



Review

The Role of Eicosanoids in Alzheimer's Disease

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Abstract: Alzheimer's disease (AD) is one of the most common neurodegenerative disorders known. Estimates from the Alzheimer's Association suggest that there are currently 5.8 million Americans living with the disease and that this will rise to 14 million by 2050. Research over the decades has revealed that AD pathology is complex and involves a number of cellular processes. In addition to the well-studied amyloid- β and tau pathology, oxidative damage to lipids and inflammation are also intimately involved. One aspect all these processes share is eicosanoid signaling. Eicosanoids are derived from polyunsaturated fatty acids by enzymatic or non-enzymatic means and serve as short-lived autocrine or paracrine agents. Some of these eicosanoids serve to exacerbate AD pathology while others serve to remediate AD pathology. A thorough understanding of eicosanoid signaling is paramount for understanding the underlying mechanisms and developing potential treatments for AD. In this review, eicosanoid metabolism is examined in terms of *in vivo* production, sites of production, receptor signaling, non-AD biological functions, and known participation in AD pathology.

Keywords: Alzheimer's disease; eicosanoid; prostaglandin; thromboxane; leukotriene; lipoxin; resolving; protectin; maresin; isoprostane

1. Introduction

Alzheimer's disease (AD) is the primary neurodegenerative disorder causing dementia in the elderly. The primary pathogenic signature is the extracellular deposition of beta amyloid protein ($A\beta$) and the intracellular accumulation of tau protein. $A\beta$ is a 36–42 residue proteolytic product formed by β - and γ -secretase cleavage of the amyloid precursor protein (APP) that ultimately precipitates as amyloid fibrils. Prior to aggregation, APP is known to complex with Zn^{2+} , Fe^{3+} , and Cu^{2+} which then mediates free radical formation and subsequent neural damage. The tau protein's main function in neurons is to modulate the stability of microtubules in axons. However, upon hyper-phosphorylation of tau, self-assembly occurs and insoluble aggregates form that block synapses and nutrient uptake, ultimately leading to neuronal death.

Eicosanoids are amphipathic, bioactive signaling molecules derived from the oxidation of arachidonic acid (AA) and other similar polyunsaturated fatty acids (PUFAs). There are multiple subfamilies of eicosanoids, including the prostaglandins, thromboxanes, leukotrienes, lipoxins, resolvins, protectins, maresins, isoprostanes, endocannabinoids, HETEs, and eoxins to name a few. Although the biological functions of eicosanoids cover a wide range, one thing many have in common is context dependency. That is, stimulation by a particular eicosanoid in one cell or tissue may in fact elicit a different and, at times, opposite effect in another cell or tissue. Eicosanoids are key paracrine and autocrine biochemical signaling molecules in the central nervous system (CNS) and are reported to be involved in numerous processes including memory and learning [1], cerebral blood flow [2], sleep [3], as well as regulation of neuroinflammation [1]. The fact that each of these neurological functions has been shown to be involved in AD etiology [4–7] strongly suggests the involvement of eicosanoid signaling in the disease.

2. Neuroinflammation

Up until the mid-1990s the central nervous system (CNS) was deemed to be “immune privileged”, that is, devoid of inflammation. However, since that time, multiple studies have shown that neuroinflammation is involved in numerous CNS disorders, including AD. See the review by Lucas et al. [8]. In particular, microglial cells, the resident macrophages of the brain, are known to produce the inflammatory cytokines IL-1, IL-6, and TNF α [9]. These cells are differentially expressed across brain regions and have been shown to correlate well with the distributions of AD related neuritic plaques [10,11]. Both APP and A β peptides are known to be strong glial activators and hence promote the release of these pro-inflammatory factors. These factors in turn are known to upregulate APP production as well as hyperphosphorylation of tau, thus amplifying the process [12]. Activated microglia are also reported to be major producers of the prostaglandin PGE $_2$ through the COX-2 pathway [13] and serve as a trigger for uncontrolled astrocyte proliferation [14], another feature of AD [15]. See the recent review by Wang and Colonna [16].

3. Free AA and cPLA $_2$ - α in AD

Free AA ((5Z,8Z,11Z,14Z)-5,8,11,14-eicosatetraenoic acid) is not only a precursor to many classes of eicosanoids, some of which are directly involved in AD, but also is an active participant in synaptic functions. AA produced by the post-synaptic neuron has been shown to act as a retrograde messenger on the pre-synaptic membrane where it increases neurotransmitter release, resulting in the induction of long-term potentiation (LTP) [17,18]. Further, AA has also been shown to facilitate inhibition of voltage-gated K $^+$ channels on the presynaptic membrane [19] and activate SNARE receptors [20], both of which are known to enhance neurotransmitter release. In contrast, treatment of mouse brains with human A β oligomers has been shown to inhibit LTP [21]. At face value, the actions of AA and A β appear juxtaposed. However, it has been proposed that excessive neurotransmitter release and excessive maintenance of LTP have detrimental effects on memory storage, thus exacerbating memory issues in AD patients [22]. Additionally, PET scans of AD patients and controls administered radiolabeled AA revealed that AA accumulation in AD brains was elevated compared to controls (26% increase in brain radioactivity normalized to integrated plasma radioactivity) and was particularly elevated in regions with a high density of neuritic plaques with activated microglia [23].

The phospholipase A $_2$ (PLA $_2$) family catalyzes the cleavage of fatty acids from glycerophospholipids at the *sn*-2 position, where AA, if present, is almost exclusively esterified. Hence, this class of enzyme provides AA for the production of eicosanoids involved in AD. The 22 known PLA $_2$ s are further classified into one of three categories [24]: cytosolic Ca $^{2+}$ -dependent PLA $_2$ (cPLA $_2$), secretory Ca $^{2+}$ -dependent PLA $_2$ (sPLA $_2$), and cytosolic Ca $^{2+}$ -independent PLA $_2$ (iPLA $_2$). Both sPLA $_2$ [25] and cPLA $_2$ [22] were found to be upregulated in AD whereas iPLA $_2$ was downregulated [26]. Since the latter is associated with housekeeping functions with a low preference for AA, its downregulation in AD makes sense. sPLA $_2$, in particular the isoform sPLA $_2$ -IIA, was found to be up-regulated in astrocytes cultured from AD post-mortem human brains compared to elderly non-demented brains and was found associated with A β -containing plaques [25]. This up-regulation was facilitated by both A β_{1-42} and IL-1 β , each of which is known to be associated with plaque formation in AD. In a transgenic murine model, expression of AD-mutant human amyloid precursor protein (hAPP) resulted in an increased production of AA in mouse neuronal cultured brain [27]. The increased production of AA was apparently caused by phosphorylation and subsequent activation of cytosolic GroupIV-PLA $_2$ in hAPP mice as compared to controls; GroupIV-PLA $_2$ has a marked preference for AA. Treatment of murine brain cell cultures with synthetic A β_{1-42} also facilitated phosphorylation/activation of GroupIV-PLA $_2$ and treatment with either A β_{1-42} or AA caused a dose-dependent reduction in neuronal viability. Further, treatment of rat cortical neuron cultures with a non-specific PLA $_2$ inhibitor has been shown to reduce the production of AA and A β_{1-40} as well as A β_{1-42} -induced neuron apoptosis [28]. Clearly, there is a yet-to-be understood synergy between AA, its production by sPLA $_2$, and amyloid peptides in AD progression.

4. Cyclooxygenases in AD

Cyclooxygenases catalyze the first step in prostanoid biosynthesis whereby arachidonic acid is converted to the endoperoxide prostaglandin H₂ (PGH₂, (Z)-7-[(1R,4S,5R,6R)-6-[(E,3S)-3-hydroxyoct-1-enyl]-2,3-dioxabicyclo[2.2.1]heptan-5-yl]hept-5-enoic acid) via the transient prostaglandin G₂ (PGG₂, (Z)-7-[(1R,4S,5R,6R)-6-[(E,3S)-3-hydroperoxyoct-1-enyl]-2,3-dioxabicyclo[2.2.1]heptan-5-yl]hept-5-enoic acid) (Figure 1). PGH₂ is a multifunctional metabolite and serves as a precursor for the enzymatic synthesis of other prostanoids: PGI₂, PGE₂, PGF₂α, PGD₂, and TXA₂. PGH₂ is a labile endoperoxide and it rapidly and non-enzymatically rearranges to both PGD₂ and PGE₂. There are two known protein isoforms of cyclooxygenase, prostaglandin G/H synthase 1 (COX-1) and prostaglandin G/H synthase 2 (COX-2). A third isoform (COX-3, COX-1b), a splice variant of COX-1, has been identified in humans and other mammals, but its involvement in human prostaglandin synthesis has largely been discounted [29]. In most tissues the COX-1 is expressed constitutively and functions to maintain the GI tract and renal function [30] whereas COX-2, normally present at undetectable levels in most cells, is induced during inflammation. In contrast, in the brain, testes, and the macula densa of the kidney, both isoforms were found to be expressed constitutively [31,32]. Both isomers have been found associated with endoplasmic reticulum (ER) and nuclear membranes [33]. Although COX-2 is expressed throughout the forebrain, the highest levels have been found in the hippocampus and cerebral cortex and located in particular groups of neurons, and are not typically found in glial cells [32] unless certain conditions prevail (e.g., chronic cerebral ischemia) [34].

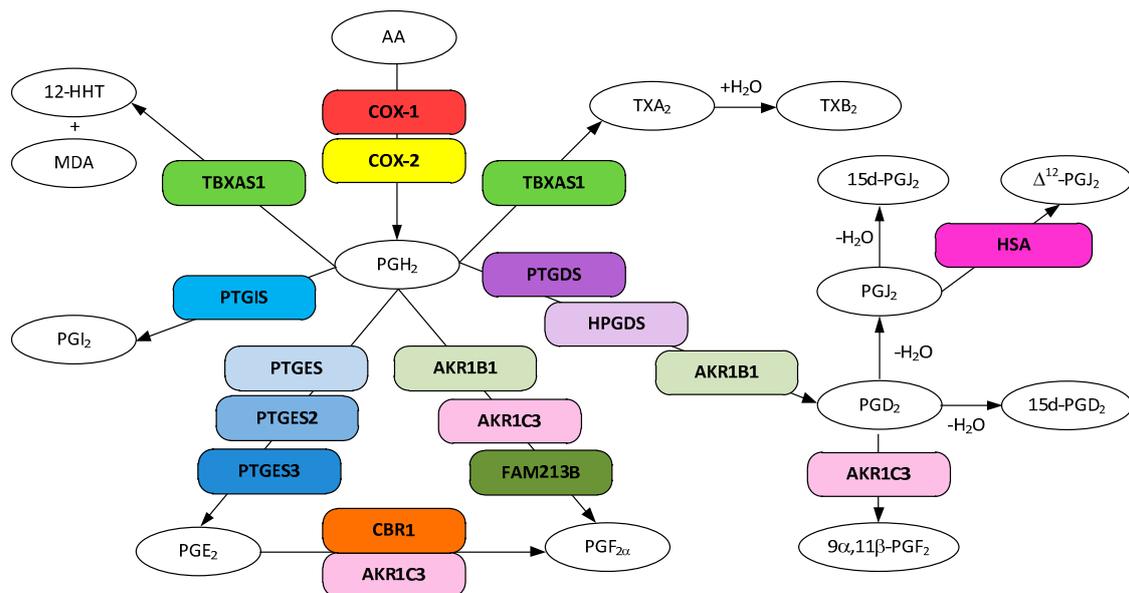


Figure 1. Metabolic pathways for prostanoid and thromboxane biosynthesis from arachidonic acid. Gene designations are given for all but the COX participating enzymes (rounded boxes) and accepted acronyms given for metabolites (ovals).

Non-steroidal anti-inflammatory agents (NSAIDs) are known inhibitors of cyclooxygenases and there are numerous reports that show unequivocally that long term use of NSAIDs is associated with a reduction in the risk of developing AD [35,36]. For example, in a population-based cohort study of 6989 subjects 55 years or older living in Ommoord, Netherlands, long term use of NSAIDs (24 months or more) reduced the relative risk of AD by 80% [37]. Further, a six-month, double-blind, placebo-controlled study revealed that the non-selective COX inhibitor indomethacin (seven times more effective for COX-1 than COX-2) appeared to protect mild to moderately impaired Alzheimer's disease patients from the degree of cognitive decline as compared to a placebo-treated group [38]. In fact, the treated group showed improved cognition. Not all studies have produced such positive

results [39] and the effect may depend on the NSAID used and its target [35] as well as the stage of AD when the treatment was begun [40].

Much of the focus on the involvement of cyclooxygenases in AD has been directed to the COX-2 isoform. Semiquantitative immunostaining of AD brain and age matched controls have revealed elevated COX-2 in CA1–CA4 subdivisions of the hippocampal pyramidal layer in AD brain compared to controls and the observed COX-2 levels correlated with amyloid plaque density [41]. However, immunostaining of post-mortem AD and control brains revealed that COX-2 positive neurons decrease over the progression of the disease once the individual has reached a clinical dementia rating (CDR) of 5 [42]. Further, COX-2 positive neurons have been shown to decrease with increasing amyloid deposit accumulation except in the very early stages (Braak stage A) where there was a moderate, but significant increase [43]. In support of this observation, treatment of neuroblastoma cells with synthetic A β peptides *in vitro* has been shown to induce the expression of COX-2 [44]. These results show that COX-2 is involved in the early stages of AD, but is unlikely to be involved in the pathology in the end stage AD. In a mouse AD model, selective inhibition of COX-2 or combined inhibition of COX-1 and COX-2 prevented the suppression of LTP by A β and improved spacial memory, whereas selective inhibition of COX-1 showed no effect on LTP suppression [45]. The authors further suggested that it is the inhibition of COX-2 concentrated in dendritic spines that prevent the deleterious effects of A β in this region. These data also support the involvement of COX-2 in the early stages of AD with diminished effects in the latter stages.

Early work largely ignores the involvement of COX-1 in AD. This possibly due to the fact that COX-2 is a more pharmacologically advantageous target than COX-1, as COX-1 inhibition can cause severe side effects, including gastric damage. Although COX-1 may not be an opportune therapeutic target, its involvement in AD is clear. Immunostaining of human brain tissue obtained from both AD patients and controls revealed that microglia express COX-1 in AD and control brains, regardless of activation state [46]. However, in AD brains, activated microglia were found surrounding and imbedded in A β plaques, suggesting the production of eicosanoids in AD positive regions. Further support for the involvement of COX-1 comes from studies utilizing Triflusal, a specific, irreversible inhibitor of COX-1 [47] which has only a moderate effect on COX-2 expression (30% reduction) [48]. In a mouse AD model, Triflusal did not alter the total accumulation of A β , but significantly reduced (50%) the neuritic plaque load and associated glial cell proliferation [49]. Further, reductions in pro-inflammatory cytokine levels as well as improved cognition were also observed. These results and the aforementioned clinical trial with indomethacin [46], a preferential COX-1 inhibitor, support the involvement of COX-1 in both early and later stages of AD. The fact that selective inhibition of COX-1 had no effect on A β suppression of LTP and selective inhibition of COX-2 did [45] indicates a mechanism of action for COX-1 that differs from that for COX-2.

5. Prostaglandins, Thromboxanes, and Their Receptors in AD.

One of the earliest reports showing the involvement of prostaglandins and thromboxanes in AD was obtained from the analysis of the cortex of post-mortem brains from five patients with pathologically verified AD as compared to eight age-matched controls [50]. The results revealed that the amounts of prostaglandin PGD₂ and the thromboxane TXB₂ were significantly elevated in AD brains as compared to control brains, not surprising given that both are strong vasoconstrictors [5]. The fact that NSAIDs inhibit cyclooxygenases (COX-1 and COX-2), the enzymes that convert arachidonic acid (AA) to prostaglandin H₂ (PGH₂), the precursor to all prostanoids and thromboxanes (Figure 1), strongly indicates that one or more of these eicosanoids is involved in AD onset.

5.1. PGD₂ and 15d-PGD₂ in AD

Prostaglandin D₂ (PGD₂, (Z)-7-[(1R,2R,5S)-5-hydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]-3-oxocyclopentyl]hept-5-enoic acid) has been shown to be the most abundant eicosanoid in the brain [51,52] and also the most elevated under pathological conditions [53]. PGD₂ is synthesized from

PGH₂ through the action of hematopoietic prostaglandin D synthase (HPGDS) and the lipocalin-type prostaglandin D synthase (PTGDS, L-PGDS), the latter shown to be one of the more abundant proteins in the brain [54]. There are two known human receptors for this prostanoid, DP₁ and DP₂ (CRTH2). HPGDS and both receptors are reported to be expressed in microglia and astrocytes [55]. Both receptors are coupled to G-proteins and upon binding to PGD₂ or its J₂ series metabolic products, are reported to have opposite effects on [cAMP] where activation of DP₁ increases [cAMP] and activation of DP₂ decreases [cAMP] while increasing intracellular [Ca²⁺] [56]. At physiological concentrations of PGD₂, activation of DP₁ receptors have been shown to rescue neurons from glutamate toxicity in cultured rat hippocampal neurons and in organotypic slices [53]. In contrast, activation of the DP₂ receptor resulted in neuronal loss. Further, stimulation of DP₂ in Th2 cells preferentially induced the production of inflammatory cytokines [48,57]. It was also established that activated astrocytes express inflammatory cytokines [58]. With this in mind it is not unreasonable that activation of DP₂ receptors in astrocytes or Th2 cells that have crossed the blood brain barrier (BBB) [59] may release inflammatory cytokines that result in neuronal loss.

Both HPGDS and the DP₁ receptor have been shown to be upregulated in microglia and reactive astrocytes within senile plaques obtained from human AD brain and in a mouse model of Alzheimer's disease [60]. The upregulation of each increased in step with A β deposition until the plaques reached the "burned out" stage where expression was diminished. Based on the known function of the DP₁ receptor in neuron rescue, its increased expression is likely a response to the toxic effect of A β production in early stages of AD. In all, these results suggest that once plaques begin to form, microglia and astrocytes become activated and produce cytokines that cause further neuronal injury. The involvement of DP₂ receptors in AD has yet to be elucidated. However, DP₂ involvement in neuronal degradation is well documented [61]. For example, inhibition of DP₂ receptors in DP₁-null twitcher mice resulted in a reduction of astrogliosis, demyelination, and oligodendroglial apoptosis [55]. Clearly, DP₂ stimulation exacerbates demyelination and enhances inflammation via astrogliosis.

PGD₂ has been shown to spontaneously dehydrate to either 15-deoxy-prostaglandin D₂ (15d-PGD₂; (Z)-7-[(1R,2S,5Z)-2-hydroxy-5-[(E)-oct-2-enylidene]cyclopent-3-en-1-yl]hept-5-enoic acid) or prostaglandin J₂ (PGJ₂) with an overall brain half-life of \approx 1.1 min [62]. 15d-PGD₂ has been established as a potent activator of the DP₂ receptor in eosinophils, but does not activate the DP₁ receptor [63]. The EC₅₀ for initiating eosinophil shape change and chemotaxis (\approx 2.2 nM) by 15d-PGD₂ was found to be similar to that obtained for that initiated by PGD₂ on DP₂ receptors expressed in HEK293 cells (1.6 mM) [56] and thus could potentially be involved in neuronal degradation. However, the data reported to date are mixed. Toll-like protein receptors (TLR) are expressed on the surface of immune cells and act as the first line of defense where they recognize various inflammatory stimuli and initiate immune cells to release an inflammatory response. It has been shown that microglia and astrocytes pre-treated with 15d-PGD₂ or PGD₂ and then stimulated with the inflammatory lipopolysaccharide (LPS) produced significantly less surface expressed TLR2 than cells that were not pretreated with 15d-PGD₂ or PGD₂ [64]. This reduction in inflammatory response suggests that a neural protective effect is more in keeping with DP₁ stimulation than DP₂ stimulation.

5.2. PGJ₂, 15d-PGJ₂, and Δ^{12} -PGJ₂ in AD

The J₂ series is formed by the spontaneous non-enzymatic dehydration of PGD₂ to prostaglandin J₂ (PGJ₂, (Z)-7-[(1S,5R)-5-[(E,3S)-3-hydroxyoct-1-enyl]-4-oxocyclopent-2-en-1-yl]hept-5-enoic acid). PGJ₂ is quite unstable itself and spontaneously and non-enzymatically dehydrates to 15d-PGJ₂ ((Z)-7-[(1S,5E)-5-[(E)-oct-2-enylidene]-4-oxocyclopent-2-en-1-yl]hept-5-enoic acid) or in the human serum albumin (HSA) catalyzed rearrangement to Δ^{12} -PGJ₂ ((Z)-7-[(1S,5E)-5-[(3S)-3-hydroxyoctylidene]-4-oxocyclopent-2-en-1-yl]hept-5-enoic acid). Biological half-lives of each member of the series appear short, but specific values are unreported.

The J₂ series of prostaglandins (e.g., PGJ₂ and Δ^{12} -PGJ₂) have proved to be some of the most neurotoxic compounds within the PGD₂ degradation pathway [65,66]. These prostaglandins have

very short reported half-lives [67]. There are no known J₂ series specific receptors reported to date. Although the EC₅₀ reported for both DP₁ and DP₂ receptors are close to that observed for PGD₂ [56,68] there are no reports of DP receptor involvement in the biological activity of PGJ₂. Both 15d-PGJ₂ and Δ¹²-PGJ₂ have been shown to have similar EC₅₀s for DP₂ receptors, but much poorer EC₅₀s for DP₁ [56,68]. The only known biological action demonstrated for 15d-PGJ₂ was as a DP₂ agonist [63]. The effect of J₂ series prostaglandins on neurons is complex and appears to act mainly through receptor-independent mechanisms. The reactivity of protein thiols with the α,β-unsaturated carbonyl center on the cyclopentanone ring of J₂ series is central to their activity and has been shown to be involved in neuron decline. The receptor-independent action of the J₂ series on intracellular proteins necessarily requires reuptake, requiring a mechanism for cross-membrane transport. PGD₂ is observed to be a substrate of prostaglandin transporters (PGTs) [69] which are known to be present in the brain [70]. Its transport and subsequent dehydration to PGJ₂ metabolites is likely involved in the intracellular action. Prostaglandins, including PGD₂ and PGJ₂ have also been shown to be transferred from cell to cell via exosomes [71].

Upon treatment of human neuroblastoma SK-N-SH cells with PGJ₂, an initial time-dependent accumulation of ubiquitinated proteins (Ub) was observed [67]. This was followed by activation of caspase cleavage of tau at D141, leading to the production of Δtau, an early event in AD pathology [72]. These events were followed later by cellular apoptosis. Both PGJ₂ and PGD₂ treatment of rat E18 cortical neuronal cells were also shown to generate Δtau. However, treatment of rat primary neuron-enriched cultures with DP₁ and DP₂ antagonists did not affect the accumulation of Ub proteins [66]. This observation, the known neuroprotective effect of PGD₂ through the DP₂ receptor, and the rapid non-enzymatic conversion of PGD₂ to PGJ₂ and its metabolites indicate that the enhanced Ub accumulation following treatment with PGD₂ is due to its metabolic byproducts.

The mechanism for the accumulation of Ub proteins involved in AD has been ascribed in part to the reaction of PGJ₂ and Δ¹²-PGJ₂ with a thiol on ubiquitin C-terminal hydrolase L1 (Uch-L1) [65], a major neurological protein that functions to remove ubiquitin from misfolded proteins that need to be directed to the proteasome pathway [73]. Inhibition of this enzyme has been shown to lead to an increase in Aβ₄₂, which in turn downregulates Uch-L1 further [74]. It has been shown that inhibition of Uch-L1 is facilitated by reaction of a single thiol with the α,β-unsaturated carbonyl center on the cyclopentanone ring of PGJ₂ series prostaglandins, leading to denaturation and aggregation of the enzyme and loss of activity [75]. As noted above, PGD₂ is known to spontaneously dehydrate to either 15d-PGD₂ or PGJ₂. It has been shown that neither PGD₂ nor 15d-PGD₂ react with Uch-L1 and that the α,β-unsaturated carbonyl ring containing PGJ₂ does. Thus, dehydration of PGD₂ to 15d-PGD₂ rather than PGJ₂ passively helps to reduce Aβ₄₂ accumulation. The conditions favoring one path over the other are currently unknown.

In contrast to the pro-inflammatory actions of the J₂ series, 15d-PGJ₂ exhibits anti-inflammatory properties. 15d-PGJ₂ is a natural ligand for peroxisome proliferator-activated receptor γ (PPARγ). PPARγ is known to participate in various biological functions including lipid homeostasis, glucose metabolism, macrophage functions, and anti-inflammatory responses [76]. It is a nuclear receptor and serves to activate a number of genes. Ischemia-reperfusion injured rat brain showed increased production of 15d-PGJ₂ and PPARγ. Intraventricular infusion of 15d-PGJ₂ into this rat model has been shown to suppress ischemic brain infarction, neuronal apoptosis necrosis in a PPARγ dependent manner [77]. PPARγ has been found to be present in elevated levels in the brains of individuals with AD as well as in other CNS disorders [78,79]. In animal models of AD, treatment with PPARγ agonists reduced amyloid plaque burden, reduced inflammation, and reduced AD behavioral impairment [78]. Similar results were observed in human AD patients and showed improved memory impairments for those with mild-to-moderate AD [80]. 15d-PGJ₂ has also been shown to suppress several genes involved in neural inflammation and AD including inducible NO synthase and tumor necrosis factor α (TNFα) in a PPARγ-dependent manner [81–84]. 15d-PGJ₂ also reduced inflammation by directly inhibiting NF-κB gene expression thereby suppressing COX-2 expression and concomitant

prostaglandin synthesis [81]. The PPAR γ -independent inhibition appeared to involve the Michael-type addition of the α,β -unsaturated carbonyl center on the cyclopentanone ring to a specific cysteine residue on the NF- κ B activator I κ B kinase (IKK) resulting in inhibition and by directly inhibiting binding of NF- κ B to DNA [76].

5.3. PGI₂ in AD

Prostaglandin I₂ (PGI₂, prostacyclin, (5Z)-5-[(3aR,4R,5R,6aS)-5-hydroxy-4-[(E,3S)-3-hydroxyoct-1-enyl]-3,3a,4,5,6,6a-hexahydrocyclopenta[b]furan-2-ylidene]pentanoic acid) is synthesized from PGH₂ by prostacyclin synthase (PTGIS) and serves as a vasodilator, platelet inhibitor, and is involved in neuron survival [85,86]. PTGIS has been observed to be localized in blood vessels throughout the brain as well as in microglia, and oligodendrocytes [87]. The strongest expression was observed in large principal neurons, pyramidal cells of the cortex and hippocampus as well as the purkinje cells of the cerebellum. PGI₂ is quite unstable at physiological pH with a measured half-life of 2–5 min, forming biologically inactive 6-keto-prostaglandin F₁ α (6-keto-PGF₁ α) [86]. The PGI₂ receptor (IP) is a G-protein coupled receptor having very low cross-reactivity with other prostanoids [88] and signals through either cAMP or IP₃/Ca²⁺ mechanisms depending on the G-protein it couples with [89]. In situ hybridization in murine brain revealed that IP receptor mRNA was expressed in about 40% of the neurons in the dorsal root ganglion, but no labeling was found in the glia [90]. Radiolabeling with the stable PGI₂/IP agonist [³H]iloprost showed high binding in the lower brainstem of rat brain and moderate binding in the thalamus, cerebral cortex, and hippocampus.

The PGI₂/IP signaling pathway plays a crucial role in the metabolism of APP. In a murine model, iloprost stimulation of IP receptors stimulated production of APP and the metalloproteinase ADAM10, resulting in an increased production of the neuroprotective soluble APP α (sAPP α) [91]. In addition, iloprost stimulation of IP receptors in human brain microvascular endothelial cells resulted in upregulation of PPAR γ , a protein known to reduce inflammation and amyloid plaque burden [91]. PGI₂ was shown to suppress the expression of interferon γ (INF γ), a cytokine associated with inflammation and known to accelerate A β ₄₂ aggregation [92]. PGI₂ was also found to suppress the activation of astrocytes, thus reducing their expression of inflammatory cytokines. In keeping with PGI₂ neuroprotection, PGI₂ has also been observed to protect mouse brain pericytes from lysophosphatidylcholine (LPV)-mediated apoptosis [93] thereby preventing BBB disruption, a known characteristic of AD [94], and AD-like neurodegeneration in mice [95].

5.4. PGE₂ in AD

Prostaglandin E₂ (PGE₂, (Z)-7-[(1R,2R,3R)-3-hydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]-5-oxocyclopentyl]hept-5-enoic acid) is synthesized from PGH₂ by microsomal PGE₂ synthase-1 (PTGES, mPGES-1), microsomal PGE₂ synthase-2 (PTGES2, mPGES-2), and cytoplasmic PGES-3 (PTGES3, cPGES), each having a different structure and several having different cellular locations [96,97]. Two of the known isoforms are glutathione requiring (PTGES, PTGES3) and one is glutathione independent (PTGES2). In normal human brains PTGES2 and PTGES3 are highly expressed in the mitochondria and nucleoplasm/cytoplasm respectively and PTGES shows very low expression and is found in the ER. Tissue samples from human middle frontal gyrus have been evaluated for the presence of specific prostaglandin E₂ synthases. PTGES has been found in neurons, microglia, and endothelial cells of the brain in both AD and controls and elevated in AD tissue, particularly in the pyramidal neurons [98]. Immunostaining revealed that PTGES co-localizes with A β in microglia-shaped cells in both AD and controls. PTGES2 has been found in neurons, activated microglia, and endothelium, but not resting microglia, astrocytes of smooth muscle cells in both AD and controls, and found to be elevated in AD pyramidal neurons [99]. The expression pattern for PTGES3 has been shown to be similar to PTGES2 in both AD patients and controls, however, its expression was found to be decreased in the pyramidal cells of AD patients [100].

PGE₂ is quite stable for a prostaglandin with a reported half-life of about 8.8 h and is metabolized to primarily 13,14-dihydro-15-keto-PGE₂ and smaller amounts of prostaglandin B₂ (PGB₂). There are four distinct subtypes (EP₁–EP₄) and nine known PGE₂ receptors, each of which couple to various G proteins, stimulating a variety of signal pathways [101].

The EP₁ receptor is highly expressed in the cerebellum, the Purkinje neurons in particular [102] and is known to couple with the G_q protein to signal through the IP₃/Ca²⁺ signaling pathway [103]. Although EP₁ is also expressed in microglia, its presence was found to be undetectable in microglia after middle cerebral artery occlusion (MCA) [104]. Stimulation of the EP₁ receptor resulted in an increase in [Ca²⁺] leading to suppression of the pro-survival protein kinase AKT, ultimately resulting in neuronal cell death in mice following an ischemia/reperfusion insult [105]. EP₁^{−/−} mice and those treated with the EP₁ antagonist SC50189 showed significantly less neural damage after being subjected to ischemia/reperfusion. These results suggest that EP₁ stimulation reduces neural viability. In support of this, another study revealed that fewer amyloid plaques were found in EP₁^{−/−} AD mice compared to AD mice [106]. Further, the EP₁^{−/−} mice were shown to be more resistant to Aβ neural toxicity than wild type mice. These results show that EP₁ stimulation is clearly involved in Aβ production and increased susceptibility to Aβ toxicity. In addition, treatment of human neuroblastoma cell line MC165 with EP₁ antagonist SC50189 reduced Aβ neurotoxicity by 50%; inhibition of the IP₃/Ca²⁺ signaling pathway produced similar results [107].

In contrast to EP₁, the EP₂ receptor involvement in AD is microglial in nature. EP₂ receptors are known to couple to both G_s and G_q proteins, leading to cAMP/PKA or IP₃/Ca²⁺/AKT signaling respectively. The fact that microglial signaling via EP₂ initiated PKA signaling [108] indicates that the G_s/cAMP signaling pathway is at work in microglia. In AD model mice, microglial EP₂ expression and Aβ₄₂ accumulation increased with aging [109]. In the same study the EP₂^{−/−} AD model showed an increase in microglial chemotaxis and Aβ clearance, a suppression of toxic inflammation, and an increase in the insulin-like growth factor 1 (IGF1) signaling, known for its involvement in neuron survival. EP₂ receptors have also been shown to be involved in the increase in lipid peroxidation and associated Aβ₄₀ and Aβ₄₁ plaque load in aged mice [110]. Microglial phagocytosis of Aβ is essential to a reduction of Aβ plaque load and progression of AD. Two studies have shown that stimulation of EP₂ reduced microglial phagocytosis. Stimulation of murine N9 microglia cells in culture with either PGE₂ or PKA agonists reduced the ability of these cells to phagocytose, whereas treatment with the EP₂ antagonist AH6809 restored the ability to phagocytose [108]. In addition, treatment of human hippocampal sections from patients who died with AD with microglia isolated from EP^{−/−} mice reduced the Aβ₄₀, Aβ₄₁, and aggregated Aβ₄₂ load, whereas microglia from WT mice had no effect [111].

The EP₃ receptor involvement in AD is the least well defined of all EP receptors. This is likely due to the fact that there are at least six known human isoforms of EP₃ identified, each of which has a particular set of G-proteins that it binds to and thus signaling pathways vary widely [112]. Isoforms EP3-I, EP3-II, EP3-III, and EP3-IV are all found in brain tissue, whereas EP3-V and EP3-VI appear to be restricted to uterine tissue. To date there are no reports on the involvement of specific EP₃ isoforms in AD, but a number involving a generic reference to the EP₃ receptor. It is established that EP₃ receptor expression is primarily in neurons [113,114] and couples with G_i proteins, leading to a decrease in cAMP as the signaling mechanism. However, under neurodegenerative conditions, expression of EP₃ in rat microglia was significantly enhanced [113]. Similar results were obtained for EP₃ expression in post-mortem human temporal cortexes. Here, basal EP₃ levels were also found in control samples, but expression in AD samples were found to be expanded to include glial cells, in particular, those areas surrounding amyloid plaques [115]. Further, protein levels for EP₃ increased from controls to samples from mildly cognitively impaired patients (MCI) to AD states, indicating that EP₃ is directly involved in the progression of AD. More specifically, EP₃ signaling has been shown to induce pro-inflammatory gene induction, cytokine production, lipid peroxidation, and generation of Aβ peptides in APP^{swe}-PS1

DE9 AD model mice. A second study using the same mouse AD model revealed that PGE₂ levels rise markedly with aging and PGE₂-EP₃ signaling impaired presynaptic LTP [116].

EP₄ signaling contrasts markedly with other EP receptors with its beneficial anti-inflammatory and AD resolving effects. Its involvement in AD is primarily via microglia. EP₄ is known to couple to G_s, G_q, and G_i proteins leading to and cAMP/PKA signaling, IP₃/Ca²⁺/AKT signaling, or a decrease in cAMP respectively [89,117]. Treatment of murine microglial-like BV-2 cells with the specific EP₄ agonist AE1-329 with and without LPS stimulation significantly increased PKA activity, confirming the cAMP/PKA signaling pathway through G_s coupling is at work in microglia [118]. Isolated microglia obtained from EP₄^{+/+} AD model mice (APP^{swe}-PS1 DE9; EP₄^{+/+}) stimulated with EP₄ specific agonist AE1-329 showed a suppressed oxidative and cytokine/chemokine response induced by Aβ₄₂ [119] while it increased the expression of anti-inflammatory factors. In particular, expression of NF-κB, IRF1, and IRF7 networks were suppressed and a marked increase in the anti-inflammatory cytokine IL-10 was observed [118]. Further, AE1-329 stimulation of EP₄ also induced phagocytosis of Aβ₄₂. Other studies have shown that the phosphorylation of tau required for deposition is not facilitated by EP₄, but instead by EP₁₋₃ [120]. Stimulation of EP₄ has also been shown to indirectly ameliorate AD damage by reducing matrix metalloproteinase (MMP)-3/-9 expressions that would otherwise compromise the integrity of the BBB by cleaving basement membrane proteins of the neurovascular unit and tight junction proteins [121].

The function of EP₄ in brain tissue is juxtaposed to that of EP₁₋₃, suggesting that its normal role involves neural homeostasis. However, during the advance of normal to MCI to AD, the homeostasis is clearly failing. In patient samples, EP₄ expression has been shown to decrease when progressing from normal to MCI to AD, particularly in neurons and glia while EP₃ expression increased [119]. Further, with aging or Aβ₄₂ accumulation, microglial EP₂ has been shown to be upregulated, increasing pro-inflammatory gene expression, suppressing beneficial chemokine production, chemotaxis [109], and phagocytosis [119]; at the same time EP₄ expression was reduced. One proposed mechanism for the reduction in EP₄ expression involves the co-internalization of EP₄ and the PS-1 subunit of γ-secretase into endosomes. The fact that an increase in EP₂ expression leads to an increase in both Aβ and γ-secretase production suggests that EP₂ expression drives EP₄ internalization. Although this observation provides an explanation for the reduction of the surface expression of EP₄ it also presents an unresolved quandary. Since both EP₄ and EP₂ are expressed on microglia and both signal through a cAMP/PKA signaling pathway, how do the opposing functions operate?

5.5. TXA₂ in AD

Thromboxane A₂ (TXA₂, (Z)-7-[(1S,3R,4S,5S)-3-[(E,3S)-3-hydroxyoct-1-enyl]-2,6-dioxabicyclo[3.1.1]heptan-4-yl]hept-5-enoic acid) is a potent vasoconstrictor and platelet activator [122], quite the opposite of PGI₂. Thromboxane A₂ (TXA₂) is synthesized from PGH₂ by thromboxane synthase (TBXAS1), a monomeric, heme-requiring, ER transmembrane protein and a member of the cytochrome P450 superfamily. TBXAS1 is expressed in most tissues, except for the skin, and in particularly high amounts in the spleen, brain, bone, immune system, and lungs. Immunostaining revealed significant expression in glial cells, macrophages, platelets, and lung fibroblasts. TXA₂ is known to be quite unstable with a reported half-life of 30 s under physiological conditions and hydrolyzes to the stable, biologically inactive thromboxane B₂ (TXB₂) [123].

There are two isoforms of the TXA₂ receptor (TBXA₂R), TPα and TPβ, which differ in the sequence and length of the C-terminal tail that determines the G-protein coupling and hence signaling pathway [124]. Stimulation of both receptors has been shown to lead to an increase in IP₃ and Ca²⁺, indicating a G_q mediated pathway for both receptor isoforms. However, their effect on cAMP production was shown to be opposing, where TPα increases cAMP and TPβ inhibits cAMP, suggesting additional coupling to G_s and G_i proteins respectively. TP receptors also couple with G₁₃ proteins, shown to result in RhoGEF activation [125], a signaling pathway known to be involved in a number of neurological disorders [126]. The TP isomer preference for G₁₃, if any, has yet to be determined.

TBXA2R in brain tissue is found in neurons [127] as well as activated microglia and macrophages [128]. Several reports have shown that stimulation of TP receptors results in an increase in the expression of APP and deposition of A β [129,130]. Further, treatment of a human QBI293 cell line expressing hAPP and human TP receptor (hTP) with siRNAs for G_q, G₁₂, and G₁₃ revealed that TP receptor stimulation led to APP expression proceeding through G_q coupling. As noted above, activation of microglia/macrophages contributes to the inflammatory response and oxidative stress associated with AD. In a murine ischemic stroke-induced model, TP receptor expression was significantly increased in microglia/macrophages localized in the damaged area [128]. Administration of the TP antagonist SQ29548 to these model mice inhibited microglia/macrophage activation and significantly reduced secretion of inflammatory cytokines (e.g., IL-1 β , IL-6, TNF α), indicating that stimulation of TP receptors facilitated the activation and cytokine release. Further, treatment of 1321N1 astrocytoma cells with the TP receptor agonist U46619 increased the production of the pro-inflammatory IL-6 and the cyclic AMP-response element protein (CREB) [131], supporting TP-mediated microglia activation. The fact that CREB induction requires an increase in cAMP suggests that the TP α isomer is involved.

TP receptors in platelets also contribute to the pathogenesis of AD. Cerebral amyloid angiopathy (CAA) is characterized by A β deposits in the walls of cerebral vessels and was found in 98% of AD patients, and ultimately led to degeneration of vessel wall components and a reduction in cerebral blood flow, thus aggravating cognitive decline. It has been shown that more than 90% of circulating A β is produced by activated platelets. A β itself has been shown to activate platelets further which is augmented with TP stimulation leading to overproduction of A β and progression of CAA [132]. Recently, it has been proposed that circulating A β produced by platelets move from blood to brain tissue and serve as “seeds” to initiate A β aggregation of brain-produced A β [118].

5.6. Isoprostanes in AD

Under conditions of oxidative stress, reactive oxygen species (ROS) are produced at higher than normal levels and can facilitate the peroxidation of PUFAS, including AA. Isoprostanes are prostaglandin-like molecules produced by non-enzymatic peroxidation of AA. It is well established that oxidative stress plays a role in AD pathogenesis. One class of products produced by oxidative stress is the F₂-isoprostanes obtained from AA, the concentration of which have been shown to be increased in brain and CSF of AD patients [133,134]. In particular, isoprostane-F_{2 α} -III (iPF_{2 α} -III, 9 α ,11 α ,15S-trihydroxy-(8 β)-prosta-5Z,13E-dien-1-oic acid) and isoprostane F_{2 α} -VI (iPF_{2 α} -VI, (8 β)-5,9 α ,11 α -trihydroxy-prosta-6E,14Z-dien-1-oic acid) were found to be higher in AD post-mortem human brains than controls [133]. This raises the question as to whether isoprostanes are merely markers of oxidative stress or actually participate in AD pathology. There is significant amount of literature supporting the latter. Numerous reports have indicated that isoprostanes bind to and activate TP receptors (e.g., [135,136]) and thus can be involved in AD pathogenesis as described above. Direct evidence for isoprostane involvement in AD was obtained through experiments where iPF_{2 α} -III was injected into Tg2576 AD model mice [137]. The iPF_{2 α} -III increased both steady-state APP levels and the concentrations of A β cleavage products. These increases were inhibited if the mice were pre-treated with a TP receptor antagonist, thus suggesting that TP receptor signaling is involved. A second study monitored urinary, plasma, and brain homogenate 8,12-iso-iPF_{2 α} -VI from Tg2576 mice and found that concentrations were higher in Tg2576 mice than WT as early as eight months of age [138]. By 12 months of age, a “surge” of A β ₄₀ and A β ₄₂ levels occurred and A β aggregates were observed in Tg2576 mouse brains and not WT brains. These results suggest that the lipid oxidative events precede plaque formation in AD.

5.7. PGF_{2 α} in AD

Prostaglandin F_{2 α} (PGF_{2 α} , (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]cyclopentyl]hept-5-enoic acid) is one of the more abundant prostanoids in the brain and spinal

cord [139] and is also found in many other tissues. It has a long half-life (15.0 ± 8.2 h) compared to other prostaglandins and is metabolized to 15-keto-PGF_{2α} and then to 13,14-dihydro-15-keto PGF_{2α} enzymatically. The functions are wide ranging and context dependent. PGF_{2α} is involved in inflammation as well as smooth muscle contraction, renal function, and blood pressure to name a few [140]. The stereoisomer 9α,11β-PGF₂ is thought to have similar functions [141]. PGF_{2α} is synthesized through the action of prostaglandin F synthases. Prostaglandin F synthase represents a collection of enzymes that ultimately produce PGF_{2α} or the stereoisomer 9α,11β-PGF₂. These enzymes are all produced in the brain and fall into one of three different structural classes: (1) aldo-keto reductase superfamily (AKR1B1, AKRC3), (2) the thioredoxin-like superfamily (FAM213B), and (3) the short-chain dehydrogenases/reductases (SDR) family (CBR1) [142,143]. Substrates for PGF_{2α} production are either PGH₂ or PGE₂ depending on the enzyme, whereas 9α,11b-PGF₂ is produced only from PGD₂. The properties of these and other NADH/NADPH-dependent reductases have been reviewed [144].

There are seven known human isoforms of the PGF_{2α} receptor (FP), each of which differs in the length and sequence of the C-terminal tail. This leaves open the possibility that signaling might occur through a variety of G proteins. However, only coupling to G_q and Rho have been observed, leading to the activation of the IP₃/Ca²⁺ signaling pathway and cytoskeletal changes respectively [145–148]. PTGFR is the most promiscuous of the prostanoid receptors, exhibiting measurable binding to a number of prostanoids. A few relative pK_i values were reported as follows: PGF_{2α} (7.9–8.5) > PGD₂ (7.3–7.7) > PGE₂ (7.0) > PGI₂, TXBA₂ where only PGD₂ and PGE₂ are likely alternate agonists under physiological conditions.

There are few reports describing the involvement of PGF_{2α} in AD and much of it provides only an indirect relationship. Immunohistochemical staining of post-mortem hippocampal tissue obtained from AD and control brains showed significantly elevated levels of the PGF_{2α} metabolite 13,14-dihydro-15-keto PGF_{2α} in AD tissue than in aged controls, implicating high PGF_{2α} concentrations at some time in the development of AD [148]. Treatment of human BV2 microglial cells with t0901317, a known liver X receptors/retinoid X receptor α (LXR/RXR) agonist, reduced the transcription of the inflammatory cytokines IL-6 and TNFα, following an inflammatory challenge with LPS or Aβ and promoted Aβ clearance in the latter challenge [149]. Addition of PGF_{2α} to the treatment regime antagonized t0901317 in a dose dependent manner suggesting that PGF_{2α} might be involved in the progression of AD.

Most of the reports focus on the action of PGF_{2α} in damaged brain tissue, in particular, oxidative damage as is found in early AD. FP^{-/-} mice subjected to ischemic-reperfusion (IR) injury showed less neurological deficit (25.3% less) and smaller infarct volumes (34.4% less) than identically treated WT mice. Similarly, mice treated with the FP antagonist AL-8810 after 48 h of permanent middle cerebral artery occlusion (pMCAO) showed less neurological dysfunction (35% less) and smaller infarct volumes (36.4%) than did saline-treated controls [134]. FP^{-/-} mice also had improved outcomes after pMCAO. In a related study, FP^{-/-} mice subjected to controlled cortical impact (CCI) showed significantly less hippocampal swelling and accumulation of astrocytic and microglial markers than identically treated WT controls [150]. Following CCI, post-treatment of WT mice with AL-8810 significantly reduced hippocampal swelling compared to untreated controls. Repeated treatments with AL-8810 had no effect, indicating that the FP receptor is only involved in early events in brain damage. These studies consistently indicate that stimulation of FP exacerbates neuronal damage following a brain insult and suggests that the FP is involved in early events following the insult and possible in early events in AD.

It is well established that treatment of neuron cultures with Aβ induces cell death. It has been shown that treatment of rat cortical neuron cultures with Aβ and 10 μM PGD₂ or PGJ₂ reduces neuron survival by 70% and 79% respectively compared to Aβ only treated cultures [151]. Repeating the experiment with 10 μM PGF_{2α} or 9α, 11β-PGF_{2α} had no effect on cell survivability. This study is consistent with PGF_{2α} or its isomer not being involved in Aβ toxicity. In light of the previous results, the FP receptor's neurotoxic activity appears to be involved in early events leading to AD and prior to Aβ release.

6. Lipoxygenases, and their Products and Receptors in AD

6.1. HETEs in AD

The biosynthesis of hydroxyeicosatetraenoic acids (HETE), lipoxins, leukotriene A₄, and hepxilins are accomplished by a group of structurally similar enzymes of the lipoxygenase family (Figure 2). Lipoxygenases represent a non-heme, iron-requiring class of enzymes that oxygenate an array of PUFA substrates; see review by Biringer [152]. The HETE family of molecules and their unstable precursors, the hydroperoxyeicosatetraenoic acids (HPETEs), are notable as precursors for the leukotriene family, lipoxin family, trioxilin family, and eoxin family of metabolites, as well serving as signaling molecules in their own right [153].

The mammalian lipoxygenase ALOX15 (12/15-LOX, 15-LOX, 15-LOX-1, 12/15LO) is a monomeric cytosolic protein that becomes membrane associated in the presence of calcium [154,155]. Both substrate and product specificity are diverse (Figure 2). ALOX15 converts arachidonic acid into 12(S)-hydroperoxyeicosatetraenoic acid (12S-HPETE, (5Z,8Z,10E,12S,14Z)-12-hydroperoxyicosa-5,8,10,14-tetraenoic acid) and 15(S)-hydroperoxyeicosatetraenoic acid (15S-HPETE, (5Z,8Z,11Z,13E,15S)-15-hydroperoxyicosa-5,8,11,13-tetraenoic acid) in a ratio of 1:9 [156,157] that are readily converted to the corresponding hydroeicosatetraenoic acids by the action of the ubiquitous glutathione peroxidases (GPX) [158]. In addition, ALOX15 not only oxygenates free fatty acids, but also membrane phospholipids when in the membrane bound state [154] and generates 15S-hydroxyeicosatetraenoic acid (15-HETE, (5Z,8Z,11Z,13E)-15-hydroxyicosa-5,8,11,13-tetraenoic acid) conjugated to phosphatidylethanolamine, an intracellular signaling molecule [159].

ALOX15 is one of the most abundant lipoxygenase isoforms in the CNS and is found in both neurons and glial cells with 12S-hydroxyeicosatetraenoic acid (12-HETE, (5Z,8Z,10E,14Z)-12-hydroxyicosa-5,8,10,14-tetraenoic acid) and 15-HETE as the major products [160]. Analysis of post-mortem brains from AD patients and controls revealed that ALOX15 is significantly upregulated in AD patients and the concentrations of both 12-HETE and 15-HETE are markedly elevated in the frontal cortex and temporal cortex, but not the cerebellum of AD brains [160]. Human ALOX15 expressed in CHO and N2A cell lines treated with selective ALOX15 inhibitors reduced A β formation in a dose dependent manner [161,162]. Further, β -secretase (BACE) and secreted APP β (sAPP β) were also reduced whereas soluble APP α and the ADAM10 protein were unchanged, indicating that either or both 12-HETE and 15-HETE modulates the BACE proteolytic cascade. A Tg2576 murine AD model overexpressing ALOX15 showed elevated levels of phosphorylated tau [163]. Further examination revealed that this process proceeded through the cdk5 kinase pathway and was independent of the effect on A β . A global lipidomic analysis of brain tissue from Tg2576 mice stably expressing human APP and tau protein revealed that the concentration of 12-HETE nearly doubled from four months of age to 10 months of age and was then reduced to nearly the four month level at 15 months when compared to WT mice of the same ages [164]. In contrast, 15-HETE concentrations decreased by 10% over the 15-month lifetime. AD progression was also monitored as a function of A β and tau production. Here it was found that A β accumulation begins at 10 months while the levels of soluble tau remained constant. These results are a clear indication that 12-HETE is involved in the early stages of AD. The continual decrease in 15-HETE with age and AD progression is consistent with the potential anti-inflammatory action of this metabolite, as it is a ligand for PPAR γ , a known anti-inflammatory receptor [76,165]. The fact that 12-HETE is also a ligand for PPAR γ [166] suggests that the concentration increase to the point of A β production may be a neuroprotective response that decreases in response to A β as its concentration increases.

in γ -secretase production while LTC₄ treatment led to a milder trend to an increase. More recently it has been shown that ALOX5 products are also involved in the increase of γ -secretase activating protein (GSAP), levels which in turn led to an increase in γ -secretase activity and A β production [175]. The effect was indirect through activation of caspase-3 which converts the GSAP precursor to GSAP.

12-HETE and 15-HETE bind to other receptors in addition to the PPAR γ binding. Only 12-HETE has been found to have a specific high-affinity membrane receptor, GPR31 (GPBA) [176,177]. Although the relationship between this receptor and AD has yet to be established, this receptor is known to be expressed in the brain [178]. Both 12-HETE and 15-HETE have been shown to bind to the leukotriene B₄ (LTB₄) receptor BLT2, albeit with lower efficiency than LTB₄ [179]. IC₅₀ values are reported to be 10 and 50 times higher and EC₅₀ values 100 and 500 times that for LBT₄ respectively, suggesting that the effect exhibited by these HETEs on BLT2 is likely minimal unless leukotriene A₄ hydrolase (LTA4H) or ALOX5 are downregulated or inhibited.

6.2. Leukotrienes and Their Receptors in AD

The leukotriene family of molecules consists of oxygenated products of arachidonic acid of which several are derivatized by glutathione. The molecules are created through the action of ALOX5 on arachidonic acid, resulting in the transient formation of 5S-HPETE which is then converted by ALOX5 to leukotriene A₄ (LTA₄, 4-[(2S,3S)-3-[(1E,3E,5Z,8Z)-tetradeca-1,3,5,8-tetraenyl]oxiran-2-yl]butanoic acid). The highly unstable LTA₄ can be converted by hydrolysis to leukotriene B₄ (LTB₄, (5S,6Z,8E,10E,12R,14Z)-5,12-dihydroxyicosa-6,8,10,14-tetraenoic acid).

LTA₄ is a non-cysteinyl leukotriene produced by ALOX5 from 5-HPETE as described above. Treatment of human neuronal cell lines producing the C-99 fragment of APP (MC65) with LTA₄ potentiated the A β toxicity of the neurons [180]. In contrast, there are no reported receptors for LTA₄ and the mechanism by which it potentiates toxicity is unknown. However, the highly chemically reactive allylic epoxide renders it quite unstable with an in vitro half-life of less than 3 s at physiological pH and temperature [181] and it is non-enzymatically converted to Δ^6 -trans-LTB₄ ((5S,6E,8E,10E,12R,14Z)-5,12-dihydroxyicosa-6,8,10,14-tetraenoic acid) and 5,6-diHETE ((8Z,11Z,14Z,17Z)-5,6-dihydroxyicosa-8,11,14,17-tetraenoic acid) [167]. In addition, LTA₄ is known to be readily converted enzymatically to either LTB₄ or LTC₄. Further, LTB₄ has been reported to be more chemically stable than its precursor LTA₄ with a considerably longer physiological half-life (25 min) [182]. For these reasons it is reasonable to assume that LTA₄ merely serves as a substrate to produce products that are responsible for the potentiation of neural toxicity.

LTB₄ is a non-cysteinyl leukotriene produced by the hydrolysis of LTA₄ by leukotriene A₄ hydrolase (LTA4H). The pro-inflammatory LTB₄ is one of the most potent chemotactic molecules known and induces recruitment and activation of monocytes, neutrophils, and eosinophils [183–185]. It is also a potent smooth muscle constrictor and has the ability to increase vascular permeability [182]. Treatment of cultured monocytes with LTB₄ has been shown to activate MAPK and PI₃/AKT pathways, and induce overproduction of IL-6, monocyte chemoattractant protein 1 and TNF α , all of which are involved in the inflammatory response.

The production of LTB₄ was shown to be enhanced in cultured microglia (murine N9) following treatment with A β [186]. When COS7 cells transfected with the C-99 protein (see above) were treated with LTB₄, A β ₄₀ and A β ₄₂ levels were significantly increased over levels in controls [187]. The net effect is a self-proliferating cycle, leading to overproduction of A β and eventual deposition. The action of LTB₄ on A β production is indirect. It has been shown that treatment of N2aAbPPswe cells with LTB₄ increased the cellular concentrations of three of the four protein subunits of the γ -secretase complex [188]. In contrast, ALOX5 increased the concentrations all four of the protein subunits, suggesting that that the fourth subunit APH-1 was induced by another ALOX5 product (e.g., LTD₄, reference [189]) or that APH-1 levels return to baseline levels within the timeframe of the measurement.

There are two known LTB₄ G-protein receptors, BLT1 (LTB₄R) and BLT2 (LTB₄R2). BLT1 is a high affinity form with a reported IC₅₀ and EC₅₀ for LTB₄ of about 60 nM and is primarily expressed

in leukocytes [190], but also found in spinal neurons [191]. It has a very high specificity for LTB₄ compared to other eicosanoids. BLT2 is a lower affinity receptor for LTB₄ with a reported IC₅₀ of 100 nM and an EC₅₀ similar to that for BLT1. Unlike BLT1, BLT2 is more ubiquitously expressed with a more promiscuous binding specificity. Interestingly, resolvin E1, a potent anti-inflammatory and pro-resolving mediator (see below) and has been shown to selectively bind to BLT1 and antagonize the LTB₄-induced calcium mobilization and attenuates NF-κB activation [192]. Although the relationship of LTB₄ activation of either receptor to the progression of AD is not yet known, its involvement in associated neuroinflammation is well established.

6.3. Cysteinyl Leukotrienes and Their Receptors in AD

The highly unstable LTA₄ can also be converted to leukotriene C₄ (LTC₄, (5S,6R,7E,9E,11Z,14Z)-6-[(2R)-2-[[[(4S)-4-amino-4-carboxybutanoyl]amino]-3-(carboxymethylamino)-3-oxopropyl]sulfanyl-5-hydroxyicosa-7,9,11,14-tetraenoic acid) by addition of glutathione. Stepwise hydrolysis of the peptide portion of attached glutathione on LTC₄ leads to the formation of leukotriene D₄ (LTD₄, (5S,6R,7E,9E,11Z,14Z)-6-[(2R)-2-amino-3-(carboxymethylamino)-3-oxopropyl]sulfanyl-5-hydroxyicosa-7,9,11,14-tetraenoic acid) and leukotriene E₄ (LTE₄, (5S,6R,7E,9E,11Z,14Z)-6-[(2R)-2-amino-2-carboxyethyl]sulfanyl-5-hydroxyicosa-7,9,11,14-tetraenoic acid) with measured physiological half-lives of 44 min [193], and 22 min respectively [194]. LTE₄ is quite stable and can be found excreted in the urine. LTC₄, LTD₄, and LTE₄ are known as the cysteinyl-leukotrienes (Cys-LT) and are potent bronchoconstrictors, are known to increase vascular permeability in postcapillary venules, and known to stimulate mucus secretion [184]. They have also been shown to be involved in normal CNS metabolism and numerous CNS disorders [195], including AD [173]. Mammalian leukotriene C₄ synthase (LTC4S, LTC₄ synthase) is a transmembrane protein expressed in a limited number of cell types and is found in mast cells, eosinophils, basophils, and monocytes [196]. The enzyme catalyzes the conjugation of GSH to the unstable LTA₄ produced by ALOX5, thus producing leukotriene C₄ (LTC₄). Subsequent synthesis of LTD₄ and LTE₄ occurs through the action of ubiquitous gamma-glutamyl transaminase (GGT1) and dipeptidase (DPEP) respectively. Although ALOX5 is found in neurons and glial cells, an additional source for the Cys-LT, substrate LTA₄ is also provided by transcellular biosynthesis whereby resident neutrophils produce and transfer the source material [167,197].

There are half a dozen known receptors that bind Cys-LTs. Thus far, only the G-protein coupled CysLT1R receptor has been shown to be directly involved in Aβ pathogenesis. This receptor showed the highest efficiency for LTD₄ (EC₅₀ = 2.5 nM) with much lower efficiencies for LTC₄ (EC₅₀ = 24 nM) and LTE₄ (EC₅₀ = 240 nM) [198]. A second receptor that may also be involved in AD is the G-protein coupled CysLT2R receptor found in both astrocytes and microglial cells. This receptor showed the highest efficiency for LTC₄ (67 nM), a slightly lower efficiency for LTD₄ (104 nM), and very low efficiency for LTE₄ (2300 nM) [199].

Application of LTD₄ to cultured neurons has been shown to increase Aβ release and decrease neuronal viability [189]. At low concentrations (20 nM), LTD₄ caused a significant increase in Aβ generation, whereas at higher concentrations (40 nM) it decreased neuronal viability. Further, the lower concentrations of LTD₄ also increased the expression of the CysLT1R receptor, increased the activity of β- or γ-secretase, and activated the pro-inflammatory NF-κB pathway. Application of the specific CysLT1R antagonist pranlukast inhibited both Aβ generation and the increase in secretase activity, linking the CysLT1R directly to the response. In keeping with the self-propagating nature of AD, in vivo and in vitro treatment of mouse neurons with Aβ₄₂ increased the expression of CysLT1R receptors [200]. Other team players in AD progression are also involved. The CysLT1R receptor is expressed in astrocytes and stimulation rat cultured astrocytes with LTD₄ resulted in stimulation of astrocyte proliferation, activation of the MAPK pathway, enhanced production of CysLTs, and the release of inflammatory chemokines and cytokines [201]. The effect of LTD₄ on astrocytes appears to play an autocrine role in the induction of reactive astrogliosis. The involvement of the CysLT2R receptor in microglial activation is controversial. Some reports have shown its upregulation in

astrocytes following an inflammatory insult [202] whereas others have reported that it is not expressed in astrocytes at all [201]. Upon microglial activation resulting from inflammation in rat brain, both CysLT1 and CysLT2R were found to be upregulated, however, the subsequent release of inflammatory IL-1 β , INF- γ , and TNF α by microglia was inhibited by the selective CysT2R receptor agonist HAMI 3379 [203]. On the other hand, the CysLT1R selective antagonist pranlukast affected only the release of IL-4, indicating that both receptors and both LTC₄ and LTD₄ are involved in the inflammatory response, albeit with somewhat different results. The function, if any, of LTE₄ in AD progression is currently unknown.

6.4. Eoxins in AD

In effect, eoxins are the C14,15 oxidized isomers of leukotrienes and are produced from arachidonic acid via ALOX15 to eoxin A₄ (EXA₄, (5Z,8Z,10E,12E)-13-[(2S,3S)-3-pentylloxiran-2-yl]trideca-5,8,10,12-tetraenoic acid) and then converted through a linear path to eoxin C₄ (EXC₄, (5Z,8Z,10E,12E,14R,15S)-14-[(2R)-2-[[[(4S)-4-amino-4-carboxybutanoyl]amino]-3-(carboxymethylamino)-3-oxopropyl]sulfanyl-15-hydroxyicosa-5,8,10,12-tetraenoic acid), eoxin D₄ (EXD₄, (5Z,8Z,10E,12E,14R,15S)-14-[(2R)-2-amino-3-(carboxymethylamino)-3-oxopropyl]sulfanyl-15-hydroxyicosa-5,8,10,12-tetraenoic acid) and eoxin E₄ (EXE₄, (5Z,8Z,10E,12E,14R,15S)-14-[(2R)-2-amino-2-carboxyethyl]sulfanyl-15-hydroxyicosa-5,8,10,12-tetraenoic acid) by the same enzymes used for the production of leukotrienes (Figure 2). Eoxins are pro-inflammatory metabolites of arachidonic acid and are produced in cells that express significant amounts of ALOX15, for example, human airway epithelial cells, eosinophils, subsets of mast cells, and dendritic cells [204]. Their biological roles have yet to be thoroughly explored, however their role in inflammation suggests they may also be involved in the progression of AD.

7. SPMs and Resolution in AD

Resolution of inflammation is essential to the maintenance of tissue homeostasis. Without it, acute inflammation becomes chronic, leading cell death and tissue dysfunction. Central to resolution are specialized pro-resolving mediators (SPM) that serve to prevent uncontrolled inflammation and promote removal of microbes, apoptotic cells and debris to return the tissue to homeostasis (review [205]). SPMs are represented by a series of eicosanoids, namely the lipoxins, resolvin D and E series, protectins, and maresins. The lipoxins are derived from AA (Figure 2) whereas the latter group are synthesized from ω 3 fatty acids (Figure 3) [206].

Resolution is key to preventing chronic inflammation that leads to AD progression. Hence, dysfunctional resolution mechanisms are paramount to AD progression. Support for this concept is increasing. For example, post mortem brain tissue and CSF obtained from human AD patients showed significantly lower levels of SPMs than non-AD controls [207]. Further, western blotting of post-mortem brain tissue showed that the expression levels of both ALX/FPR2 and ChemR23, known SPM receptors, were upregulated in AD patients compared to non-AD controls [207]. ALX/FPR2 was significantly upregulated in glial cells whereas ChemR23 was upregulated in both glial cells and neurons. The upregulation of ChemR23 was most likely a response to lower agonist levels whereas the upregulation of ALX/FPR2 may also be due to an interaction with A β as discussed below.

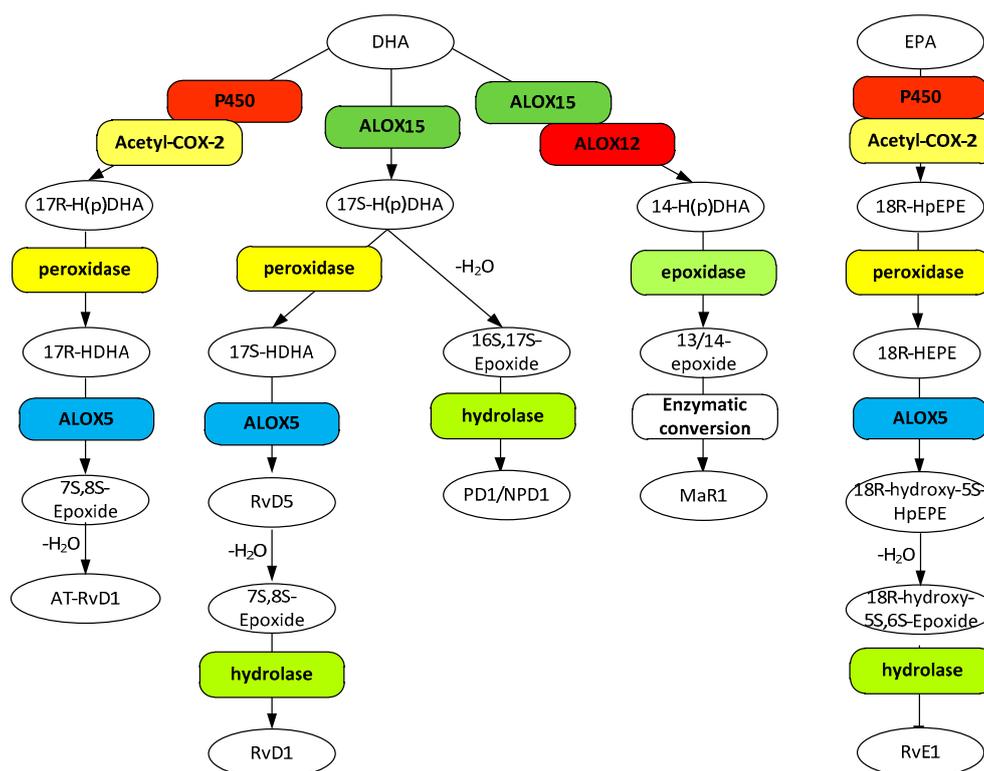


Figure 3. Metabolic pathways for D resolvins (RvD1 and AT-RvD1), protectin-1 (PD1/NPD1), and maresin 1 (MaR1) biosynthesis from docosahexaenoic acid (DHA) and the biosynthesis of resolvin E1 from eicosapentaenoic acid (EPA). Gene designations are given for all but the COX participating enzymes (rounded boxes) and accepted acronyms given for metabolites (ovals).

7.1. Lipoxins in AD

The lipoxins represent a family of metabolites that are either directly or indirectly produced by lipoxygenases ALOX5 and ALOX12 (Figure 2). Lipoxin A₄ (LXA₄, (5S,6R,7E,9E,11Z,13E,15S)-5,6,15-trihydroxyicosa-7,9,11,13-tetraenoic acid) and lipoxin B₄ (LXB₄, (5S,6E,8Z,10E,12E,14R,15S)-5,14,15-trihydroxyicosa-6,8,10,12-tetraenoic acid) are synthesized through the production of LTA₄ via ALOX5 which in turn is converted to both LXA₄ and LXB₄ by ALOX12. The 15-epi derivatives, 15-epi-LXA₄ ((5S,6R,7E,9E,11Z,13E,15R)-5,6,15-trihydroxyicosa-7,9,11,13-tetraenoic acid) and 15-epi-LXB₄ ((5S,6E,8Z,10E,12E,14R,15R)-5,14,15-trihydroxyicosa-6,8,10,12-tetraenoic acid) are synthesized from 15R-HETE by ALOX5 through an unstable epoxy intermediate [188]. 15R-HETE is produced from AA by aspirin inhibited (acetylated) COX-2 rather than the PGH₂ produced by non-acetylated COX-2. Both LXA₄ and LXB₄ are known to be highly unstable ($t_{1/2} < 30$ s) in vivo and are subject to rapid dehydrogenation and reduction to a series of inactive products [208,209]. The 15-epi derivatives are two-fold more stable [210].

Only one LX receptor has been identified to date, the G-protein coupled ALX/FPR2. It is expressed in pyramidal cells neurons, as well as astrocytes and microglia [207]. This receptor binds other ligands, including peptides, and is involved in numerous inflammatory-related biological processes that are beyond the scope of this review; see the reviews by Chiang et al. [211] and Romano et al. [212]. It has been shown that both LXA₄ and 15-epi-LXA₄ act through ALX/FPR2 [213] with high and similar binding efficiencies ($IC_{50} = 0.01\text{--}0.1$ nM). LXB₄ and presumably 15-epi-LXB₄ act through an unknown receptor. It has been shown that the neuroprotective effect of LXB₄ on retinal tissues cannot be blocked with specific antagonists for ALX/FPR2 and RvD2 receptors (GPR18) [214].

Each of these lipoxins has been shown to induce anti-inflammatory and pro-resolution mechanisms, including repression of leukocyte-mediated injury and pro-inflammatory cytokine production, as well

as inhibition of cell proliferation and migration [213,215,216]. For example, LXB₄, LXA₄, 15-epi-LXA₄, and stable analogs have been shown to block TNF- α secretion from stimulated human T cells involved in T cell-mediated inflammation [217]. In addition, in a traumatic brain injury mouse model, LXA₄ was shown not only to inhibit TNF- α release but also other pro-inflammatory cytokines IL-1 β and IL-6 while the same time it decreased BBB permeability [218]. In a complementary fashion, treatment of AD model mice with 15-epi-LXA₄ increased levels of anti-inflammatory IL-10 and transforming growth factor- β (TGF β) [213]. These lipoxins are also reported to be potent activators of monocytes, known to play a role in A β elimination, through stimulation of chemotaxis and adherence [208,219]. LXA₄ and 15-epi-LXA₄ have been shown to be equipotent at reversing the pro-inflammatory LTB₄-initiated human PMN migration [210,220]. Lipoxins are also involved directly in neuroprotection. Both LXA₄ and LXB₄ have been reported to promote neuroprotection in retina with LXB₄ consistently being more potent [214].

In addition to the general anti-inflammatory pro-resolving actions of lipoxins, more specific actions involving aggravation of AD progression have been reported. Treatment of AD model Tg2576 mice with 15-epi-LXA₄ decreased the production of pro-inflammatory mediators (e.g., TNF- α , IL-1 β) and at the same time increased the levels of anti-inflammatory proteins (e.g., TGF β , IL-10) [221]. The resulting altered environment, apparently dependent on the activation of astrocytes, activated microglia into an alternative phagocytic phenotype that enhanced the clearance of A β plaques. In another mouse model study, LXA₄ levels were found to decrease with age in both non-transgenic and AD-model mice and more markedly so in the latter [222]. However, restoring LXA₄-like levels by administration of 15-epi-LXA₄ enhanced the cognitive performance of the AD-model mice, reduced A β levels, and decreased levels of phosphorylated tau. The role of LXA₄ in slowing AD progression was also confirmed in a study of CSF from AD patients and post-mortem hippocampal tissue from other AD patients where LXA₄ levels were found to be lower than in non-AD subjects [207]. Further, LXA₄ levels were found to correlate to mini-mental state examination (MMSE) scores, suggesting that pro-resolution eicosanoids may inhibit AD-related cognitive decline. In contrast, the ALX/FPR2 receptor levels were found to be abnormally high in these patients. This can be rationalized by the fact that there are also pro-inflammatory ligands for this receptor, including A β ₄₂ [223], and that inflammation has been shown to enhance its expression [207,224].

7.2. Resolvins, Protectins, and Maresins in AD

Resolvins, protectins, and maresins represent oxidized products of ω 3 PUFAs that are actively involved in the resolution of inflammation. A complete description of all of these SPMs is beyond the scope of this review. Instead, the focus will be on a few classes, namely the resolvins D1 group, the protectin D1 group, resolvins E1, maresin 1, and their known and potential involvement in AD.

The resolvins D1 group is formed by a pathway similar to lipoxin pathway, where the product is formed from hydroperoxidation of docosahexaenoic acid (DHA, 4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoic acid) at C-17 by either aspirin acetylated-COX-2 or ALOX15 leading to 17R-hydroperoxy-DHA and 17S-hydroperoxy-DHA respectively followed by reduction and then hydroperoxidation by ALOX5, enzymatic epoxidation, and hydrolysis leading to formation of the tri-hydroxy resolvins that differ only in their stereochemistry at C-17. The 17R isomer formed through the action of acetylated COX-2 is referred to as AT-RvD1 ((4Z,7S,8R,9E,11E,13Z,15E,17R,19Z)-7,8,17-trihydroxydocosa-4,9,11,13,15,19-hexaenoic acid) and the ALOX15 derived 17S as RvD1 ((4Z,7S,8R,9E,11E,13Z,15E,17S,19Z)-7,8,17-trihydroxydocosa-4,9,11,13,15,19-hexaenoic acid). Both lipoxins and resolvins D1s are enzymatically degraded by eicosanoid oxidases to biologically inactive substances. RvD1, however, has a reported half-life about four times that of LXA₄ (<10 min) and AT-RvD1 was shown to be many times more stable yet [225]. As observed for LXA₄ and 15-epi-LXA₄, both resolvins have been shown to be equally effective at reducing polymorphonuclear leukocyte (PMN) infiltration in vivo and as effective as the

anti-inflammatory indomethacin [226]. It has been determined that RvD1 activates the LXA₄ receptor ALX/FPR2 as well as GPR32 [227]. Receptors specific for AT-RvD1 have yet to be reported.

Analysis of CSF obtained from AD-patients revealed that the levels of RvD1 correlate well with MMSE scores [207]. Incubation of human microglial cells (CHME3) with RvD1 significantly reduced the A β -induced inflammation in human microglia and the A β -induced increase in CD40 production [228]. This reduction is particularly important in AD, as the concentration of CD40 has been reported to be increased in AD brain and, when bound to its ligand, promotes cell death and the production of A β .

Resolvin E1 (RvE1, (5S,6Z,8E,10E,12R,14Z,16E,18R)-5,12,18-trihydroxyicosa-6,8,10,14,16-pentaenoic acid) is synthesized from eicosapentaenoic acid (EPA, (5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentenoic acid) in a manner like that of AT-RvD1. EPA is hydroperoxidated by either acetylated-COX-2 or cytochrome P450 to an 18R peroxy derivative which is subsequently reduced and then hydroperoxidated by ALOX5, followed by dehydration and then hydrolysis to form the final product. A minimum of four pathways have been identified for in vivo degradation of RvE1 with at least one of the products retaining at least some of the RvE1 activities [229]. An unpublished clinical study revealed an overall half-life for RvE1 of 7 h [230]. RvE1 was shown to be twice as effective as indomethacin in reducing PMN infiltration [227] making it about twice as effective as the resolving D1 group. There are two known receptors for RvE1, the G-protein coupled ChemR23 and BLT1. The ChemR23 receptor is similar in action to that of the ALX/FPR2 receptor in that it interacts with eicosanoid and peptide ligands, the former shown to result in a reduction in PMN migration [231]. This receptor is abundantly expressed in monocytes in lower amounts in neutrophils and T lymphocytes [231] as well as in pyramidal cells, neurons, astrocytes, and microglia [207]. Binding of RvE1 to the BLT1 receptor has been shown to attenuate the pro-inflammatory action of the LTB₄ agonist rather than elicit any specific stimulatory effect itself [192].

Treatment of AD model mice (5xFAD) with either RvE1 or LXA₄ reduced the concentrations of A β ₄₀, A β ₄₂, and inflammatory cytokines and chemokines, the latter reduced to levels in control mice [232]. When given in combination, additional improvements were observed, including reduced activation of microglia and astrocytes and a decrease in the extent of A β pathology.

Protectin D1/neuroprotection D1 (PD1/NPD1, (4Z,7Z,10R,11E,13E,15Z,17S,19Z)-10,17-dihydroxydocosa-4,7,11,13,15,19-hexaenoic acid) is synthesized from DHA through hydroperoxidation by ALOX15 followed by a reduction and then hydrolysis to the final product. The half-life and degradation pathway(s) have not been reported. NPD1 has been shown to be nearly 50% more effective than either RvD1 or 15-epi-LXA₄ in reducing PMN migration. Thus far only one NPD1 receptor has been identified, the G-protein coupled 37 receptor (GPR37) that is found in macrophages, but not microglia [233].

Treatment of aging human brain cells with NPD1 has been shown to reduce A β peptide release [234]. Treatment of human neuronal-glia (HNG) cells with NPD1 challenged with A β ₄₂ or transfected with β APP^{sw} (Swedish double mutant APP695^{swe}) reduced the A β ₄₂-triggered expression of COX-2 and the pro-inflammatory element B94 [234]. This down-regulation of COX-2 and B94 was facilitated through suppression of β -secretase-1, activation of α -secretase and up-regulation sAPP α . The net effect is a switching from the amyloidogenic to the non-amyloidogenic pathway [235]. Further, treatment of human fetal brain tissue HN cells with NPD1 repressed A β ₄₂ activation of pro-inflammatory genes and at the same time upregulated antiapoptotic genes encoding Bcl-2, Bcl-xl, and Bfl-1(A1), thus promoting cytoprotection [236]. Interestingly, it was also shown that sAPP α , known to be upregulated by NPD1, also stimulated the biosynthesis of NPD1, thus amplifying the effect.

Maresin 1 (MaR1, (4Z,7R,8E,10E,12Z,14S,16Z,19Z)-7,14-dihydroxydocosa-4,8,10,12,16,19-hexaenoic acid) is also synthesized from DHA through hydroperoxidation by either ALOX15 or ALOX12 followed by a reduction and then hydrolysis to the final product. The half-life and degradation pathway(s) have not been reported. Reports have indicated that MaR1 may be the most potent of the SPMs in resolution of inflammation [228]. A specific receptor for MaR1 has yet to be reported.

Incubation of human microglial cells (CHME3) with MaR1 significantly reduced the A β -induced inflammation in human microglia and the A β -induced increase in CD40 production [228]. Further, of all the SPMs tested, only MaR1 increased, and significantly so, the phagocytosis of A β ₄₂. MaR1 has also been shown to downregulate pro-inflammatory markers CD11b-activated, MHC-II, CD86, and CD33, but had no effect on the anti-inflammatory markers CD163 and CD206.

8. Conclusions

Eicosanoids are clearly paramount to AD pathology, be it promoting progression of the disease or resolution in the early phases. It is also apparent that disruption of normal inflammation homeostasis is at the center of AD progression and appears to be the most reversible aspect of early AD. A better understanding of inflammation resolution and how to promote and control it is of major import to developing treatment regimens for AD. As shown in the preceding paragraphs, the majority of eicosanoid metabolites are related in some way to the onset, progression, or resolution of AD. A brief synopsis of their involvement is presented below.

Prostanoid biosynthesis begins with the production of free AA through the action of PLA_{2S} on AA-containing phospholipids. Studies have shown that AA itself has a detrimental effect on neuronal viability and participates in a yet-to-be understood synergy with amyloid peptides [22,23,27]. Cyclooxygenases (COX-1 and COX-2) catalyze the first reaction of the prostanoid pathway to produce PGH₂, the major precursor to other prostanoids. Numerous studies have shown that inhibition of COX-1 and COX-2 by NSAIDs can reduce the risk of AD [35–38], however, not all studies have shown such positive results [39,40] and the effect may depend on the parameters employed in each study, such as the NSAIDs used, the stage of AD when treatment was begun, as well as the diversity of the population involved in the study. More focused and carefully controlled studies would shed more light on this subject. Interestingly, the NSAID aspirin acetylates COX-2 resulting in a dramatic change in its activity that can increase the production of resolvins that are known inflammation resolving mediators and have been shown to reduce the production of A β peptides [232], another factor not considered in the aforementioned studies.

Eicosanoids can be crudely categorized with respect to their influence on AD in the following manner: (1) pro-inflammatory and AD promoting, (2) anti-inflammatory and AD resolving, and (3) mixed effects depending on context or when conflicting data was observed. TXA₂, isoprostanes, 5-HETE, LTB₄, and the cystenyl leukotrienes (LTC₄ and LTD₄) clearly fall into the first category as they have been shown to promote A β production [174,189]. On the other hand, studies have shown that the involvement of PGF_{2 α} in AD appears to be indirect and only slightly AD promoting, in particular, in very early stages of AD [149–152]. This may very well be due to the large number of PGF_{2 α} isoforms that signal through a variety of different G protein-mediated pathways and hence may promote different intracellular processes. Lastly, the eoxins are known pro-inflammatory effectors and thus may be involved in AD progression, however, their direct involvement in AD progression has yet to be demonstrated.

The second category consists of PGI₂, the lipoxins, the resolvins, the neuroprotectins, and the maresins. PGI₂ has been reported to promote the production of the neuroprotective sAPP α and to upregulate the anti-inflammatory receptor PPAR γ , clearly promoting resolution of AD [91]. The lipoxins, LXA₄, LXB₄, and 15-epi-LXA₄ have been shown to reduce the secretion of pro-inflammatory mediators such as TNF α , while LXA₄ has also been shown to promote the release of anti-inflammatory factors [221–223]. The more direct AD resolving properties of LXA₄ and 15-epi-LXA₄ have been demonstrated by their ability to reduce A β and phosphorylated tau levels [222]. Resolvin D1 and maresin 1 have been shown to reduce A β -induced inflammation in microglia and CD40 production, a factor known to enhance production of A β [228]. Resolvin E1 has been reported to attenuate the pro-inflammatory effects of LTB₄ and reduce the concentrations of A β peptides [232]. Lastly, protectin D1 has also been shown to reduce A β concentrations while at the same time increasing concentrations of the neuroprotective sAPP α [236].

The third category is the most diverse of the three and deserves much further study. PGE₂ is generally considered to be the prime pro-inflammatory prostaglandin. Indeed, it has been demonstrated that stimulation of EP₁ and EP₂ receptors by PGE₂ reduces neural survivability, enhances Aβ production, and reduces microglial phagocytosis [106–110]. Stimulation of the EP₃ receptor has been reported to mildly support the progression of AD, however, its involvement is complicated by the number of different isoforms that utilize different G protein mediations [113]. In contrast, stimulation of the EP₄ receptor has been shown to produce an anti-inflammatory response as well as induction Aβ phagocytosis [118–120], and thus the overall effect of PGE₂ is dependent on the relative expression of the different receptors. The function of PGD₂ has also been shown to be receptor dependent, where stimulation of DP₁ favors neuronal rescue and stimulation of DP₂ promotes neuronal loss [56,64]. Clearly, receptor expression is another area requiring further study. The effect of the J₂ series of prostaglandins, 15-HETE and 12-HETE, on AD progression is not understood. Some reports have shown that they enhance Aβ formation, suggesting promotion of AD progression [72,75]. On the other hand, other reports have indicated that all of these are ligands for the anti-inflammatory PPARγ receptor, suggesting quite the opposite [76–80]. Certainly, more work needs to be done to determine what conditions favor one path over the other.

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References

1. Tassoni, D.; Kaur, G.; Weisinger, R.S.; Sinclair, A.J. The role of eicosanoids in the brain. *Asia Pac. J. Clin. Nutr.* **2008**, *17* (Suppl. 1), 220–228.
2. Peterson, E.C.; Wang, Z.; Britz, G. Regulation of cerebral blood flow. *Int. J. Vasc. Med.* **2011**, *2011*, 823525. [[CrossRef](#)] [[PubMed](#)]
3. Hayaishi, O. Molecular mechanisms of sleep-wake regulation: Roles of prostaglandins D2 and E2. *FASEB J.* **1991**, *5*, 2575–2581. [[CrossRef](#)] [[PubMed](#)]
4. Bowen, J.; Teri, L.; Kukull, W.; McCormick, W.; McCurry, S.M.; Larson, E.B. Progression to dementia in patients with isolated memory loss. *Lancet* **1997**, *349*, 763–765. [[CrossRef](#)]
5. Niwa, K.; Porter, V.A.; Kazama, K.; Cornfield, D.; Carlson, G.A.; Iadecola, C. A beta-peptides enhance vasoconstriction in cerebral circulation. *Am. J. Physiol. Heart Circ. Physiol.* **2001**, *281*, H2417–H2424. [[CrossRef](#)] [[PubMed](#)]
6. Ju, Y.E.; Lucey, B.P.; Holtzman, D.M. Sleep and Alzheimer disease pathology—a bidirectional relationship. *Nat. Rev. Neurol.* **2014**, *10*, 115–119. [[CrossRef](#)] [[PubMed](#)]
7. Ardura-Fabregat, A.; Boddeke, E.W.G.M.; Boza-Serrano, A.; Brioschi, S.; Castro-Gomez, S.; Ceyzériat, K.; Dansokho, C.; Dierkes, T.; Gelders, G.; Heneka, M.T.; et al. Targeting Neuroinflammation to Treat Alzheimer’s Disease. *CNS Drugs* **2017**, *31*, 1057–1082. [[CrossRef](#)] [[PubMed](#)]
8. Lucas, S.M.; Rothwell, N.J.; Gibson, R.M. The role of inflammation in CNS injury and disease. *Br. J. Pharmacol.* **2006**, *147* (Suppl. 1), S232–S240. [[CrossRef](#)]
9. Solito, E.; Sastre, M. Microglia function in Alzheimer’s disease. *Front. Pharmacol.* **2012**, *3*. [[CrossRef](#)]
10. Sheng, J.G.; Griffin, W.S.; Royston, M.C.; Mrak, R.E. Distribution of interleukin-1-immunoreactive microglia in cerebral cortical layers: Implications for neuritic plaque formation in Alzheimer’s disease. *Neuropathol. Appl. Neurobiol.* **1998**, *24*, 278–283. [[CrossRef](#)]
11. Griffin, W.S.; Sheng, J.G.; Roberts, G.W.; Mrak, R.E. Interleukin-1 expression in different plaque types in Alzheimer’s disease: Significance in plaque evolution. *J. Neuropathol. Exp. Neurol.* **1995**, *54*, 276–281. [[CrossRef](#)] [[PubMed](#)]
12. Erta, M.; Quintana, A.; Hidalgo, J. Interleukin-6, a Major Cytokine in the Central Nervous System. *Int. J. Biol. Sci.* **2012**, *8*, 1254–1266. [[CrossRef](#)] [[PubMed](#)]

13. Yui, K.; Imataka, G.; Nakamura, H.; Ohara, N.; Naito, Y. Eicosanoids derived from arachidonic acid and their family prostaglandins and cyclooxygenase in psychiatric disorders. *Curr. Neuropharmacol.* **2015**, *13*, 776–785. [[CrossRef](#)] [[PubMed](#)]
14. Zhang, D.; Hu, X.; Qian, L.; Wilson, B.; Lee, C.; Flood, P.; Langenbach, R.; Hong, J.S. Prostaglandin E2 released from activated microglia enhances astrocyte proliferation in vitro. *Toxicol. Appl. Pharmacol.* **2009**, *238*, 64–70. [[CrossRef](#)] [[PubMed](#)]
15. Sastre, M.; Klockgether, T.; Heneka, M.T. Contribution of inflammatory processes to Alzheimer's disease: Molecular mechanisms. *Int. J. Dev. Neurosci.* **2006**, *24*, 167–176. [[CrossRef](#)] [[PubMed](#)]
16. Wang, S.; Colonna, M. Microglia in Alzheimer's disease: A target for immunotherapy. *J. Leukoc. Biol.* **2019**. [[CrossRef](#)] [[PubMed](#)]
17. Nishizaki, T.; Nomura, T.; Matsuoka, T.; Tsujishita, Y. Arachidonic acid as a messenger for the expression of long-term potentiation. *Biochem. Biophys. Res. Commun.* **1999**, *254*, 446–449. [[CrossRef](#)] [[PubMed](#)]
18. Cooke, S.F.; Bliss, T.V. Plasticity in the human central nervous system. *Brain* **2006**, *129*, 1659–1673. [[CrossRef](#)]
19. Angelova, P.R.; Müller, W.S. Arachidonic acid potently inhibits both postsynaptic-type Kv4.2 and presynaptic-type Kv1.4 IA potassium channels. *Eur. J. Neurosci.* **2009**, *29*, 1943–1950. [[CrossRef](#)]
20. Vitale, N.; Thiersé, D.; Bader, M.F. Melittin promotes exocytosis in neuroendocrine cells through the activation of phospholipase A₂. *Regul. Pept.* **2010**, *165*, 111–116. [[CrossRef](#)]
21. Shankar, G.M.; Li, S.; Mehta, T.H.; Garcia-Munoz, A.; Shepardson, N.E.; Smith, I.; Brett, F.M.; Farrell, M.A.; Rowan, M.J.; Lemere, C.A.; et al. Amyloid-beta protein dimers isolated directly from Alzheimer's brains impair synaptic plasticity and memory. *Nat. Med.* **2008**, *14*, 837–842. [[CrossRef](#)] [[PubMed](#)]
22. Thomas, M.H.; Pelleieux, P.; Vitale, N.; Olivier, J.L. Arachidonic acid in Alzheimer's disease. *J. Neurol. Neuromed.* **2016**, *1*, 1–6.
23. Esposito, G.; Giovacchini, G.; Liow, J.S.; Bhattacharjee, A.K.; Greenstein, D.; Schapiro, M.; Hallett, M.; Herscovitch, P.; Eckelman, W.C.; Carson, R.E.; et al. Imaging neuroinflammation in Alzheimer's disease with radiolabeled arachidonic acid and PET. *J. Nucl. Med.* **2008**, *49*, 1414–1421. [[CrossRef](#)] [[PubMed](#)]
24. Chalbot, S.; Zetterberg, H.; Blennow, K.; Fladby, T.; Grundke-Iqbal, I.; Iqbal, K. Cerebrospinal fluid secretory Ca²⁺-dependent phospholipase A2 activity is increased in Alzheimer disease. *Clin. Chem.* **2009**, *55*, 2171–2179. [[CrossRef](#)] [[PubMed](#)]
25. Moses, G.S.; Jensen, M.D.; Lue, L.F.; Walker, D.G.; Sun, A.Y.; Simonyi, A.; Sun, G.Y. Secretory PLA2-IIA: A new inflammatory factor for Alzheimer's disease. *J. Neuroinflamm.* **2006**, *3*, 28. [[CrossRef](#)] [[PubMed](#)]
26. Yagami, T. Cerebral arachidonate cascade in dementia: Alzheimer's disease and vascular dementia. *Curr. Neuropharmacol.* **2006**, *4*, 87–100. [[CrossRef](#)] [[PubMed](#)]
27. Sanchez-Mejia, R.O.; Newman, J.W.; Toh, S.; Yu, G.Q.; Zhou, Y.; Halabisky, B.; Cissé, M.; Scarce-Lavie, K.; Cheng, I.H.; Gan, L.; et al. Phospholipase A2 reduction ameliorates cognitive deficits in a mouse model of Alzheimer's disease. *Nat. Neurosci.* **2008**, *11*, 1311–1318. [[CrossRef](#)] [[PubMed](#)]
28. 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.; et al. Cytosolic phospholipase A2 mediates neuronal apoptosis induced by soluble oligomers of the amyloid-beta peptide. *FASEB J.* **2005**, *19*, 85–87. [[CrossRef](#)] [[PubMed](#)]
29. Kis, B.; Snipes, J.A.; Busija, D.W. Acetaminophen and the cyclooxygenase-3 puzzle: Sorting out facts, fictions, and uncertainties. *J. Pharmacol. Exp. Ther.* **2005**, *315*, 1–7. [[CrossRef](#)]
30. Yokoyama, C.; Tanabe, T. Cloning of human gene encoding prostaglandin endoperoxide synthase and primary structure of the enzyme. *Biochem. Biophys. Res. Commun.* **1989**, *165*, 888–894. [[CrossRef](#)]
31. Cuendet, M.; Mesecar, A.D.; DeWitt, D.L.; Pezzuto, J.M. An ELISA method to measure inhibition of the COX enzymes. *Nat. Protoc.* **2006**, *1*, 1915–1921. [[CrossRef](#)] [[PubMed](#)]
32. Yamagata, K.; Andreasson, K.I.; Kaufmann, W.E.; Barnes, C.A.; Worley, P.F. Expression of a mitogen-inducible cyclooxygenase in brain neurons: Regulation by synaptic activity and glucocorticoids. *Neuron* **1993**, *11*, 371–386. [[CrossRef](#)]
33. Nemeth, J.F.; Hochgesang, G.P., Jr.; Marnett, L.J.; Caprioli, R.M. Characterization of the Glycosylation Sites in Cyclooxygenase-2 Using Mass Spectrometry. *Biochemistry* **2001**, *40*, 3109–3116. [[CrossRef](#)] [[PubMed](#)]
34. Tomimoto, H.; Akiyuchi, I.; Wakita, H.; Lin, J.-X.; Budka, H. Cyclooxygenase-2 is induced in microglia during chronic cerebral ischemia in humans. *Acta Neuropathol.* **2000**, *99*, 26–30. [[CrossRef](#)] [[PubMed](#)]
35. In 't Veld, B.A.; Launer, L.J.; Hoes, A.W.; Ott, A.; Hofman, A.; Breteler, M.M.; Stricker, B.H. NSAIDs and incident Alzheimer's disease. *Rotterdam Study Neurobiol. Aging* **1998**, *19*, 607–611. [[CrossRef](#)]

36. Zhang, C.; Wang, Y.; Wang, D.; Zhang, J.; Zhang, F. NSAID Exposure and Risk of Alzheimer's Disease: An Updated Meta-Analysis from Cohort Studies. *Front. Aging Neurosci.* **2018**, *10*, 83. [[CrossRef](#)] [[PubMed](#)]
37. In 't Veld, B.A.; Ruitenbergh, A.; Hofman, A.; Launer, L.J.; van Duijn, C.M.; Stijnen, T.; Breteler, M.M.; Stricker, B.H. Nonsteroidal antiinflammatory drugs and the risk of Alzheimer's disease. *N. Engl. J. Med.* **2001**, *345*, 1515–1521. [[CrossRef](#)]
38. Rogers, J.; Kirby, L.C.; Hempelman, S.R.; Berry, D.L.; McGeer, P.L.; Kaszniak, A.W.; Zalinski, J.; Cofield, M.; Mansukhani, L.; Willson, P.; et al. Clinical trial of indomethacin in Alzheimer's disease. *Neurology* **1993**, *43*, 1609–1611. [[CrossRef](#)] [[PubMed](#)]
39. Aisen, P.S. The potential of anti-inflammatory drugs for the treatment of Alzheimer's disease. *Lancet Neurol.* **2002**, *1*, 279–284. [[CrossRef](#)]
40. Minghetti, L. Cyclooxygenase-2 (COX-2) in inflammatory and degenerative brain diseases. *J. Neuropathol. Exp. Neurol.* **2004**, *63*, 901–910. [[CrossRef](#)]
41. Ho, L.; Pieroni, C.; Winger, D.; Purohit, D.P.; Aisen, P.S.; Pasinetti, G.M. Regional distribution of cyclooxygenase-2 in the hippocampal formation in Alzheimer's disease. *J. Neurosci. Res.* **1999**, *57*, 295–303. [[CrossRef](#)]
42. Yermakova, A.V.; O'Banion, M.K. Downregulation of neuronal cyclooxygenase-2 expression in end stage Alzheimer's disease. *Neurobiol. Aging* **2001**, *22*, 823–836. [[CrossRef](#)]
43. Hoozemans, J.J.; Veerhuis, R.; Rozemuller, A.J.; Arendt, T.; Eikelenboom, P. Neuronal COX-2 expression and phosphorylation of pRb precede p38 MAPK activation and neurofibrillary changes in AD temporal cortex. *Neurobiol. Dis.* **2004**, *15*, 492–499. [[CrossRef](#)] [[PubMed](#)]
44. Pasinetti, G.M.; Aisen, P.S. Cyclooxygenase-2 expression is increased in frontal cortex of Alzheimer's disease brain. *Neuroscience* **1998**, *87*, 319–324. [[CrossRef](#)]
45. Kotilinek, L.A.; Westerman, M.A.; Wang, Q.; Panizzon, K.; Lim, G.P.; Simonyi, A.; Lesne, S.; Falinska, A.; Younkin, L.H.; Younkin, S.G.; et al. Cyclooxygenase-2 inhibition improves amyloid-beta-mediated suppression of memory and synaptic plasticity. *Brain* **2008**, *131*, 651–664. [[CrossRef](#)]
46. Yermakova, A.V.; Rollins, J.; Callahan, L.M.; Rogers, J.; O'Banion, M.K. Cyclooxygenase-1 in human Alzheimer and control brain: Quantitative analysis of expression by microglia and CA3 hippocampal neurons. *J. Neuropathol. Exp. Neurol.* **1999**, *58*, 1135–1146. [[CrossRef](#)]
47. Kalantzi, K.I.; Tsoumani, M.E.; Goudevenos, I.A.; Tselepis, A.D. Pharmacodynamic properties of antiplatelet agents: Current knowledge and future perspectives. *Expert Rev. Clin. Pharmacol.* **2012**, *5*, 319–336. [[CrossRef](#)]
48. Anninos, H.; Andrikopoulos, G.; Pastrovas, S.; Sakellariou, D.; Theodorakis, G.; Vardas, P. Triflusal: An old drug in modern antiplatelet therapy. Review of its action, use, safety and effectiveness. *Hellenic J. Cardiol.* **2009**, *50*, 199–207.
49. Coma, M.; Serenó, L.; Da Rocha-Souto, B.; Scotton, T.C.; España, J.; Sánchez, M.B.; Rodríguez, M.; Agulló, J.; Guardia-Laguarta, C.; Garcia-Alloza, M.; et al. Triflusal reduces dense-core plaque load, associated axonal alterations and inflammatory changes, and rescues cognition in a transgenic mouse model of Alzheimer's disease. *Neurobiol. Dis.* **2010**, *38*, 482–491. [[CrossRef](#)]
50. Iwamoto, N.; Kobayashi, K.; Kosaka, K. The formation of prostaglandins in the postmortem cerebral cortex of Alzheimer-type dementia patients. *J. Neurol.* **1989**, *236*, 80–84. [[CrossRef](#)]
51. Shaik, J.S.; Miller, T.M.; Graham, S.H.; Manole, M.D.; Poloyac, S.M. Rapid and simultaneous quantitation of prostanoids by UPLC-MS/MS in rat brain. *J. Chromatogr. B Anal. Technol. Biomed. Life Sci.* **2014**, *15*, 945–946. [[CrossRef](#)] [[PubMed](#)]
52. Ogorochi, T.; Narumiya, S.; Mizuno, N.; Yamashita, K.; Miyazaki, H.; Hayaishi, O. Regional distribution of prostaglandins D2, E2, and F2 alpha and related enzymes in postmortem human brain. *J. Neurochem.* **1984**, *43*, 71–82. [[CrossRef](#)] [[PubMed](#)]
53. Liang, X.; Wu, L.; Hand, T.; Andreasson, K. Prostaglandin D2 mediates neuronal protection via the DP1 receptor. *J. Neurochem.* **2005**, *92*, 477–486. [[CrossRef](#)] [[PubMed](#)]
54. Hoozemans, J.J.; van Haastert, E.S.; Veerhuis, R.; Arendt, T.; Scheper, W.; Eikelenboom, P.; Rozemuller, A.J. Maximal COX-2 and ppRb expression in neurons occurs during early Braak stages prior to the maximal activation of astrocytes and microglia in Alzheimer's disease. *J. Neuroinflamm.* **2005**, *21*, 27. [[CrossRef](#)] [[PubMed](#)]

55. Mohri, I.; Taniike, M.; Taniguchi, H.; Kanekiyo, T.; Aritake, K.; Inui, T.; Fukumoto, N.; Eguchi, N.; Kushi, A.; Sasai, H.; et al. Prostaglandin D2-mediated microglia/astrocyte interaction enhances astrogliosis and demyelination in twitcher. *J. Neurosci.* **2006**, *26*, 4383–4393. [[CrossRef](#)] [[PubMed](#)]
56. Sawyer, N.; Cauchon, E.; Chateaneuf, A.; Cruz, R.P.; Nicholson, D.W.; Metters, K.M.; O'Neill, G.P.; Gervais, F.G. Molecular pharmacology of the human prostaglandin D2 receptor, CRTH2. *Br. J. Pharmacol.* **2002**, *137*, 1163–1172. [[CrossRef](#)] [[PubMed](#)]
57. Sredni-Kenigsbuch, D. TH1/TH2 cytokines in the central nervous system. *Int. J. Neurosci.* **2002**, *112*, 665–703. [[CrossRef](#)] [[PubMed](#)]
58. Zhang, L.; Xie, H.; Cui, L. Activation of astrocytes and expression of inflammatory cytokines in rats with experimental autoimmune encephalomyelitis. *Exp. Ther. Med.* **2018**, *16*, 4401–4406. [[CrossRef](#)] [[PubMed](#)]
59. Biernacki, K.; Prat, A.; Blain, M.; Antel, J.P. Regulation of Th1 and Th2 lymphocyte migration by human adult brain endothelial cells. *J. Neuropathol. Exp. Neurol.* **2001**, *60*, 1127–1136. [[CrossRef](#)] [[PubMed](#)]
60. Mohri, I.; Kadoyama, K.; Kanekiyo, T.; Sato, Y.; Kagitani-Shimono, K.; Saito, Y.; Suzuki, K.; Kudo, T.; Takeda, M.; Urade, Y.; et al. Hematopoietic prostaglandin D synthase and DP1 receptor are selectively upregulated in microglia and astrocytes within senile plaques from human patients and in a mouse model of Alzheimer disease. *J. Neuropathol. Exp. Neurol.* **2007**, *66*, 469–480. [[CrossRef](#)] [[PubMed](#)]
61. Jandl, K.; Heinemann, A. The therapeutic potential of CRTH2/DP2 beyond allergy and asthma. *Prostagland. Other Lipid Mediat.* **2017**, *133*, 42–48. [[CrossRef](#)]
62. Figueiredo-Pereira, M.E.; Corwin, C.; Babich, J. Prostaglandin J2: A potential target for halting inflammation-induced neurodegeneration. *Ann. N. Y. Acad. Sci.* **2016**, *1363*, 125–137. [[CrossRef](#)] [[PubMed](#)]
63. Monneret, G.; Li, H.; Vasilescu, J.; Rokach, J.; Powell, W.S. 15-Deoxy-delta 12,14-prostaglandins D2 and J2 are potent activators of human eosinophils. *J. Immunol.* **2002**, *168*, 3563–3569. [[CrossRef](#)]
64. Yoon, H.J.; Jeon, S.B.; Kim, I.H.; Park, E.J. Regulation of TLR2 expression by prostaglandins in brain glia. *J. Immunol.* **2008**, *180*, 8400–8409. [[CrossRef](#)] [[PubMed](#)]
65. Heinemann, A.; Schulgoi, R.; Sabroe, I.; Hartnell, A.; Peskar, B.A. Delta 12-prostaglandin J2, a plasma metabolite of prostaglandin D2, causes eosinophil mobilization from the bone marrow and primes eosinophils for chemotaxis. *J. Immunol.* **2003**, *170*, 4752–4758. [[CrossRef](#)] [[PubMed](#)]
66. Liu, H.; Li, W.; Rose, M.E.; Pascoe, J.L.; Miller, T.M.; Ahmad, M.; Poloyac, S.M.; Hickey, R.W.; Graham, S.H. Prostaglandin D2 toxicity in primary neurons is mediated through its bioactive cyclopentenone metabolites. *Neurotoxicology* **2013**, *39*, 35–44. [[CrossRef](#)]
67. Arnaud, L.T.; Myeku, N.; Figueiredo-Pereira, M.E. Proteasome-caspase-cathepsin sequence leading to tau pathology induced by prostaglandin J2 in neuronal cells. *J. Neurochem.* **2009**, *110*, 328–342. [[CrossRef](#)] [[PubMed](#)]
68. Wright, D.H.; Metters, K.M.; Abramovitz, M.; Ford-Hutchinson, A.W. Characterization of the recombinant human prostanoid DP receptor and identification of L-644,698, a novel selective DP agonist. *Br. J. Pharmacol.* **1998**, *123*, 1317–1324. [[CrossRef](#)]
69. Itoh, S.; Lu, R.; Bao, Y.; Morrow, J.D.; Roberts, L.J.; Schuster, V.L. Structural determinants of substrates for the prostaglandin transporter PGT. *Mol. Pharmacol.* **1996**, *50*, 738–742.
70. Kanai, N.; Lu, R.; Satriano, J.A.; Bao, Y.; Wolkoff, A.W.; Schuster, V.L. Identification and characterization of a prostaglandin transporter. *Science* **1995**, *268*, 866–869. [[CrossRef](#)]
71. Subra, C.; Grand, D.; Laulagnier, K.; Stella, A.; Lambeau, G.; Paillasse, M.; De Medina, P.; Monsarrat, B.; Perret, B.; Silvente-Poirot, S.; et al. Exosomes account for vesicle-mediated transcellular transport of activatable phospholipases and prostaglandins. *J. Lipid Res.* **2010**, *51*, 2105–2120. [[CrossRef](#)] [[PubMed](#)]
72. Rissman, R.A.; Poon, W.W.; Blurton-Jones, M.; Oddo, S.; Torp, R.; Vitek, M.P.; LaFerla, F.M.; Rohn, T.T.; Cotman, C.W. Caspase-cleavage of tau is an early event in Alzheimer disease tangle pathology. *J. Clin. Investig.* **2004**, *114*, 121–130. [[CrossRef](#)] [[PubMed](#)]
73. Gong, B.; Leznik, E. The role of ubiquitin C-terminal hydrolase L1 in neurodegenerative disorders. *Drug News Perspect.* **2007**, *20*, 365–370. [[CrossRef](#)] [[PubMed](#)]
74. Guglielmo, M.; Monteleone, D.; Vaschiaveo, V.; Repetto, I.E.; Manassero, G.; Tabaton, M.; Tamagno, E. The Decrease of Uch-L1 Activity Is a Common Mechanism Responsible for A β 42 Accumulation in Alzheimer's and Vascular Disease. *Front. Aging Neurosci.* **2017**, *9*, 320. [[CrossRef](#)] [[PubMed](#)]

75. Koharudin, L.M.; Liu, H.; Di Maio, R.; Kodali, R.B.; Graham, S.H.; Gronenborn, A.M. Cyclopentenone prostaglandin-induced unfolding and aggregation of the Parkinson disease-associated UCH-L1. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 6835–6840. [[CrossRef](#)]
76. Uchida, K.; Shibata, T. 15-Deoxy-Delta(12,14)-prostaglandin J2: An electrophilic trigger of cellular responses. *Chem. Res. Toxicol.* **2008**, *21*, 138–144. [[CrossRef](#)] [[PubMed](#)]
77. Lin, T.N.; Cheung, W.M.; Wu, J.S.; Chen, J.J.; Lin, H.; Chen, J.J.; Liou, J.Y.; Shyue, S.K.; Wu, K.K. 15d-prostaglandin J2 protects brain from ischemia-reperfusion injury. *Arterioscler. Thromb. Vasc. Biol.* **2006**, *26*, 481–487. [[CrossRef](#)]
78. Jiang, Q.; Heneka, M.; Landreth, G.E. The role of peroxisome proliferator-activated receptor-gamma (PPARgamma) in Alzheimer's disease: Therapeutic implications. *CNS Drugs* **2008**, *22*, 1–14. [[CrossRef](#)]
79. Kummer, M.P.; Heneka, M.T. PPARs in Alzheimer's Disease. *PPAR Res.* **2008**, *2008*, 403896. [[CrossRef](#)]
80. Govindarajulu, M.; Pinky, P.D.; Bloemer, J.; Ghanei, N.; Suppiramaniam, V.; Amin, R. Signaling Mechanisms of Selective PPAR γ Modulators in Alzheimer's Disease. *PPAR Res.* **2018**, *2018*, 2010675. [[CrossRef](#)]
81. Paulitschke, V.; Gruber, S.; Hofstätter, E.; Haudek-Prinz, V.; Klepeisz, P.; Schicher, N.; Jonak, C.; Petzelbauer, P.; Pehamberger, H.; Gerner, C.; et al. Proteome analysis identified the PPAR γ ligand 15d-PGJ2 as a novel drug inhibiting melanoma progression and interfering with tumor-stroma interaction. *PLoS ONE* **2012**, *7*, e46103. [[CrossRef](#)] [[PubMed](#)]
82. Clark, I.A.; Alleva, L.M.; Vissel, B. The roles of TNF in brain dysfunction and disease. *Pharmacol. Ther.* **2010**, *128*, 519–548. [[CrossRef](#)]
83. Licinio, J.; Prolo, P.; McCann, S.M.; Wong, M.L. Brain iNOS: Current understanding and clinical implications. *Mol. Med. Today* **1999**, *5*, 225–232. [[CrossRef](#)]
84. Nathan, C.; Calingasan, N.; Nezezon, J.; Ding, A.; Lucia, M.S.; La Perle, K.; Fuortes, M.; Lin, M.; Ehrst, S.; Kwon, N.S.; et al. Protection from Alzheimer's-like disease in the mouse by genetic ablation of inducible nitric oxide synthase. *J. Exp. Med.* **2005**, *202*, 1163–1169. [[CrossRef](#)] [[PubMed](#)]
85. Stitham, J.; Midgett, C.; Martin, K.A.; Hwa, J. Prostacyclin: An inflammatory paradox. *Front. Pharmacol.* **2011**, *2*, 24. [[CrossRef](#)] [[PubMed](#)]
86. Satoh, T.; Ishikawa, Y.; Kataoka, Y.; Cui, Y.; Yanase, H.; Kato, K.; Watanabe, Y.; Nakadate, K.; Matsumura, K.; Hatanaka, H.; et al. CNS-specific prostacyclin ligands as neuronal survival-promoting factors in the brain. *Eur. J. Neurosci.* **1999**, *11*, 3115–3124. [[CrossRef](#)] [[PubMed](#)]
87. Siegle, I.; Klein, T.; Zou, M.H.; Fritz, P.; Kömhoff, M. Distribution and cellular localization of prostacyclin synthase in human brain. *J. Histochem. Cytochem.* **2000**, *48*, 631–641. [[CrossRef](#)] [[PubMed](#)]
88. Crider, J.Y.; Xu, S.X.; Sharif, N.A. Pharmacology of functional endogenous IP prostanoid receptors in NCB-20 cells: Comparison with binding data from human platelets. *Prostagland. Leukot. Essent. Fat. Acids.* **2001**, *65*, 253–258. [[CrossRef](#)] [[PubMed](#)]
89. Smyth, E.M.; Nestor, P.V.; FitzGerald, G.A. Agonist-dependent phosphorylation of an epitope-tagged human prostacyclin receptor. *J. Biol. Chem.* **1996**, *271*, 33698–33704. [[CrossRef](#)] [[PubMed](#)]
90. Oida, H.; Namba, T.; Sugimoto, Y.; Ushikubi, F.; Ohishi, H.; Ichikawa, A.; Narumiya, S. In situ hybridization studies of prostacyclin receptor mRNA expression in various mouse organs. *Br. J. Pharmacol.* **1995**, *116*, 2828–2837. [[CrossRef](#)] [[PubMed](#)]
91. He, T.; Santhanam, A.V.; Lu, T.; d'Uscio, L.V.; Katusic, Z.S. Role of prostacyclin signaling in endothelial production of soluble amyloid precursor protein- α in cerebral microvessels. *J. Cereb. Blood Flow Metab.* **2017**, *37*, 106–122. [[CrossRef](#)] [[PubMed](#)]
92. Wang, P.; Guan, P.P.; Yu, X.; Zhang, L.C.; Su, Y.N.; Wang, Z.Y. Prostaglandin I₂ Attenuates Prostaglandin E₂-Stimulated Expression of Interferon γ in a β -Amyloid Protein- and NF- κ B-Dependent Mechanism. *Sci. Rep.* **2016**, *6*, 20879. [[CrossRef](#)] [[PubMed](#)]
93. Muramatsu, R.; Kuroda, M.; Matoba, K.; Lin, H.; Takahashi, C.; Koyama, Y.; Yamashita, T. Prostacyclin prevents pericyte loss and demyelination induced by lysophosphatidylcholine in the central nervous system. *J. Biol. Chem.* **2015**, *290*, 11515–11525. [[CrossRef](#)] [[PubMed](#)]
94. Sengillo, J.D.; Winkler, E.A.; Walker, C.T.; Sullivan, J.S.; Johnson, M.; Zlokovic, B.V. Deficiency in mural vascular cells coincides with blood-brain barrier disruption in Alzheimer's disease. *Brain Pathol.* **2013**, *23*, 303–310. [[CrossRef](#)] [[PubMed](#)]
95. Sagare, A.P.; Bell, R.D.; Zhao, Z.; Ma, Q.; Winkler, E.A.; Ramanathan, A.; Zlokovic, B.V. Pericyte loss influences Alzheimer-like neurodegeneration in mice. *Nat. Commun.* **2013**, *4*, 2932. [[CrossRef](#)]

96. Tanikawa, N.; Ohmiya, Y.; Ohkubo, H.; Hashimoto, K.; Kangawa, K.; Kojima, M.; Ito, S.; Watanabe, K. Identification and characterization of a novel type of membrane-associated prostaglandin E synthase. *Biochem. Biophys. Res. Commun.* **2002**, *291*, 884–889. [[CrossRef](#)] [[PubMed](#)]
97. Tanioka, T.; Nakatani, Y.; Semmyo, N.; Murakami, M.; Kudo, I. Molecular identification of cytosolic prostaglandin E2 synthase that is functionally coupled with cyclooxygenase-1 in immediate prostaglandin E2 biosynthesis. *J. Biol. Chem.* **2000**, *275*, 32775–32782. [[CrossRef](#)] [[PubMed](#)]
98. Chaudhry, U.A.; Zhuang, H.; Crain, B.J.; Doré, S. Elevated microsomal prostaglandin-E synthase-1 in Alzheimer's disease. *Alzheimers Dement.* **2008**, *4*, 6–13. [[CrossRef](#)] [[PubMed](#)]
99. Chaudhry, U.; Zhuang, H.; Doré, S. Microsomal prostaglandin E synthase-2: Cellular distribution and expression in Alzheimer's disease. *Exp. Neurol.* **2010**, *223*, 359–365. [[CrossRef](#)] [[PubMed](#)]
100. Chaudhry, U.A.; Dore, S. Cytosolic prostaglandin E synthase: Expression patterns in control and Alzheimer's disease brains. *Am. J. Alzheimers Dis. Other Demen.* **2009**, *24*, 46–51. [[CrossRef](#)] [[PubMed](#)]
101. Sugimoto, Y.; Narumiya, S. Prostaglandin E receptors. *J. Biol. Chem.* **2007**, *282*, 11613–11617. [[CrossRef](#)] [[PubMed](#)]
102. Candelario-Jalil, E.; Slawik, H.; Ridelis, I.; Waschbisch, A.; Akundi, R.S.; Hüll, M.; Fiebich, B.L. Regional distribution of the prostaglandin E2 receptor EP1 in the rat brain: Accumulation in Purkinje cells of the cerebellum. *J. Mol. Neurosci.* **2005**, *27*, 303–310. [[CrossRef](#)]
103. Cho, W.H.; Choi, C.H.; Park, J.Y.; Kang, S.K.; Kim, Y.K. 15-deoxy-(Delta12,14)-prostaglandin J2 (15d-PGJ2) induces cell death through caspase-independent mechanism in A172 human glioma cells. *Neurochem. Res.* **2006**, *31*, 1247–1254. [[CrossRef](#)] [[PubMed](#)]
104. Kawano, T.; Anrather, J.; Zhou, P.; Park, L.; Wang, G.; Frys, K.A.; Kunz, A.; Cho, S.; Orio, M.; Iadecola, C. Prostaglandin E2 EP1 receptors: Downstream effectors of COX-2 neurotoxicity. *Nat. Med.* **2006**, *12*, 225–229. [[CrossRef](#)] [[PubMed](#)]
105. Shimamura, M.; Zhou, P.; Casolla, B.; Qian, L.; Capone, C.; Kurinami, H.; Iadecola, C.; Anrather, J. Prostaglandin E2 type 1 receptors contribute to neuronal apoptosis after transient forebrain ischemia. *J. Cereb. Blood Flow Metab.* **2013**, *33*, 1207–1214. [[CrossRef](#)] [[PubMed](#)]
106. Zhen, G.; Kim, Y.T.; Li, R.C.; Yocum, J.; Kapoor, N.; Langer, J.; Dobrowolski, P.; Maruyama, T.; Narumiya, S.; Doré, S. PGE2 EP1 receptor exacerbated neurotoxicity in a mouse model of cerebral ischemia and Alzheimer's disease. *Neurobiol. Aging* **2012**, *33*, 2215–2219. [[CrossRef](#)] [[PubMed](#)]
107. Li, X.; Rose, S.E.; Montine, K.S.; Keene, C.D.; Montine, T.J. Antagonism of neuronal prostaglandin E(2) receptor subtype 1 mitigates amyloid β neurotoxicity in vitro. *J. Neuroimmune Pharmacol.* **2013**, *8*, 87–93. [[CrossRef](#)]
108. He, G.L.; Luo, Z.; Yang, J.; Shen, T.T.; Chen, Y.; Yang, X.S. Curcumin Ameliorates the Reduction Effect of PGE2 on Fibrillar β -Amyloid Peptide (1-42)-Induced Microglial Phagocytosis through the Inhibition of EP2-PKA Signaling in N9 Microglial Cells. *PLoS ONE* **2016**, *11*, e0147721. [[CrossRef](#)]
109. Johansson, J.U.; Woodling, N.S.; Wang, Q.; Panchal, M.; Liang, X.; Trueba-Saiz, A.; Brown, H.D.; Mhatre, S.D.; Loui, T.; Andreasson, K.I. Prostaglandin signaling suppresses beneficial microglial function in Alzheimer's disease models. *J. Clin. Investig.* **2015**, *125*, 350–364. [[CrossRef](#)]
110. Liang, X.; Wang, Q.; Hand, T.; Wu, L.; Breyer, R.M.; Montine, T.J.; Andreasson, K. Deletion of the prostaglandin E2 EP2 receptor reduces oxidative damage and amyloid burden in a model of Alzheimer's disease. *J. Neurosci.* **2005**, *25*, 10180–10187. [[CrossRef](#)]
111. Shie, F.S.; Breyer, R.M.; Montine, T.J. Microglia lacking E Prostanoid Receptor subtype 2 have enhanced Abeta phagocytosis yet lack Abeta-activated neurotoxicity. *Am. J. Pathol.* **2005**, *166*, 1163–1172. [[CrossRef](#)]
112. Kotani, M.; Tanaka, I.; Ogawa, Y.; Suganami, T.; Matsumoto, T.; Muro, S.; Yamamoto, Y.; Sugawara, A.; Yoshimasa, Y.; Sagawa, N.; et al. Multiple signal transduction pathways through two prostaglandin E receptor EP3 subtype isoforms expressed in human uterus. *J. Clin. Endocrinol. Metab.* **2000**, *85*, 4315–4322. [[CrossRef](#)] [[PubMed](#)]
113. Slawik, H.; Volk, B.; Fiebich, B.; Hüll, M. Microglial expression of prostaglandin EP3 receptor in excitotoxic lesions in the rat striatum. *Neurochem. Int.* **2004**, *45*, 653–660. [[CrossRef](#)] [[PubMed](#)]
114. Natura, G.; Bär, K.J.; Eitner, A.; Boettger, M.K.; Richter, F.; Hensellek, S.; Ebersberger, A.; Leuchtweis, J.; Maruyama, T.; Hofmann, G.O.; et al. Neuronal prostaglandin E2 receptor subtype EP3 mediates antinociception during inflammation. *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 13648–13653. [[CrossRef](#)] [[PubMed](#)]

115. Shi, J.; Wang, Q.; Johansson, J.U.; Liang, X.; Woodling, N.S.; Priyam, P.; Loui, T.M.; Merchant, M.; Breyer, R.M.; Montine, T.J.; et al. Inflammatory prostaglandin E2 signaling in a mouse model of Alzheimer disease. *Ann. Neurol.* **2012**, *72*, 788–798. [[CrossRef](#)] [[PubMed](#)]
116. Maingret, V.; Barthet, G.; Deforges, S.; Jiang, N.; Mulle, C.; Amédée, T. PGE2-EP3 signaling pathway impairs hippocampal presynaptic long-term plasticity in a mouse model of Alzheimer's disease. *Neurobiol. Aging* **2017**, *50*, 13–24. [[CrossRef](#)] [[PubMed](#)]
117. Nishigaki, N.; Negishi, M.; Ichikawa, A. Two Gs-coupled prostaglandin E receptor subtypes, EP2 and EP4, differ in desensitization and sensitivity to the metabolic inactivation of the agonist. *Mol. Pharmacol.* **1996**, *50*, 1031–1037. [[PubMed](#)]
118. Shi, J.; Johansson, J.; Woodling, N.S.; Wang, Q.; Montine, T.J.; Andreasson, K. The prostaglandin E2 E-prostanoid 4 receptor exerts anti-inflammatory effects in brain innate immunity. *J. Immunol.* **2010**, *184*, 7207–7218. [[CrossRef](#)] [[PubMed](#)]
119. Woodling, N.S.; Wang, Q.; Priyam, P.G.; Larkin, P.; Shi, J.; Johansson, J.U.; Zagol-Ikapitte, I.; Boutaud, O.; Andreasson, K.I. Suppression of Alzheimer-associated inflammation by microglial prostaglandin-E2 EP4 receptor signaling. *J. Neurosci.* **2014**, *34*, 5882–5894. [[CrossRef](#)] [[PubMed](#)]
120. Cao, L.L.; Guan, P.P.; Liang, Y.Y.; Huang, X.S.; Wang, P. Cyclooxygenase-2 is Essential for Mediating the Effects of Calcium Ions on Stimulating Phosphorylation of Tau at the Sites of Ser 396 and Ser 404. *J. Alzheimers Dis.* **2019**, *68*, 1095–1111. [[CrossRef](#)]
121. DeMars, K.M.; McCrea, A.O.; Siwarski, D.M.; Sanz, B.D.; Yang, C.; Candelario-Jalil, E. Protective Effects of L-902,688, a Prostanoid EP4 Receptor Agonist, against Acute Blood-Brain Barrier Damage in Experimental Ischemic Stroke. *Front. Neurosci.* **2018**, *20*, 89. [[CrossRef](#)] [[PubMed](#)]
122. Goppelt-Struebe, M. Molecular mechanisms involved in the regulation of prostaglandin biosynthesis by glucocorticoids. *Biochem. Pharmacol.* **1997**, *53*, 1389–1395. [[CrossRef](#)]
123. Verstraete, M. Introduction: Thromboxane in biological systems and the possible impact of its inhibition. *Br. J. Clin. Pharmacol.* **1983**, *15* (Suppl. 1), 7S–11S. [[CrossRef](#)] [[PubMed](#)]
124. Hirata, T.; Ushikubi, F.; Kakizuka, A.; Okuma, M.; Narumiya, S. Two thromboxane A2 receptor isoforms in human platelets. Opposite coupling to adenylyl cyclase with different sensitivity to Arg60 to Leu mutation. *J. Clin. Investig.* **1996**, *97*, 949–956. [[CrossRef](#)] [[PubMed](#)]
125. Nakahata, N. Thromboxane A2: Physiology/pathophysiology, cellular signal transduction and pharmacology. *Pharmacol. Ther.* **2008**, *118*, 18–35. [[CrossRef](#)] [[PubMed](#)]
126. Suzuki, N.; Hajicek, N.; Kozasa, T. Regulation and physiological functions of G12/13-mediated signaling pathways. *Neurosignals* **2009**, *17*, 55–70. [[CrossRef](#)] [[PubMed](#)]
127. Wacker, M.J.; Tevis, O.; Hanke, J.; Howard, T.; Gilbert, W.; Orr, J.A. Characterization of thromboxane A2 receptor and TRPV1 mRNA expression in cultured sensory neurons. *Neurosci. Lett.* **2012**, *515*, 12–17. [[CrossRef](#)] [[PubMed](#)]
128. Yan, A.; Zhang, T.; Yang, X.; Shao, J.; Fu, N.; Shen, F.; Fu, Y.; Xia, W. Thromboxane A2 receptor antagonist SQ29548 reduces ischemic stroke-induced microglia/macrophages activation and enrichment, and ameliorates brain injury. *Sci. Rep.* **2016**, *6*, 35885. [[CrossRef](#)]
129. Herbst-Robinson, K.J.; Liu, L.; James, M.; Yao, Y.; Xie, S.X.; Brunden, K.R. Inflammatory Eicosanoids Increase Amyloid Precursor Protein Expression via Activation of Multiple Neuronal Receptors. *Sci. Rep.* **2015**, *5*, 18286. [[CrossRef](#)]
130. Soper, J.H.; Sugiyama, S.; Herbst-Robinson, K.; James, M.J.; Wang, X.; Trojanowski, J.Q.; Smith, A.B., III; Lee, V.M.; Ballatore, C.; Brunden, K.R. Brain-penetrant tetrahydronaphthalene thromboxane A2-prostanoid (TP) receptor antagonists as prototype therapeutics for Alzheimer's disease. *ACS Chem. Neurosci.* **2012**, *21*, 928–940. [[CrossRef](#)]
131. Obara, Y.; Kurose, H.; Nakahata, N. Thromboxane A2 promotes interleukin-6 biosynthesis mediated by an activation of cyclic AMP-response element-binding protein in 1321N1 human astrocytoma cells. *Mol. Pharmacol.* **2005**, *68*, 670–679. [[CrossRef](#)] [[PubMed](#)]
132. Shen, M.Y.; Hsiao, G.; Fong, T.H.; Chen, H.M.; Chou, D.S.; Lin, C.H.; Sheu, J.R.; Hsu, C.Y. Amyloid beta peptide-activated signal pathways in human platelets. *Eur. J. Pharmacol.* **2008**, *588*, 259–266. [[CrossRef](#)] [[PubMed](#)]

133. Praticò, D.; Lee, V.M.-Y.; Trojanowski, J.Q.; Rokach, J.; Fitzgerald, G.A. Increased F2-isoprostanes in Alzheimer's disease: Evidence for enhanced lipid peroxidation in vivo. *FASEB J.* **1998**, *12*, 1777–1783. [[CrossRef](#)] [[PubMed](#)]
134. Montine, T.J.; Markesbery, W.R.; Morrow, J.D.; Roberts, L.J., II. Cerebrospinal fluid F2-isoprostane levels are increased in Alzheimer's disease. *Ann. Neurol.* **1998**, *44*, 410–413. [[CrossRef](#)]
135. Benndorf, R.A.; Schwedhelm, E.; Gnann, A.; Taheri, R.; Kom, G.; Didié, M.; Steenpass, A.; Ergün, S.; Böger, R.H. Isoprostanes inhibit vascular endothelial growth factor-induced endothelial cell migration, tube formation, and cardiac vessel sprouting in vitro, as well as angiogenesis in vivo via activation of the thromboxane A(2) receptor: A potential link between oxidative stress and impaired angiogenesis. *Circ. Res.* **2008**, *103*, 1037–1046. [[PubMed](#)]
136. Tang, M.; Cyrus, T.; Yao, Y.; Vocun, L.; Praticò, D. Involvement of thromboxane receptor in the proatherogenic effect of isoprostane F2 α -III: Evidence from apolipoprotein E- and LDL receptor-deficient mice. *Circulation* **2005**, *112*, 2867–2874. [[CrossRef](#)] [[PubMed](#)]
137. Shineman, D.W.; Zhang, B.; Leight, S.N.; Pratico, D.; Lee, V.M. Thromboxane receptor activation mediates isoprostane-induced increases in amyloid pathology in Tg2576 mice. *J. Neurosci.* **2008**, *28*, 4785–4794. [[CrossRef](#)] [[PubMed](#)]
138. Praticò, D.; Uryu, K.; Leight, S.; Trojanowski, J.Q.; Lee, V.M. Increased lipid peroxidation precedes amyloid plaque formation in an animal model of Alzheimer amyloidosis. *J. Neurosci.* **2001**, *21*, 4183–4187. [[CrossRef](#)] [[PubMed](#)]
139. Woodward, D.F.; Jones, R.L.; Narumiya, S. International Union of Basic and Clinical Pharmacology. LXXXIII: Classification of prostanoid receptors, updating 15 years of progress. *Pharmacol. Rev.* **2011**, *63*, 471–538. [[CrossRef](#)]
140. Scali, C.; Prosperi, C.; Bracco, L.; Piccini, C.; Baronti, R.; Ginestroni, A.; Sorbi, S.; Pepeu, G.; Casamenti, F. Neutrophils CD11b and fibroblasts PGE(2) are elevated in Alzheimer's disease. *Neurobiol. Aging* **2002**, *23*, 523–530. [[CrossRef](#)]
141. Liston, T.E.; Roberts, L.J., II. Transformation of prostaglandin D2 to 9 α , 11 β -(15S)-trihydroxyprosta-(5Z,13E)-dien-1-oic acid (9 α , 11 β -prostaglandin F2); a unique biologically active prostaglandin produced enzymatically in vivo in humans. *Proc. Natl. Acad. Sci. USA* **1985**, *82*, 6030–6034. [[CrossRef](#)] [[PubMed](#)]
142. Silvestri, C.; Martella, A.; Poloso, N.J.; Piscitelli, F.; Capasso, R.; Izzo, A.; Woodward, D.F.; Di Marzo, V. Anandamide-derived Prostanoid F2 α Negatively Regulates Adipogenesis. *J. Biol. Chem.* **2013**, *288*, 23307–23321. [[CrossRef](#)] [[PubMed](#)]
143. Watanabe, K.; Yoshida, R.; Shimizu, T.; Hayaishi, O. Enzymatic formation of prostaglandin F2 α from prostaglandin H2 and D2. Purification and properties of prostaglandin F synthetase from bovine lung. *J. Biol. Chem.* **1985**, *260*, 7035–7041. [[PubMed](#)]
144. Matsunaga, T.; Shintani, S.; Hara, A. Multiplicity of mammalian reductases for xenobiotic carbonyl compounds. *Drug Metab. Pharmacokinet.* **2006**, *21*, 1–18. [[CrossRef](#)] [[PubMed](#)]
145. Abramovitz, M.; Boie, Y.; Nguyen, T.; Rushmore, T.H.; Bayne, M.A.; Metters, K.M.; Slipetz, D.M.; Grygorczyk, R. Cloning and expression of a cDNA for the human prostanoid FP receptor. *J. Biol. Chem.* **1994**, *269*, 2632–2636. [[PubMed](#)]
146. Sales, K.J.; Milne, S.A.; Williams, A.R.; Anderson, R.A.; Jabbour, H.N. Expression, localization, and signaling of prostaglandin F2 α receptor in human endometrial adenocarcinoma: Regulation of proliferation by activation of the epidermal growth factor receptor and mitogen-activated protein kinase signaling pathways. *J. Clin. Endocrinol. Metab.* **2004**, *89*, 986–993. [[CrossRef](#)]
147. Casadesus, G.; Smith, M.A.; Basu, S.; Hua, J.; Capobianco, D.E.; Siedlak, S.L.; Zhu, X.; Perry, G. Increased isoprostane and prostaglandin are prominent in neurons in Alzheimer disease. *Mol. Neurodegener.* **2007**, *2*, 2. [[CrossRef](#)] [[PubMed](#)]
148. Pierce, K.L.; Fujino, H.; Srinivasan, D.; Regan, J.W. Activation of FP prostanoid receptor isoforms lead to Rho-mediated changes in cell morphology and in the cell cytoskeleton. *J. Biol. Chem.* **1999**, *274*, 35944–35949. [[CrossRef](#)]
149. Zhuang, J.; Zhang, H.; Zhou, R.; Chen, L.; Chen, J.; Shen, X. Regulation of prostaglandin F2 α against β amyloid clearance and its inflammation induction through LXR/RXR heterodimer antagonism in microglia. *Prostaglandins Other Lipid Mediat.* **2013**, *106*, 45–52. [[CrossRef](#)]

150. Glushakov, A.V.; Robbins, S.W.; Bracy, C.L.; Narumiya, S.; Doré, S. Prostaglandin F₂ α FP receptor antagonist improves outcomes after experimental traumatic brain injury. *J. Neuroinflamm.* **2013**, *10*, 132. [[CrossRef](#)]
151. Yagami, T.; Ueda, K.; Asakura, K.; Sakaeda, T.; Kuroda, T.; Hata, S.; Kambayashi, Y.; Fujimoto, M. Effects of S-2474, a novel nonsteroidal anti-inflammatory drug, on amyloid beta protein-induced neuronal cell death. *Br. J. Pharmacol.* **2001**, *134*, 673–681. [[CrossRef](#)] [[PubMed](#)]
152. Biringer, R.G. The Enzymes of the Human Eicosanoid Pathway. *Res. Rep. Med. Sci.* **2018**, *2*, 106. Available online: <https://www.omicsonline.org/open-access/the-enzymes-of-the-human-eicosanoid-pathway-106840.html> (accessed on 13 June 2019).
153. Brash, A.R. Lipoxygenases: Occurrence, functions, catalysis, and acquisition of substrate. *J. Biol. Chem.* **1999**, *274*, 23679–23682. [[CrossRef](#)] [[PubMed](#)]
154. Andersson, E.; Schain, F.; Svedling, M.; Claesson, H.E.; Forsell, P.K. Interaction of human 15-lipoxygenase-1 with phosphatidylinositol bisphosphates results in increased enzyme activity. *Biochim. Biophys. Acta* **2006**, *1761*, 1498–1505. [[CrossRef](#)] [[PubMed](#)]
155. Walther, M.; Wiesner, R.; Kuhn, H. Investigations into calcium-dependent membrane association of 15-lipoxygenase-1. Mechanistic roles of surface-exposed hydrophobic amino acids and calcium. *J. Biol. Chem.* **2004**, *279*, 3717–3725. [[CrossRef](#)] [[PubMed](#)]
156. Bryant, R.W.; Bailey, J.M.; Schewe, T.; Rapoport, S.M. Positional specificity of a reticulocyte lipoxygenase. Conversion of arachidonic acid to 15-S-hydroperoxy-eicosatetraenoic acid. *J. Biol. Chem.* **1982**, *257*, 6050–6055. [[PubMed](#)]
157. Kühn, H.; Sprecher, H.; Brash, A.R. On singular or dual positional specificity of lipoxygenases. The number of chiral products varies with alignment of methylene groups at the active site of the enzyme. *J. Biol. Chem.* **1990**, *265*, 16300–16305. [[PubMed](#)]
158. Funk, C.D.; Furci, L.; FitzGerald, G.A. Molecular cloning, primary structure, and expression of the human platelet/erythroleukemia cell 12-lipoxygenase. *Proc. Natl. Acad. Sci. USA* **1990**, *87*, 5638–5642. [[CrossRef](#)] [[PubMed](#)]
159. Zhao, J.; O'Donnell, V.B.; Balzar, S.; St Croix, C.M.; Trudeau, J.B.; Wenzel, S.E. 15-Lipoxygenase 1 interacts with phosphatidylethanolamine-binding protein to regulate MAPK signaling in human airway epithelial cells. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 14246–14251. [[CrossRef](#)] [[PubMed](#)]
160. Praticò, D.; Zhukareva, V.; Yao, Y.; Uryu, K.; Funk, C.D.; Lawson, J.A.; Trojanowski, J.Q.; Lee, V.M. 12/15-lipoxygenase is increased in Alzheimer's disease: Possible involvement in brain oxidative stress. *Am. J. Pathol.* **2004**, *164*, 1655–1662. [[CrossRef](#)]
161. Succol, F.; Praticò, D. A role for 12/15 lipoxygenase in the amyloid beta precursor protein metabolism. *J. Neurochem.* **2007**, *103*, 380–387. [[PubMed](#)]
162. Yang, H.; Zhuo, J.M.; Chu, J.; Chinnici, C.; Praticò, D. Amelioration of the Alzheimer's disease phenotype by absence of 12/15-lipoxygenase. *Biol. Psychiatry* **2010**, *68*, 922–929. [[CrossRef](#)] [[PubMed](#)]
163. Giannopoulos, P.F.; Joshi, Y.B.; Chu, J.; Praticò, D. The 12-15-lipoxygenase is a modulator of Alzheimer's-related tau pathology in vivo. *Aging Cell* **2013**, *12*, 1082–1090. [[CrossRef](#)] [[PubMed](#)]
164. Tajima, Y.; Ishikawa, M.; Maekawa, K.; Murayama, M.; Senoo, Y.; Nishimaki-Mogami, T.; Nakanishi, H.; Ikeda, K.; Arita, M.; Taguchi, R.; et al. Lipidomic analysis of brain tissues and plasma in a mouse model expressing mutated human amyloid precursor protein/tau for Alzheimer's disease. *Lipids Health Dis.* **2013**, *12*, 68. [[CrossRef](#)] [[PubMed](#)]
165. Shappell, S.B.; Gupta, R.A.; Manning, S.; Whitehead, R.; Boeglin, W.E.; Schneider, C.; Case, T.; Price, J.; Jack, G.S.; Wheeler, T.M.; et al. 15S-Hydroxyeicosatetraenoic acid activates peroxisome proliferator-activated receptor gamma and inhibits proliferation in PC3 prostate carcinoma cells. *Cancer Res.* **2001**, *61*, 497–503. [[PubMed](#)]
166. Sun, L.; Xu, Y.W.; Han, J.; Liang, H.; Wang, N.; Cheng, Y. 12/15-Lipoxygenase metabolites of arachidonic acid activate PPAR γ : A possible neuroprotective effect in ischemic brain. *J. Lipid Res.* **2015**, *56*, 502–514. [[CrossRef](#)] [[PubMed](#)]
167. Farias, S.E.; Zarini, S.; Precht, T.; Murphy, R.C.; Heidenreich, K.A. Transcellular biosynthesis of cysteinyl leukotrienes in rat neuronal and glial cells. *J. Neurochem.* **2007**, *103*, 1310–1318. [[CrossRef](#)]
168. Ochs, M.J.; Sorg, B.L.; Pufahl, L.; Grez, M.; Suess, B.; Steinhilber, D. Post-transcriptional regulation of 5-lipoxygenase mRNA expression via alternative splicing and nonsense-mediated mRNA decay. *PLoS ONE* **2012**, *7*, e31363. [[CrossRef](#)]

169. Hammarberg, T.; Provost, P.; Persson, B.; Rådmark, O. The N-terminal domain of 5-lipoxygenase binds calcium and mediates calcium stimulation of enzyme activity. *J. Biol. Chem.* **2000**, *275*, 38787–38793. [[CrossRef](#)]
170. Romano, M. Lipid mediators: Lipoxin and aspirin-triggered 15-epi-lipoxins. *Inflamm. Allergy Drug Targets* **2006**, *5*, 81–90. [[CrossRef](#)]
171. Romano, M. Lipoxin and aspirin-triggered lipoxins. *Sci. World J.* **2010**, *10*, 1048–1064. [[CrossRef](#)] [[PubMed](#)]
172. Ikonovic, M.D.; Abrahamson, E.E.; Uz, T.; Manev, H.; Dekosky, S.T. Increased 5-lipoxygenase immunoreactivity in the hippocampus of patients with Alzheimer's disease. *J. Histochem. Cytochem.* **2008**, *56*, 1065–1073. [[CrossRef](#)] [[PubMed](#)]
173. Chu, J.; Praticò, D. 5-lipoxygenase as an endogenous modulator of amyloid β formation in vivo. *Ann. Neurol.* **2011**, *69*, 34–46. [[CrossRef](#)] [[PubMed](#)]
174. Firuzi, O.; Zhuo, J.; Chinnici, C.M.; Wisniewski, T.; Praticò, D. 5-Lipoxygenase gene disruption reduces amyloid-beta pathology in a mouse model of Alzheimer's disease. *FASEB J.* **2008**, *22*, 1169–1178. [[CrossRef](#)] [[PubMed](#)]
175. Chu, J.; Praticò, D. The 5-Lipoxygenase as modulator of Alzheimer's γ -secretase and therapeutic target. *Brain Res. Bull.* **2016**, *126 Pt 2*, 207–212. [[CrossRef](#)]
176. Andberg, M.B.; Hamberg, M.; Haeggström, J.Z. Mutation of tyrosine 383 in leukotriene A4 hydrolase allows conversion of leukotriene A4 into 5S,6S-dihydroxy-7,9-trans-11,14-cis-eicosatetraenoic acid. Implications for the epoxide hydrolase mechanism. *J. Biol. Chem.* **1997**, *272*, 23057–23063. [[CrossRef](#)] [[PubMed](#)]
177. Honn, K.V.; Guo, Y.; Cai, Y.; Lee, M.J.; Dyson, G.; Zhang, W.; Tucker, S.C. 12-HETER1/GPR31, a high-affinity 12(S)-hydroxyeicosatetraenoic acid receptor, is significantly up-regulated in prostate cancer and plays a critical role in prostate cancer progression. *FASEB J.* **2016**, *30*, 2360–2369. [[CrossRef](#)]
178. Pridans, C.; Raper, A.; Davis, G.M.; Alves, J.; Sauter, K.A.; Lefevre, L.; Regan, T.; Meek, S.; Sutherland, L.; Thomson, A.J.; et al. Pleiotropic Impacts of Macrophage and Microglial Deficiency on Development in Rats with Targeted Mutation of the Csf1r Locus. *J. Immunol.* **2018**, *201*, 2683–2699. [[CrossRef](#)]
179. Guo, Y.; Zhang, W.; Giroux, C.; Cai, Y.; Ekambaram, P.; Dilly, A.K.; Hsu, A.; Zhou, S.; Maddipati, K.R.; Liu, J.; et al. Identification of the orphan G protein-coupled receptor GPR31 as a receptor for 12-(S)-hydroxyeicosatetraenoic acid. *J. Biol. Chem.* **2011**, *286*, 33832–33840. [[CrossRef](#)]
180. Currais, A.; Quehenberger, O.; Armando, A.M.; Daugherty, D.; Maher, P.; Schubert, D. Amyloid proteotoxicity initiates an inflammatory response blocked by cannabinoids. *NPJ Aging Mech. Dis.* **2016**, *2*, 16012. [[CrossRef](#)]
181. Zimmer, J.S.; Dyckes, D.F.; Bernlohr, D.A.; Murphy, R.C. Fatty acid binding proteins stabilize leukotriene A4: Competition with arachidonic acid but not other lipoxygenase products. *J. Lipid Res.* **2004**, *45*, 2138–2144. [[CrossRef](#)] [[PubMed](#)]
182. Bray, M.A. The pharmacology and pathophysiology of leukotriene B4. *Br. Med. Bull.* **1983**, *39*, 249–254. [[CrossRef](#)] [[PubMed](#)]
183. Haeggström, J.Z. Structure, function, and regulation of leukotriene A4 hydrolase. *Am. J. Respir. Crit. Care Med.* **2000**, *161 Pt 2*, S25–S31. [[CrossRef](#)]
184. Samuelsson, B. Leukotrienes: Mediators of immediate hypersensitivity reactions and inflammation. *Science* **1983**, *220*, 568–575. [[CrossRef](#)] [[PubMed](#)]
185. Crooks, S.W.; Stockley, R.A. Leukotriene B4. *Int. J. Biochem. Cell Biol.* **1998**, *30*, 173–178. [[CrossRef](#)]
186. Paris, D.; Town, T.; Parker, T.A.; Tan, J.; Humphrey, J.; Crawford, F.; Mullan, M. Inhibition of Alzheimer's beta-amyloid induced vasoactivity and proinflammatory response in microglia by a cGMP-dependent mechanism. *Exp. Neurol.* **1999**, *157*, 211–221. [[CrossRef](#)] [[PubMed](#)]
187. Amtul, Z.; Uhrig, M.; Wang, L.; Rozmahel, R.F.; Beyreuther, K. Detrimental effects of arachidonic acid and its metabolites in cellular and mouse models of Alzheimer's disease: Structural insight. *Neurobiol. Aging* **2012**, *33*, e21–e31. [[CrossRef](#)] [[PubMed](#)]
188. Joshi, Y.B.; Di Meco, A.; Praticò, D. Modulation of amyloid- β production by leukotriene B4 via the γ -secretase pathway. *J. Alzheimers Dis.* **2014**, *38*, 503–506. [[CrossRef](#)] [[PubMed](#)]
189. Wang, X.Y.; Tang, S.S.; Hu, M.; Long, Y.; Li, Y.Q.; Liao, M.X.; Ji, H.; Hong, H. Leukotriene D4 induces amyloid- β generation via CysLT(1)R-mediated NF- κ B pathways in primary neurons. *Neurochem. Int.* **2013**, *62*, 340–347. [[CrossRef](#)] [[PubMed](#)]
190. Tager, A.M.; Luster, A.D. BLT1 and BLT2: The leukotriene B(4) receptors. *Prostagland. Leukot. Essent. Fat. Acids* **2003**, *69*, 123–134. [[CrossRef](#)]

191. Okubo, M.; Yamanaka, H.; Kobayashi, K.; Noguchi, K. Leukotriene synthases and the receptors induced by peripheral nerve injury in the spinal cord contribute to the generation of neuropathic pain. *Glia* **2010**, *58*, 599–610. [[CrossRef](#)] [[PubMed](#)]
192. Arita, M.; Ohira, T.; Sun, Y.P.; Elangovan, S.; Chiang, N.; Serhan, C.N. Resolvin E1 selectively interacts with leukotriene B4 receptor BLT1 and ChemR23 to regulate inflammation. *J. Immunol.* **2007**, *178*, 3912–3917. [[CrossRef](#)] [[PubMed](#)]
193. Piomelli, D.; Feinmark, S.J.; Cannon, P.J. Leukotriene biosynthesis by canine and human coronary arteries. *J. Pharmacol. Exp. Ther.* **1987**, *241*, 763–770. [[PubMed](#)]
194. Sirois, P.; Brousseau, Y.; Salari, H.; Borgeat, P. Correlation between the myotropic activity of leukotriene A4 on guinea-pig lung, trachea and ileum and its biotransformation in situ. *Prostaglandins* **1985**, *30*, 21–36. [[CrossRef](#)]
195. Gelosa, P.; Colazzo, F.; Tremoli, E.; Sironi, L.; Castiglioni, L. Cysteinyl Leukotrienes as Potential Pharmacological Targets for Cerebral Diseases. *Mediat. Inflamm.* **2017**, 3454212. [[CrossRef](#)] [[PubMed](#)]
196. Lam, B.K.; Austen, K.F. Leukotriene C4 synthase. A pivotal enzyme in the biosynthesis of the cysteinyl leukotrienes. *Am. J. Respir. Crit. Care Med.* **2000**, *161 Pt 2*, S16–S19. [[CrossRef](#)]
197. Capra, V.; Thompson, M.D.; Sala, A.; Cole, D.E.; Folco, G.; Rovati, G.E. Cysteinyl-leukotrienes and their receptors in asthma and other inflammatory diseases: Critical update and emerging trends. *Med. Res. Rev.* **2007**, *27*, 469–527. [[CrossRef](#)] [[PubMed](#)]
198. Ghosh, A.; Chen, F.; Thakur, A.; Hong, H. Cysteinyl Leukotrienes and Their Receptors: Emerging Therapeutic Targets in Central Nervous System Disorders. *CNS Neurosci. Ther.* **2016**, *22*, 943–951. [[CrossRef](#)] [[PubMed](#)]
199. Heise, C.E.; O’Dowd, B.F.; Figueroa, D.J.; Sawyer, N.; Nguyen, T.; Im, D.S.; Stocco, R.; Bellefeuille, J.N.; Abramovitz, M.; Cheng, R.; et al. Characterization of the human cysteinyl leukotriene 2 receptor. *J. Biol. Chem.* **2000**, *275*, 30531–30536. [[CrossRef](#)] [[PubMed](#)]
200. Tang, S.S.; Hong, H.; Chen, L.; Mei, Z.L.; Ji, M.J.; Xiang, G.Q.; Li, N.; Ji, H. Involvement of cysteinyl leukotriene receptor 1 in A β 1-42-induced neurotoxicity in vitro and in vivo. *Neurobiol. Aging* **2014**, *35*, 590–599. [[CrossRef](#)] [[PubMed](#)]
201. Ciccarelli, R.; D’Alimonte, I.; Santavenere, C.; D’Auro, M.; Ballerini, P.; Nargi, E.; Buccella, S.; Nicosia, S.; Folco, G.; Caciagli, F.; et al. Cysteinyl-leukotrienes are released from astrocytes and increase astrocyte proliferation and glial fibrillary acidic protein via cys-LT1 receptors and mitogen-activated protein kinase pathway. *Eur. J. Neurosci.* **2004**, *20*, 1514–1524. [[CrossRef](#)] [[PubMed](#)]
202. Zhao, C.Z.; Zhao, B.; Zhang, X.Y.; Huang, X.Q.; Shi, W.Z.; Liu, H.L.; Fang, S.H.; Lu, Y.B.; Zhang, W.P.; Tang, F.D.; et al. Cysteinyl leukotriene receptor 2 is spatiotemporally involved in neuron injury, astrocytosis and microgliosis after focal cerebral ischemia in rats. *Neuroscience* **2011**, *189*, 1–11. [[CrossRef](#)] [[PubMed](#)]
203. Shi, Q.J.; Wang, H.; Liu, Z.X.; Fang, S.H.; Song, X.M.; Lu, Y.B.; Zhang, W.P.; Sa, X.Y.; Ying, H.Z.; Wei, E.Q. HAMI 3379, a CysLT2R antagonist, dose- and time-dependently attenuates brain injury and inhibits microglial inflammation after focal cerebral ischemia in rats. *Neuroscience* **2015**, *291*, 53–69. [[CrossRef](#)] [[PubMed](#)]
204. Feltenmark, S.; Gautam, N.; Brunnström, A.; Griffiths, W.; Backman, L.; Edenius, C.; Lindbom, L.; Björkholm, M.; Claesson, H.E. Eoxins are proinflammatory arachidonic acid metabolites produced via the 15-lipoxygenase-1 pathway in human eosinophils and mast cells. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 680–685. [[CrossRef](#)] [[PubMed](#)]
205. Serhan, C.N.; Krishnamoorthy, S.; Recchiuti, A.; Chiang, N. Novel anti-inflammatory–Pro-resolving mediators and their receptors. *Curr. Top. Med. Chem.* **2011**, *11*, 629–647. [[CrossRef](#)] [[PubMed](#)]
206. Dyall, S.C. Long-chain omega-3 fatty acids and the brain: A review of the independent and shared effects of EPA, DPA and DHA. *Front. Aging Neurosci.* **2015**, *7*, 52. [[CrossRef](#)] [[PubMed](#)]
207. Wang, X.; Zhu, M.; Hjorth, E.; Cortés-Toro, V.; Eyjolfsdottir, H.; Graff, C.; Nennesmo, I.; Palmblad, J.; Eriksdotter, M.; Sambamurti, K.; et al. Resolution of inflammation is altered in Alzheimer’s disease. *Alzheimers Dement.* **2015**, *11*, 40–50. [[CrossRef](#)] [[PubMed](#)]
208. Maddox, J.F.; Serhan, C.N. Lipoxin A4 and B4 are potent stimuli for human monocyte migration and adhesion: Selective inactivation by dehydrogenation and reduction. *J. Exp. Med.* **1996**, *183*, 137–146. [[CrossRef](#)] [[PubMed](#)]
209. Levy, B.D. Lipoxins and lipoxin analogs in asthma. *Prostagland. Leukot. Essent. Fat. Acids.* **2005**, *73*, 231–237. [[CrossRef](#)] [[PubMed](#)]

210. Fierro, I.M.; Colgan, S.P.; Bernasconi, G.; Petasis, N.A.; Clish, C.B.; Arita, M.; Serhan, C.N. Lipoxin A4 and aspirin-triggered 15-epi-lipoxin A4 inhibit human neutrophil migration: Comparisons between synthetic 15 epimers in chemotaxis and transmigration with microvessel endothelial cells and epithelial cells. *J. Immunol.* **2003**, *170*, 2688–2694. [CrossRef]
211. Chiang, N.; Fierro, I.M.; Gronert, K.; Serhan, C.N. Activation of lipoxin A(4) receptors by aspirin-triggered lipoxins and select peptides evokes ligand-specific responses in inflammation. *J. Exp. Med.* **2000**, *191*, 1197–1208. [CrossRef] [PubMed]
212. Romano, M.; Recchia, I.; Recchiuti, A. Lipoxin receptors. *Sci. World J.* **2007**, *7*, 1393–1412. [CrossRef] [PubMed]
213. Chandrasekharan, J.A.; Sharma-Walia, N. Lipoxins: Nature's way to resolve inflammation. *J. Inflamm. Res.* **2015**, *8*, 181–192. [PubMed]
214. Livne-Bar, I.; Wei, J.; Liu, H.H.; Alqawlaq, S.; Won, G.J.; Tuccitto, A.; Gronert, K.; Flanagan, J.G.; Sivak, J.M. Astrocyte-derived lipoxins A4 and B4 promote neuroprotection from acute and chronic injury. *J. Clin. Investig.* **2017**, *127*, 4403–4414. [CrossRef] [PubMed]
215. McMahon, B.; Godson, C. Lipoxins: Endogenous regulators of inflammation. *Am. J. Physiol. Ren. Physiol.* **2004**, *286*, F189–F201. [CrossRef] [PubMed]
216. Maderna, P.; Godson, C. Phagocytosis of apoptotic cells and the resolution of inflammation. *Biochim. Biophys. Acta* **2003**, *1639*, 141–151. [CrossRef] [PubMed]
217. Ariel, A.; Chiang, N.; Arita, M.; Petasis, N.A.; Serhan, C.N. Aspirin-triggered lipoxin A4 and B4 analogs block extracellular signal-regulated kinase-dependent TNF-alpha secretion from human T cells. *J. Immunol.* **2003**, *170*, 6266–6272. [CrossRef]
218. Luo, C.L.; Li, Q.Q.; Chen, X.P.; Zhang, X.M.; Li, L.L.; Li, B.X.; Zhao, Z.Q.; Tao, L.Y. Lipoxin A4 attenuates brain damage and downregulates the production of pro-inflammatory cytokines and phosphorylated mitogen-activated protein kinases in a mouse model of traumatic brain injury. *Brain Res.* **2013**, *1502*, 1–10. [CrossRef]
219. Maddox, J.F.; Hachicha, M.; Takano, T.; Petasis, N.A.; Fokin, V.V.; Serhan, C.N. Lipoxin A4 stable analogs are potent mimetics that stimulate human monocytes and THP-1 cells via a G-protein-linked lipoxin A4 receptor. *J. Biol. Chem.* **1997**, *272*, 6972–6978. [CrossRef]
220. Takano, T.; Fiore, S.; Maddox, J.F.; Brady, H.R.; Petasis, N.A.; Serhan, C.N. Aspirin-triggered 15-epi-lipoxin A4 (LXA4) and LXA4 stable analogues are potent inhibitors of acute inflammation: Evidence for anti-inflammatory receptors. *J. Exp. Med.* **1997**, *185*, 1693–1704. [CrossRef]
221. Medeiros, R.; Kitazawa, M.; Passos, G.F.; Baglietto-Vargas, D.; Cheng, D.; Cribbs, D.H.; LaFerla, F.M. Aspirin-triggered lipoxin A4 stimulates alternative activation of microglia and reduces Alzheimer disease-like pathology in mice. *Am. J. Pathol.* **2013**, *182*, 1780–1789. [CrossRef] [PubMed]
222. Dunn, H.C.; Ager, R.R.; Baglietto-Vargas, D.; Cheng, D.; Kitazawa, M.; Cribbs, D.H.; Medeiros, R. Restoration of lipoxin A4 signaling reduces Alzheimer's disease-like pathology in the 3xTg-AD mouse model. *J. Alzheimers Dis.* **2015**, *43*, 893–903. [CrossRef] [PubMed]
223. Le, Y.; Gong, W.; Tiffany, H.L.; Tumanov, A.; Nedospasov, S.; Shen, W.; Dunlop, N.M.; Gao, J.L.; Murphy, P.M.; Oppenheim, J.J.; et al. Amyloid (beta)42 activates a G-protein-coupled chemoattractant receptor, FPR-like-1. *J. Neurosci.* **2001**, *21*, RC123. Available online: <http://www.jneurosci.org/content/21/2/RC123.long> (accessed on 13 June 2019). [CrossRef]
224. Waechter, V.; Schmid, M.; Herova, M.; Weber, A.; Günther, V.; Marti-Jaun, J.; Wüst, S.; Rösinger, M.; Gemperle, C.; Hersberger, M. Characterization of the promoter and the transcriptional regulation of the lipoxin A4 receptor (FPR2/ALX) gene in human monocytes and macrophages. *J. Immunol.* **2012**, *188*, 1856–1867. [CrossRef] [PubMed]
225. Sun, Y.P.; Oh, S.F.; Uddin, J.; Yang, R.; Gotlinger, K.; Campbell, E.; Colgan, S.P.; Petasis, N.A.; Serhan, C.N. Resolvin D1 and its aspirin-triggered 17R epimer. Stereochemical assignments, anti-inflammatory properties, and enzymatic inactivation. *J. Biol. Chem.* **2007**, *282*, 9323–9334. [CrossRef] [PubMed]
226. Hong, S.; Gronert, K.; Devchand, P.R.; Moussignac, R.L.; Serhan, C.N. Novel docosatrienes and 17S-resolvins generated from docosahexaenoic acid in murine brain, human blood, and glial cells. Autacoids in anti-inflammation. *J. Biol. Chem.* **2003**, *278*, 14677–14687. [CrossRef]
227. Serhan, C.N.; Petasis, N.A. Resolvins and protectins in inflammation resolution. *Chem. Rev.* **2011**, *111*, 5922–5943. [CrossRef] [PubMed]

228. Zhu, M.; Wang, X.; Hjorth, E.; Colas, R.A.; Schroeder, L.; Granholm, A.C.; Serhan, C.N.; Schultzberg, M. Pro-Resolving Lipid Mediators Improve Neuronal Survival and Increase A β 42 Phagocytosis. *Mol. Neurobiol.* **2016**, *53*, 2733–2749. [[CrossRef](#)]
229. Hong, S.; Porter, T.F.; Lu, Y.; Oh, S.F.; Pillai, P.S.; Serhan, C.N. Resolvin E1 metabolome in local inactivation during inflammation-resolution. *J. Immunol.* **2008**, *180*, 3512–3519. [[CrossRef](#)]
230. Salic, K.; Morrison, M.C.; Verschuren, L.; Wielinga, P.Y.; Wu, L.; Kleemann, R.; Gjorstrup, P.; Kooistra, T. Resolvin E1 attenuates atherosclerosis in absence of cholesterol-lowering effects and on top of atorvastatin. *Atherosclerosis* **2016**, *250*, 158–165. [[CrossRef](#)]
231. Arita, M.; Bianchini, F.; Aliberti, J.; Sher, A.; Chiang, N.; Hong, S.; Yang, R.; Petasis, N.A.; Serhan, C.N. Stereochemical assignment, antiinflammatory properties, and receptor for the omega-3 lipid mediator resolvin E1. *J. Exp. Med.* **2005**, *201*, 713–722. [[CrossRef](#)] [[PubMed](#)]
232. Kantarci, A.; Aytan, N.; Palaska, I.; Stephens, D.; Crabtree, L.; Benincasa, C.; Jenkins, B.G.; Carreras, I.; Dedeoglu, A. Combined administration of resolvin E1 and lipoxin A4 resolves inflammation in a murine model of Alzheimer’s disease. *Exp. Neurol.* **2018**, *300*, 111–120. [[CrossRef](#)] [[PubMed](#)]
233. Bang, S.; Xie, Y.K.; Zhang, Z.J.; Wang, Z.; Xu, Z.Z.; Ji, R.R. GPR37 regulates macrophage phagocytosis and resolution of inflammatory pain. *J. Clin. Investig.* **2018**, *128*, 3568–3582. [[CrossRef](#)] [[PubMed](#)]
234. Zhao, Y.; Calon, F.; Julien, C.; Winkler, J.W.; Petasis, N.A.; Lukiw, W.J.; Bazan, N.G. Docosahexaenoic acid-derived neuroprotectin D1 induces neuronal survival via secretase- and PPAR γ -mediated mechanisms in Alzheimer’s disease models. *PLoS ONE* **2011**, *6*, e15816. [[CrossRef](#)] [[PubMed](#)]
235. Stark, D.T.; Bazan, N.G. Neuroprotectin D1 induces neuronal survival and downregulation of amyloidogenic processing in Alzheimer’s disease cellular models. *Mol. Neurobiol.* **2011**, *43*, 131–138. [[CrossRef](#)] [[PubMed](#)]
236. Lukiw, W.J.; Cui, J.G.; Marcheselli, V.L.; Bodker, M.; Botkjaer, A.; Gotlinger, K.; Serhan, C.N.; Bazan, N.G. A role for docosahexaenoic acid-derived neuroprotectin D1 in neural cell survival and Alzheimer disease. *J. Clin. Investig.* **2005**, *115*, 2774–2783. [[CrossRef](#)] [[PubMed](#)]



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