokoyama, C., Inoue, H., Brugger, R., Lottspeich, F., Ullrich, V., Tanabe, T. (1994) Isolation and molecular cloning of prostacyclin synthase from bovine endothelial cells. *J. Biol. Chem.* **269**, 19897-19903.
- [43] Harris, M. E., Wang, Y., Pedigo, Jr. N. W., Hensley, K., Butterfield, D. A., Carney, J. M. (1996) Amyloid β peptide (25-35) inhibits Na^+ -dependent glutamate uptake in rat hippocampal astrocyte cultures. *J. Neurochem.* **67**, 277-286.
- [44] Hata, A. N., Zent, R., Breyer, M. D., Breyer, R. M. (2003) Expression and molecular pharmacology of the mouse CRTH2 receptor. *J. Pharmacol. Exp. Ther.* **306**, 463-470.
- [45] Headley, P. M., Grillner, S. (1990) Excitatory amino acids and synaptic transmission: the evidence for a physiological function. *Trends Pharmacol. Sci.* **11**, 205-211.
- [46] Hirai, H., Tanaka, K., Yoshie, O., Ogawa, K., Kenmotsu, K., Takamori, Y., Ichimasa, M., Sugamura, K., Nakamura, M., Takano, S., Nagata, K. (2001) Prostaglandin D₂ selectively induces chemotaxis in T helper type 2 cells, eosinophils, and basophils via seven-transmembrane receptor CRTH2. *J. Exp. Med.* **193**, 255-261.
- [47] Hirata, M., Kakizuka, A., Aizawa, M., Ushikubi, F., Narumiya, S. (1994) Molecular characterization of a mouse prostaglandin D receptor and functional expression of the cloned gene. *Proc. Natl. Acad. Sci. USA* **91**, 11192-11196.
- [48] Hsiao, K., Chapman, P., Nilsen, S., Eckman, C., Harigaya, Y., Younkin, S., Yang, F., Cole, G. (1996) Correlative memory deficits, A β elevation, and amyloid plaques in transgenic mice. *Science* **274**, 99-102.
- [49] Hwang, D. Y., Chae, K. R., Kang, T. S., Hwang, J. H., Lim, C. H., Kang, H. K., Goo, J. S., Lee, M. R., Lim, H. J., Min, S. H., Cho, J. Y., Hong, J. T., Song, C. W., Paik, S. G., Cho, J. S., Kim, Y. K. (2002) Alterations in behavior, amyloid β -42, caspase-3, and Cox-2 in mutant PS2 transgenic mouse model of Alzheimer's disease. *FASEB J.* **16**, 805-813.
- [50] Iadecola, C., Forster, C., Nogawa, S., Clark, H. B., Ross, M. E. (1999) Cyclooxygenase-2 immunoreactivity in the human brain following cerebral ischemia. *Acta Neuropathol.* **98**, 9-14.
- [51] Iadecola, C., Sugimoto, K., Niwa, K., Kazama, K., Ross, M. E. (2001) Increased susceptibility to ischemic brain injury in cyclooxygenase-1 deficient mice. *J. Cereb. Blood Flow Metab.* **21**, 1436-1441.
- [52] Iadecola, C., Niwa, K., Nogawa, S., Zhao, M., Nagayama, M., Araki, E., Morham, S., Ross, M. E. (2001) Reduced susceptibility to ischemic brain injury and N-methyl-D-aspartate-mediated neurotoxicity in cyclooxygenase-2-deficient mice. *Proc. Natl. Acad. Sci. USA* **98**, 1294-1299.
- [53] Inestrosa, N. C., Godoy, J. A., Quintanilla, R. A., Koenig, C. S., Bronfman, M. (2005) Peroxisome proliferator-activated receptor γ is expressed in hippocampal neurons and its activation prevents β -amyloid neurodegeneration: role of Wnt signaling. *Exp. Cell Res.* **304**, 91-104.
- [54] in't Veld, B. A., Ruitenbergh, A., Hofman, A., Stricker, B. H., Breteler, M. M. (2001) Antihypertensive drugs and incidence of dementia: the Rotterdam Study. *Neurobiol. Aging* **22**, 407-412.
- [55] Iwamoto, N., Kobayashi, K., Kosaka, K. (1989) The formation of prostaglandins in the postmortem cerebral cortex of Alzheimer-type dementia patients. *J. Neurol.* **236**, 80-84.
- [56] Jang, J. H., Surh, Y. J. (2005) β -amyloid-induced apoptosis is associated with cyclooxygenase-2 up-regulation via the mitogen-activated protein kinase-NF- κ B signaling pathway. *Free Radic. Biol. Med.* **38**, 1604-1613.
- [57] Johnson, J. K., Head, E., Kim, R., Starr, A., Cotman, C. W. (1999) Clinical and pathological evidence for a frontal variant of Alzheimer disease. *Arch. Neurol.* **56**, 1233-1239.
- [58] Kalmijn, S., Launer, L. J., Lindemans, J., Bots, M. L., Hofman, A., Breteler, M. M. (1999) Total homocysteine and cognitive decline in a community-based sample of elderly subjects: the Rotterdam Study. *Am. J. Epidemiol.* **150**, 283-289.
- [59] Kaufmann, W. E., Worley, P. F., Pegg, J., Bremer, M., Isakson, P. (1996) COX-2, a synaptically induced enzyme, is expressed by excitatory neurons at postsynaptic sites in rat cerebral cortex. *Proc. Natl. Acad. Sci. USA* **93**, 2317-2321.
- [60] Kimura, S., Saito, H., Minami, M., Togashi, H., Nakamura, N., Nemoto, M., Parvez, H. S. (2000) Pathogenesis of vascular dementia in stroke-prone spontaneously hypertensive rats. *Toxicology* **153**, 167-78.
- [61] Kliewer, S. A., Lenhard, J. M., Willson, T. M., Patel, I., Morris, D. C. and Lehmann, J. M. (1998) A prostaglandin J metabolite binds peroxisome proliferator-activated receptor γ and promotes adipocyte differentiation. *Cell* **83**, 813-819.
- [62] Kolko, M., DeCoster, M. A., Rodriguez de Turco, E. B., Bazan, N. G. (1996) Synergy by secretory phospholipase A₂ and glutamate on inducing cell death and sustained arachidonic acid metabolic changes in primary cortical cultures. *J. Biol. Chem.* **271**, 32722-32726.
- [63] Kriem, B., Sponne, I., Fifre, A., Malaplate-Armand, C., Lozac'h-Pillot, K., Koziel, V., Yen-Potin, F. T., Bihain, B., Oster, T., Olivier, J. L., Pillot, T. (2005) Cytosolic phospholipase A₂ mediates neuronal apoptosis induced by soluble oligomers of the amyloid- β peptide. *FASEB J.* **19**, 85-87.
- [64] Lambert, M. P., Barlow, A. K., Chromy, B. A., Edwards, C., Freed, R., Liosatos, M., Morgan, T. E., Rozovsky, I., Trommer, B., Viola, K. L., Wals, P., Zhang, C., Finch, C. E., Krafft, G. A., Klein, W. L. (1998) Diffusible, nonfibrillar ligands derived from A β 1-42 are potent central nervous system neurotoxins. *Proc. Natl. Acad. Sci. USA* **95**, 6448-6453.
- [65] Launer, L. (2003) Nonsteroidal anti-inflammatory drug use and the risk for Alzheimer's disease: dissecting the epidemiological evidence. *Drugs* **63**, 731-739.
- [66] Lee, E. O., Shin, Y. J., Chong, Y. H. (2004) Mechanisms involved in prostaglandin E₂-mediated neuroprotection against TNF- α : possible involvement of multiple signal transduction and β -catenin/T-cell factor. *J. Neuroimmunol.* **155**, 21-31.
- [67] Lee, S. F., Shah, S., Yu, C., Wigley, W. C., Li, H., Lim, M., Pedersen, K., Han, W., Thomas, P., Lundkvist, J., Hao, Y. H., Yu, G. (2004) A conserved GXXXG motif in A β -1 is critical for assembly and activity of the γ -secretase complex. *J. Biol. Chem.* **279**, 4144-4152.
- [68] Levy, E., Carman, M. D., Fernandez-Madrid, I. J., Power, M. D., Lieberburg, I., van Duinen, S. G., Bots, G. T., Luyendijk, W., Frangione, B. (1990) Mutation of the Alzheimer's disease amyloid gene in hereditary cerebral hemorrhage, Dutch type. *Science* **248**, 1124-1126.
- [69] Levy-Lahad, E., Wasco, W., Poorkaj, P., Romano, D. M., Oshima, J., Pettingell, W. H., Yu, C. E., Jondro, P. D., Schmidt, S. D., Wang, K., Crowley, A. C., Fu, Y. H., Guenette, S. Y., Galas, D., Nemens, E., Wijisman, E. M., Bird, T. D., Schellenberg, G. D. and Tanzi, R. E. (1995) Candidate gene for the chromosome 1 familial Alzheimer's disease locus. *Science* **269**, 973-977.
- [70] Li, Y., Sharov, V. G., Jiang, N., Zaloga, C., Sabbah, H. N., Chopp, M. (1995) Ultrastructural and light microscopic evidence of apoptosis after middle cerebral artery occlusion in the rat. *Am. J. Pathol.* **146**, 1045-1051.
- [71] Li, Y. M., Xu, M., Lai, M. T., Huang, Q., Castro, J. L., DiMuzio-Mower, J., Harrison, T., Lellis, C., Nadin, A., Neduvellil, J. G., Register, R. B., Sardana, M. K., Shearman, M. S., Smith, A. L., Shi, X. P., Yin, K. C., Shafer, J. A., Gardell, S. J. (2000) Photoactivated gamma-secretase inhibitors directed to the active site covalently label presenilin 1. *Nature* **405**, 689-694.
- [72] Liang, X., Wu, L., Hand, T., Andreasson, K. (2005) Prostaglandin D₂ mediates neuronal protection via the DP1 receptor. *J. Neurochem.* **92**, 477-486.
- [73] Lin, L. L., Wartmann, M., Lin, A. Y., Knopf, J. L., Seth, A., Davis, R. J. (1993) cPLA₂ is phosphorylated and activated by MAP kinase. *Cell* **72**, 269-278.
- [74] Lin, T. N., Wang, Q., Simonyi, A., Chen, J. J., Cheung, W. M., He, Y. Y., Xu, J., Sun, A. Y., Hsu, C. Y., Sun, G. Y. (2004) Induction of secretory phospholipase A₂ in reactive astrocytes in response to transient focal cerebral ischemia in the rat brain. *J. Neurochem.* **90**, 637-645.
- [75] Massoud, F., Devi, G., Stern, Y., Lawton, A., Goldman, J. E., Liu, Y., Chin, S. S., Mayeux, R. (1999) A clinicopathological comparison of community-based and clinic-based cohorts of patients with dementia. *Arch. Neurol.* **56**, 1368-1373.
- [76] Manolio, T. A., Burke, G. L., O'Leary, D. H., Evans, G., Beauchamp, N., Knepper, L., Ward, B. (1999) Relationships of cerebral MRI findings to ultrasonographic carotid atherosclerosis in older adults: the Cardiovascular Health Study. CHS Collaborative Research Group. *Arterioscler. Thromb. Vasc. Biol.* **19**, 356-365.
- [77] McCullough, L., Wu, L., Haughey, N., Liang, X., Hand, T., Wang, Q., Breyer, R. M., Andreasson, K. (2004) Neuroprotective function

- of the PGE₂ EP₂ receptor in cerebral ischemia. *J. Neurosci.* **24**, 257-268.
- [78] McDowell I. (2001) Alzheimer's disease: insights from epidemiology. *Aging* (Milano), **13**, 143-162.
- [79] McGeer, P.L. (2000) Cyclooxygenase-2 inhibitors: relational and therapeutic potential for Alzheimer's disease. *Drugs Aging* **17**, 1-11.
- [80] Meldrum, B. S. (2000) Glutamate as a neurotransmitter in the brain: review of physiology and pathology. *J. Nutr.* **130**, 1007S-1015S.
- [81] Mentis, M. J., Salerno, J., Horwitz, B., Grady, C., Schapiro, M. B., Murphy, D. G., Rapoport, S. I. (1994) Reduction of functional neuronal connectivity in long-term treated hypertension. *Stroke* **25**, 601-607.
- [82] Mitchell, J. A., Warner, T. D. (1999) Cyclooxygenase-2: pharmacology, physiology, biochemistry and relevance to NSAID therapy. *Br. J. Pharmacol.* **128**, 1121-1132.
- [83] Miyao, S., Takano, A., Teramoto, J., Takahashi, A. (1992) Leukoaraiosis in relation to prognosis for patients with lacunar infarction. *Stroke* **23**, 1434-1438.
- [84] Molloy, G. Y., Rattray, M., Williams, R. J. (1998) Genes encoding multiple forms of phospholipase A₂ are expressed in rat brain. *Neurosci. Lett.* **258**, 139-142.
- [85] Montine, T.J., Sidell, K.R., Crews, B.C., Markesbery, W.R., Marnett, L.J., Roberts, L.J., Morrow J.D. (1999) Elevated CSF prostaglandin E₂ levels in patients with probable AD. *Neurology* **53**, 1495-1498.
- [86] Morris, R. G., Moser, E. I., Riedel, G., Martin, S. J., Sandin, J., Day, M., O'Carroll, C. (2003) Elements of a neurobiological theory of the hippocampus: the role of activity-dependent synaptic plasticity in memory. *Philos. Transact.: Biol. Sci.* **358**, 773-786.
- [87] Murakami, M., Nakatani, Y., Atsumi, G., Inoue, K., Kudo, I. (1997) Regulatory functions of phospholipase A₂. *Crit. Rev. Immunol.* **17**, 225-283.
- [88] Murakami, M., Yoshihara, K., Shimbara, S., Lambeau, G., Gelb, M. H., Singer, A. G., Sawada, M., Inagaki, N., Nagai, H., Ishihara, M., Ishikawa, Y., Ishii, T., Kudo, I. (2002) Cellular arachidonate-releasing function and inflammation-associated expression of group IIF secretory phospholipase A₂. *J. Biol. Chem.* **277**, 19145-19155.
- [89] Murakami, M., Kudo, I. (2002) Phospholipase A₂. *J. Biochem. (Tokyo)*, **131**, 285-292.
- [90] Murakami, M., Kambe, T., Shimbara, S., Kudo, I. (1999) Functional coupling between various phospholipase A₂s and cyclooxygenases in immediate and delayed prostanoid biosynthetic pathways. *J. Biol. Chem.* **274**, 3103-3115.
- [91] Muthalif, M. M., Hefner, Y., Canaan, S., Harper, J., Zhou, H., Parmentier, J. H., Aebbersold, R., Gelb, M. H., Malik, K. U. (2001) Functional interaction of calcium/calmodulin-dependent protein kinase II and cytosolic phospholipase A₂. *J. Biol. Chem.* **276**, 39653-39660.
- [92] Narumiya S. (1996) Prostanoid receptors and signal transduction. *Prog. Brain Res.* **113**, 231-241.
- [93] Narumiya, S., FitzGerald, G. A. (2001) Genetic and pharmacological analysis of prostanoid receptor function. *J. Clin. Invest.* **108**, 25-30.
- [94] Needleman, P., Turk, J., Jakschik, B. A., Morrison, A. R., Lefkowitz, J. B. (1986) Arachidonic acid metabolism. *Ann. Rev. Biochem.* **55**, 69-102.
- [95] Needleman, P., Moncada, S., Bunting, S., Vane, J.R., Hamberg, M., Samuelsson, B. (1976) Identification of an enzyme in platelet microsomes which generates thromboxane A₂ from prostaglandin endoperoxides. *Nature* **261**, 558-560.
- [96] Negishi, M., Sugimoto, Y., Ichikawa, A. (1995) Prostaglandin E receptors. *J. Lipid Med. Cell Signal.* **12**, 379-391.
- [97] Niwa, K., Haensel, C., Ross, M.E., Iadecola, C. (2001) Cyclooxygenase-1 participants in selected vasodilator responses of the cerebral circulation. *Circ. Res.* **88**, 600-608.
- [98] Nogawa, S., Zhang, F., Ross, M.E., Iadecola, C. (1997) Cyclooxygenase-2 gene expression in neurons contributes to ischemic brain damage. *J. Neurosci.* **17**, 2746-2755.
- [99] Nunan J, Small DH. (2002) Proteolytic processing of the amyloid-beta protein precursor of Alzheimer's disease. *Essays Biochem.* **38**, 37-49.
- [100] Nunomura A, Perry G, Aliev G, Hirai K, Takeda A, Balraj EK, Jones PK, Ghanbari H, Wataya T, Shimohama S, Chiba S, Atwood CS, Petersen RB, Smith MA. (2001) Oxidative damage is the earliest event in Alzheimer disease. *J. Neuropathol. Exp. Neurol.* **60**, 759-767.
- [101] Ohno, K., Sakai, T., Fukushima, M., Narumiya, S., Fujiwara, M. (1988) Site and mechanisms of growth inhibition by prostaglandins IV. Effect of cyclopentenone prostaglandins on cell progression of G1-enriched HeLa S3 cells. *J. Pharmacol. Exp. Ther.* **245**, 294-299.
- [102] Oka, S., Arita, H. (1991) Inflammatory factors stimulate expression of group II phospholipase A₂ in rat cultured astrocytes. *J. Biol. Chem.* **266**, 9956-9960.
- [103] Ott, A., Breteler, M. M., van Harskamp, F., Claus, J. J., van der Cammen, T. J., Grobbee, D. E., Hofman, A. (1995) Prevalence of Alzheimer's disease and vascular dementia: association with education. The Rotterdam study. *Br. Med. J.* **310**, 970-973.
- [104] Ott, A., Stolk, R. P., Hofman, A., van Harskamp, F., Grobbee, D. E., Breteler, M. M. (1996) Association of diabetes mellitus and dementia: the Rotterdam Study. *Diabetologia* **39**, 1392-1397.
- [105] Ott, A., Slioter, A. J., Hofman, A., van Harskamp, F., Witteman, J. C., Van Broeckhoven, C., van Duijn, C. M., Breteler, M. M. (1998) Smoking and risk of dementia and Alzheimer's disease in a population-based cohort study: the Rotterdam Study. *Lancet* **351**, 1840-1843.
- [106] Owada, Y., Tominaga, T., Yoshimoto, T., Kondo, H. (1994) Molecular cloning of rat cDNA for cytosolic phospholipase A₂ and the increased gene expression in the dentate gyrus following transient forebrain ischemia. *Mol. Brain Res.* **25**, 364-368.
- [107] Paola, D., Domenicotti, C., Nitti, M., Vitali, A., Borghi, R., Cottalasso, D., Zaccheo, D., Odetti, P., Strocchi, P., Marinari, U. M., Tabaton, M., Pronzato, M. A. (2000) Oxidative stress induces increase in intracellular amyloid β -protein production and selective activation of β I and β II PKCs in NT2 cells. *Biochem. Biophys. Res. Commun.* **268**, 642-646.
- [108] Pasinetti, G.M., Aisen, P.S. (1998). Cyclooxygenase-2 expression is increased in frontal cortex of Alzheimer's disease brain. *Neuroscience* **87**, 319-324.
- [109] Pei, J. J., Tanaka, T., Tung, Y. C., Braak, E., Iqbal, K., Grundke-Iqbal, I. (1997) Distribution, levels, and activity of glycogen synthase kinase-3 in the Alzheimer disease brain. *J. Neuropathol. Exp. Neurol.* **56**, 70-78.
- [110] Phillis, J. W., O'Regan, M. H. (2003) The role of phospholipases, cyclooxygenases, and lipoxygenases in cerebral ischemic/traumatic injuries. *Crit. Rev. Neurobiol.* **15**, 61-90.
- [111] Pratico D, Rokach J, Tangirala RK. (1999) Brains of aged apolipoprotein E-deficient mice have increased levels of F₂-isoprostanes, *in vivo* markers of lipid peroxidation. *J. Neurochem.* **73**, 736-741.
- [112] Pratico, D., Lee, V. M.-Y., Trojanowski, J.Q., Rokach, J., FitzGerald, G.A. (1998) Increased F₂-isoprostanes in Alzheimer's disease: evidence of enhanced lipid peroxidation *in vivo*. *FASEB J.* **12**, 1777-1783.
- [113] Pratico, D., Delanty, N. (2000) Oxidative injury in diseases of the central nervous system: focus on Alzheimer's disease. *Am. J. Med.* **109**, 577-585.
- [114] Rapoport, M., Ferreira, A. (2000) PD98059 prevents neurite degeneration induced by fibrillar beta-amyloid in mature hippocampal neurons. *J. Neurochem.* **74**, 125-133.
- [115] Rogers, J., Kirby, L.C., Hempelman, S.R., Berry, D.L., McGeer, P.L., Kaszniak, A.W., Zalsinski, J., Cofield, M., Mansukhani, L., Willson, P., Kogan, F. (1993). Clinical Trial of indomethacin in Alzheimer's disease. *Neurology* **43**, 1609-1611.
- [116] Rohn, T. T., Wong, S. M., Cotman, C. W., Cribbs, D. H. (2001) 15-deoxy- $\Delta^{12,14}$ -prostaglandin J₂, a specific ligand for peroxisome proliferator-activated receptor- γ , induces neuronal apoptosis. *Neuroreport* **12**, 839-843.
- [117] Sairanen, T., Ristimäki, A., Karjalainen-Lindsberg, M.-L., Paetau, A., Kaste, M., Lindsberg, P. (1998) Cyclooxygenase-2 is induced globally in infarcted human brain. *Annu. Neurol.* **43**, 738-747.
- [118] Salerno, J. A., Murphy, D. G., Horwitz, B., DeCarli, C., Haxby, J. V., Rapoport, S. I., Schapiro, M.B. (1992) Brain atrophy in hypertension. A volumetric magnetic resonance imaging study. *Hypertension* **20**, 340-348.
- [119] Sanchez-Moreno, C., Dashe, J.F., Scott, T., Thaler, D., Folstein, M.F., Martin, A. (2004) Decreased levels of plasma vitamin C and increased concentrations of inflammatory and oxidative stress markers after stroke. *Stroke* **35**, 163-168.

- [120] Satoh T., Ishikawa Y., Kataoka Y., Cui Y., Yanase H., Kato K., Watanabe Y., Nakadate K., Matsumura K., Hatanaka H., Kataoka K., Noyori R., Suzuki M. (1999) CNS-specific prostacyclin ligands as neuronal survival-promoting factors in the brain. *Eur. J. Neurosci.*, **113**, 3115-3124.
- [121] Satoh, K., Nagano, Y., Shimomura, C., Suzuki, N., Saeki, Y., Yokota, H. (2000) Expression of prostaglandin E synthase mRNA is induced in β -amyloid treated rat astrocytes. *Neurosci. Lett.* **283**, 221-223.
- [122] Schehr, R. S. (1996) New treatments for acute stroke. *Nat. Biotechnol.* **14**, 1549-1554.
- [123] Schievella, A.R., Regier M.K., Smith W.L., Lin L.-L. (1995) Calcium-mediated translocation of cytosolic phospholipase A₂ to the nuclear envelope and endoplasmic reticulum. *J. Biol. Chem.* **270**, 30749-30754.
- [124] Schellenberg, G. D., Bird, T. D., Wijsman, E. M., Orr, H. T., Anderson, L., Nemens, E., White, J. A., Bonnycastle, L., Weber, J. L., Alonso, M. E., Potter, H., Heston, L. L., Martin, G. M. (1992) Genetic linkage evidence for a familial Alzheimer's disease locus on chromosome 14. *Science* **258**, 668-71.
- [125] Selkoe, D. J. (1991) The molecular pathology of Alzheimer's disease. *Neuron* **6**, 487-498.
- [126] Selkoe, D. J. (1994) Alzheimer's disease: a central role for amyloid. *J. Neuropathol. Exp. Neurol.* **53**, 438-447.
- [127] Shie, F. S., Montine, K. S., Breyer, R. M., Montine, T. J. (2005) Microglial EP2 as a new target to increase amyloid β phagocytosis and decrease amyloid β -induced damage to neurons. *Brain Pathol.* **15**, 134-138.
- [128] Shimizu, T., Yamamoto, A., and Hayaishi, O. (1982) Specific binding of prostaglandin D₂ to rat brain synaptic membrane. *J. Biol. Chem.* **257**, 13570-13575.
- [129] Six, D. A., Dennis, E. A. (2000) The expanding superfamily of phospholipase A₂ enzymes: classification and characterization. *Biochim. Biophys. Acta* **1488**, 1-19.
- [130] Sonkusare, S. K., Kaul, C. L., Ramarao P. (2005) Dementia of Alzheimer's disease and other neurodegenerative disorders-memantine, a new hope *Pharmacol. Res.* **51**, 1-17.
- [131] Streifler, J. Y., Eliasziw, M., Benavente, O. R., Alamowitch, S., Fox, A. J., Hachinski, V. C., Barnett, H. J. (2002) North American Symptomatic Carotid Endarterectomy Trial Group. Prognostic importance of leukoaraiosis in patients with symptomatic internal carotid artery stenosis. *Stroke* **33**, 1651-1655.
- [132] Stephenson, D.T., Lemere, C.A., Selkoe, D.J., Clemens, J.A. (1996) Cytosolic phospholipase A₂ (cPLA₂) immunoreactivity is elevated in Alzheimer's disease brain. *Neurobiol. Dis.* **3**, 51-63.
- [133] Sundararajan, S., Gamboa, J.L., Victor, N.A., Wanderi, E.W., Lust, W.D., Landreth, G.E. (2005) Peroxisome proliferator-activated receptor- γ ligands reduce inflammation and infarction size in transient focal ischemia. *Neuroscience* **130**, 685-696.
- [134] Takahashi, R. H., Almeida, C. G., Kearney, P. F., Yu, F., Lin, M. T., Milner, T. A., Gouras, G. K. (2004) Oligomerization of Alzheimer's β -amyloid within processes and synapses of cultured neurons and brain. *J. Neurosci.* **24**, 3592-3599.
- [135] Takechi, H., Matsumura, K., Watanabe, Y., Kato, K., Noyori, R., Suzuki, M. (1996) A novel subtype of the prostacyclin receptor expressed in the central nervous system. *J. Biol. Chem.* **271**, 5901-5906.
- [136] Takashima, A., Noguchi, K., Sato, K., Hoshino, T., Imahori, K. (1993) Tau protein kinase I is essential for amyloid β -protein-induced neurotoxicity. *Proc. Natl. Acad. Sci. USA* **90**, 7789-7793.
- [137] Talbot, K., Young, R. A., Jolly-Tornetta, C., Lee, V. M., Trojanowski, J. Q., Wolf, B. A. (2000) A frontal variant of Alzheimer's disease exhibits decreased calcium-independent phospholipase A₂ activity in the prefrontal cortex. *Neurochem. Int.* **37**, 17-31.
- [138] Tomimoto, H., Shibata, M., Ihara, M., Akiguchi, I., Ohtani, R., Bucka, H. (2002) A comparative study on the expression of cyclooxygenase and 5-lipoxygenase during cerebral ischemia in humans. *Acta Neuropathol. (Berl)*, **104**, 601-607.
- [139] Trommer, B. L., Shah, C., Yun, S. H., Gamkrelidze, G., Pasternak, E. S., Blaine, Stine W., Manelli, A., Sullivan, P., Pasternak, J. F., LaDu, M. J. (2005) ApoE isoform-specific effects on LTP: blockade by oligomeric amyloid- β 1-42. *Neurobiol. Dis.* **18**, 75-82.
- [140] Ueda, K., Fukui, Y., Kageyama, H. (1994) Amyloid β protein-induced neuronal cell death: neurotoxic properties of aggregated amyloid β protein. *Brain Res.* **639**, 240-244.
- [141] Ueda, K., Yagami, T., Kageyama, H., Kawasaki, K. (1996) Protein kinase inhibitor attenuates apoptotic cell death induced by amyloid β protein in culture of the rat cerebral cortex. *Neurosci. Lett.* **203**, 175-178.
- [142] Ueda, K., Shinohara, S., Yagami, T., Asakura, K., Kawasaki, K. (1997) Amyloid β protein potentiates Ca²⁺ influx through L-type voltage-sensitive Ca²⁺ channels: A possible involvement of free radicals. *J. Neurochem.* **68**, 265-271.
- [143] Urade, Y., Eguchi, N. (2002) Lipocalin-type and hematopoietic prostaglandin D synthases as a novel example of functional convergence. *Prostaglandins Other Lipid Mediat.* **68-69**, 375-382.
- [144] Umemura, K., Kawai, H., Ishihara, H., Nakashima, M. (1995) Inhibitory effect of clopidogrel, vapiprost and argatroban on the middle cerebral artery thrombosis in the rat. *Jpn. J. Pharmacol.* **67**, 253-258.
- [145] Vadas, P., Pruzanski, W. (1986) Role of secretory phospholipases A₂ in the pathobiology of disease. *Lab. Invest.* **55**, 391-404.
- [146] Valentin, E., Ghomashchi, F., Gelb, M. H., Lazdunski, M., Lambeau, G. (1999) On the diversity of secreted phospholipases A₂. Cloning, tissue distribution, and functional expression of two novel mouse group II enzymes. *J. Biol. Chem.* **274**, 31195-31202.
- [147] van Kooten, F., Ciabattini, G., Koudstaal, P.J., Grobbee, D.E., Kluft, C., Patrono, C. (1999) Increased thromboxane biosynthesis is associated with poststroke dementia. *Stroke* **30**, 1542-1547.
- [148] Walsh D. M., Klyubin, I., Fadeeva, J. V., Cullen, W. K., Anwyl, R., Wolfe, M. S., Rowan, M. J., Selkoe, D. J. (2002) Naturally secreted oligomers of amyloid beta protein potentially inhibit hippocampal long-term potentiation *in vivo*. *Nature* **416**, 535-539.
- [149] Watanabe, K. (2002) Prostaglandin F synthase. *Prostaglandins Other Lipid Mediat.* **68-69**, 401-407.
- [150] Watanabe, Y., Tokumoto, H., Yamashita, A., Narumiya, S., Mizuno, N., Hayaishi, O. (1985) Specific binding of prostaglandin D₂, E₂, F_{2 α} in postmortem human brain. *Brain Res.* **342**, 110-116.
- [151] Winchester, S. K., Imamura, T., Gross, G. A., Muglia, L. M., Vogt, S. K., Wright, J., Watanabe, K., Tai, H. H., Muglia, L. J. (2002) Coordinate regulation of prostaglandin metabolism for induction of parturition in mice. *Endocrinology* **143**, 2593-2598.
- [152] Wisniewski, T., Frangione, B. (1996) Molecular biology of brain aging and neurodegenerative disorders. *Acta Neurobiol. Exp. (Wars)*, **56**, 267-279.
- [153] Wong, P.T., McGeer PL, McGeer, E.G. (1992) Decreased prostaglandin synthesis in postmortem cerebral cortex from patients with Alzheimer's disease. *Neurochem. Int.* **21**, 197-202.
- [154] Wright, D.H., Nantel, F., Metters, K.M., Ford-Hutchinson, A.W. (1999) A novel biological role for prostaglandin D₂ is suggested by distribution studies of the rat DP prostanoid receptor. *Eur. J. Pharmacol.* **377**, 101-115.
- [155] Xiang, Z., Ho, L., Valdellon, J., Borchelt, D., Kelley, K., Spielman, L., Aisen, P. S., Pasinetti, G. M. (2002) Cyclooxygenase (COX)-2 and cell cycle activity in a transgenic mouse model of Alzheimer's disease neuropathology. *Neurobiol. Aging* **23**, 327-334.
- [156] Xu, S., Venge, P. (2000) Lipocalins as biochemical markers of disease. *Biochim. Biophys. Acta* **1482**, 298-307.
- [157] Yagami, T., Ueda, K., Asakura, K., Sakaeda T., Kuroda T., Hata, S., Kambayashi, Y., Fujimoto, M. (2001) Effects of S-2474, a novel nonsteroidal anti-inflammatory drug, on amyloid β protein-induced neuronal cell death. *Br. J. Pharmacol.* **134**, 673-681.
- [158] Yagami, T., Ueda, K., Asakura, K., Kuroda, T., Hata, S., Sakaeda, T., Kambayashi, Y., Fujimoto, M. (2002) Effects of endothelin B receptor agonists on amyloid β protein-induced neuronal cell death. *Brain Res.* **948**, 72-81.
- [159] Yagami, T., Ueda, K., Asakura, K., Sakaeda, T., Nakazato, H., Kuroda, T., Hata, S., Sakaguchi, G., Itoh, N., Kambayashi, Y., Tsuzuki H. (2002) Gas6 rescues cortical neurons from amyloid β protein-induced apoptosis. *Neuropharmacology* **43**, 1289-1296.
- [160] Yagami, T., Nakazato, H., Ueda, K., Asakura, K., Kuroda, T., Hata, S., Sakaeda, T., Sakaguchi, G., Itoh, N., Hashimoto, Y., Hiroshige, T., Kambayashi, Y. (2003) Prostaglandin E₂ rescues cortical neurons from amyloid beta protein-induced apoptosis. *Brain Res.* **959**, 328-335.
- [161] Yagami, T., Ueda, K., Sakaeda, T., Itoh, N., Sakaguchi, G., Noboru, O., Hori, Y., Fujimoto M. (2004) Protective effects of a

- selective L-type voltage-sensitive calcium channel blocker, S-312d, on neuronal cell death. *Biochem. Pharmacol.* **67**, 1153-1165.
- [162] Yagami, T., Ueda, K., Asakura, K., Hata, S., Kuroda, T., Sakaeda, T., Takasu, N., Tanaka, K., Gemba, T., Hori, Y. (2002) Human group IIA secretory phospholipase A₂ induces neuronal cell death via apoptosis. *Mol. Pharmacol.* **61**, 114-126.
- [163] Yagami, T., Ueda, K., Asakura, K., Nakazato, H., Hata, S., Kuroda, T., Sakaeda, T., Sakaguchi, G., Itoh, N., Hashimoto, Y., Hori, Y. (2003) Human group IIA secretory phospholipase A₂ potentiates Ca²⁺ influx through L-type voltage-sensitive Ca²⁺ channel. *J. Neurochem.* **85**, 749-758.
- [164] Yagami, T., Ueda, K., Asakura, K., Hata, S., Kuroda, T., Kishino, J., Sakaeda, T., Sakaguchi, G., Itoh, H., Hori, Y. (2002) Group IB secretory phospholipase A₂ induces cell death in cultured cortical neurons: A possible involvement of its binding sites. *Brain Res.* **949**, 197-201.
- [165] Yagami, T., Ueda, K., Asakura, K., Sakaeda, S., Hata, S., Kuroda, T., Sakaguchi, G., Itoh, N., Hashimoto, Y., Hori, Y. (2003) Porcine pancreatic group IB secretory phospholipase A₂ potentiates Ca²⁺ influx through L-type voltage-sensitive Ca²⁺ channel. *Brain Res.* **960**, 71-80.
- [166] Yagami, T., Ueda, K., Asakura, K., Hayasaki-Kajiwar, Y., Nakazato, H., Sakaeda, T., Hata, S., Kuroda, T., Takasu, N., Hori, Y. (2002) Group IB secretory phospholipase A₂ induces neuronal cell death via apoptosis. *J. Neurochem.* **81**, 449-461.
- [167] Yagami, T., Takahara, Y., Ishibashi, C., Sakaguchi, G., Itoh, N., Ueda, K., Nakazato, H., Okamura, N., Hiramatsu, Y., Honma, T., Arimura, A., Sakaeda, T., Katsuura, G. (2004) Amyloid β protein impairs motor function via thromboxane A₂ in the rat striatum. *Neurobiol. Dis.* **16**, 481-489.
- [168] Yagami, T., Ueda, K., Asakura, K., Takasu, N., Sakaeda, T., Itoh, N., Sakaguchi, G., Kishino, J., Nakazato, H., Katsuyama, Y., Nagasaki, T., Okamura, N., Hori, Y., Hanasaki, K., Arimura, A., Fujimoto, M. (2003) Novel binding sites of 15-deoxy- $\Delta^{12,14}$ -prostaglandin J₂ in plasma membranes from primary rat cortical neurons. *Exp. Cell Res.* **291**, 212-227.
- [169] Yang, H. C., Mosior, M., Ni, B., Dennis, E. A. (1999) Regional distribution, ontogeny, purification, and characterization of the Ca²⁺-independent phospholipase A₂ from rat brain. *J. Neurochem.* **73**, 1278-1287.
- [170] Yamagata, K., Andreasson, K.I., Kaufmann, W.E., Barnes, C.A., Worley, P.F. (1993) Expression of a mitogen-inducible cyclooxygenase in brain neurons: Regulation by synaptic activity and glucocorticoids. *Neuron* **11**, 371-386.
- [171] Yokota, C., Kaji, T., Kuge, Y., Inoue, H., Tamaki, N., Minematsu, K. (2004) Temporal and topographic profiles of cyclooxygenase-2 expression during 24 h of focal brain ischemia in rats. *Neurosci. Lett.* **357**, 219-222.
- [172] Younkin, S. G. (1995) Evidence that A β 42 is the real culprit in Alzheimer's disease. *Ann Neurol.* **37**, 287-288.

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