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Therapeutic Implications of the Prostaglandin Pathway in Alzheimer's Disease

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Abstract

An important pathologic hallmark of Alzheimer's disease (AD) is neuroinflammation, a process characterized in AD by disproportionate activation of cells (microglia and astrocytes, primarily) of the non-specific innate immune system within the CNS. While inflammation itself is not intrinsically detrimental, a delicate balance of pro- and anti-inflammatory signals must be maintained to ensure that long-term exaggerated responses do not damage the brain over time. Non-steroidal anti-inflammatory drugs (NSAIDs) represent a broad class of powerful therapeutics that temper inflammation by inhibiting cyclooxygenase-mediated signaling pathways including prostaglandins, which are the principal mediators of CNS neuroinflammation. While historically used to treat discrete or systemic inflammatory conditions, epidemiologic evidence suggests that protracted NSAID use may delay AD onset, as well as decrease disease severity and rate of progression. Unfortunately, clinical trials with NSAIDs have thus far yielded disappointing results, including premature discontinuation of a large-scale prevention trial due to unexpected cardiovascular side effects. Here we review the literature and make the argument that more targeted exploitation of downstream prostaglandin signaling pathways may offer significant therapeutic benefits for AD while minimizing adverse side effects. Directed strategies such as these may ultimately help to delay the deleterious consequences of brain aging and might someday lead to new therapies for AD and other chronic neurodegenerative diseases.

Keywords

Alzheimer's disease; prostaglandin; neuroinflammation; cyclooxygenase; NSAID

1. Neuroinflammation in AD

Alzheimer's disease (AD) is an incurable neurodegenerative disorder affecting tens of millions of Americans and their families. Sporadic, or late onset, AD (LOAD) is slowly progressive, with age representing the single greatest risk factor. While the neuropathologic hallmarks of the disease include both intra- and extracellular aggregation of neurotoxic peptides within discrete brain regions, widespread neuroinflammation prominently accompanies these lesions [1–4]. Indeed, inflammatory molecules, including prostaglandins and cytokines, increase in cerebral spinal fluid (CSF) and brain parenchyma with age [5–8]

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and are associated with age-dependent cognitive impairment [9–11], suggesting that exacerbated or persistent neuroinflammation is a potentially significant driver of pathogenesis and disease progression in age-related neurodegenerative diseases [12], and especially in AD [13]. Furthermore, this inflammatory milieu is present in both the initial asymptomatic latent disease phase [14] in addition to more advanced stages of AD, supporting the development of targeted anti-inflammatory pharmacotherapy approaches aimed at prevention as well as treatment [15].

2. NSAIDs and AD: Epidemiology

Anti-inflammatory drugs are widely used for a variety of conditions, from simple headaches and fevers to serious autoimmune disorders such as rheumatoid arthritis (RA). Noting that various molecular signatures of inflammation are markedly increased in the brains of AD subjects [1, 16, 17], more than twenty years ago McGeer, Rogers, and colleagues observed that coincidence of AD and RA was significantly below the levels expected in the general population, implicating anti-inflammatory drugs as potentially neuroprotective. Specifically, the authors calculated general AD prevalence to be 2.7% in patients older than 64 years, and according to hospital discharge statistics, found that a diagnosis of AD and RA in the same patient existed in 29 of 13,246 individuals (0.2%) [18]. Furthermore, only 2 of 169 autopsied putative AD cases were documented to have preexisting RA, and the coincidence of both disorders was less than 0.5% (6 of 1332) in RA and AD clinics [18]. They inferred from this association that chronic anti-inflammatory treatment may provide a significant preventive or therapeutic intervention for AD.

3. NSAIDs and AD: Clinical trials

Although epidemiological findings were ultimately met with skepticism because of the unusually low AD prevalence cited compared to other reported observations [19], Rogers et al conducted a short-term double-blind placebo-controlled clinical trial using the non-steroidal anti-inflammatory drug (NSAID) indomethacin [20]. They reported reduced cognitive impairment in patients prescribed 100 to 150 mg/d of indomethacin after six months of treatment compared to controls [20]. Unfortunately, the study was hampered by poor tolerance of drug side effects and significant participant dropout, and did not address the effects of NSAIDs during the prodromal asymptomatic phase of AD since inclusion criteria for study subjects included previous AD diagnosis. Several clinical trials followed mostly in patients with clinical AD with varying limited success [21–25]. Even so, administration of non-selective [26–31] and selective [26, 32] COX inhibitors in various murine AD models results in significant reduction of amyloid pathology and associated neuroinflammation, as well as improved performance in cognitive testing. Combined with existing epidemiological evidence [1, 16–18] supporting this protective role for NSAIDs in the development of AD, the ADAPT study tested the preventive efficacy of selective and non-selective COX inhibitors in AD [33, 34], but it was abruptly discontinued due to significant cardiovascular side effects [35, 36]. Noteworthy, a subset of participants in that trial who did not develop AD early in the trial were shown to have a lower incidence of AD with long-term follow up, suggesting a subgroup in the study in whom NSAID administration may have provided a preventive benefit [36, 37]. However, for others in the trial, NSAID administration was poorly tolerated and in others may have unmasked latent AD [35, 36]. The study authors acknowledge that the therapeutic effect of NSAIDs likely varies as a function of AD stage and progression [33, 34], confirming that increased efficacy might be achieved through prophylactic NSAID administration years in advance of clinical onset. Thus, while NSAIDs demonstrated neuroprotection in numerous experimental studies, there appeared to be limited clinical benefit for patients with AD (Table 1). Zahr and Ashe offer a possible explanation for this unfortunate contradiction, proposing that

current animal models of AD more accurately reflect early latent phases of disease, failing to accurately capture the more clinically observed time course[38]. If true, this suggests that NSAID clinical trials should focus on prevention over intervention, a perspective supported by the original observation in RA subjects where NSAID regimens were likely initiated during latent disease phase in predisposed individuals. An additional consideration is the deleterious side effects associated with chronic NSAID use, especially selective COX-2 inhibitors like celecoxib and rofecoxib, in elderly patients [35, 39]. Thus, a more effective, less toxic alternative is needed.

4. Cyclooxygenase and AD

NSAIDs inhibit cyclooxygenase (COX) enzymes, the rate-limiting mediators of prostanoid biosynthesis. Prostanoids are a broad class of arachidonic acid-derived paracrine signaling molecules that include thromboxanes, prostaglandins, and prostacyclins. Under normal conditions, a constitutive pool of prostanoids ubiquitously regulates a host of diverse physiological processes, including vasomotor tone, platelet aggregation, ovulation, and neonatal development [40–43]. However, a second highly responsive and inducible prostanoid pool of primarily prostaglandin E2 (PGE₂) mediates the initiation and propagation of inflammation, and is thought to contribute to the disproportionate inflammatory response in AD, and to many other pathological processes such as carcinogenesis and metastasis [44, 45]. As endogenous lipid signaling molecules, the prostanoids are not proactively synthesized and stored within cells for future release, but are rather generated *on demand* in response to a variety of inflammatory triggers. One of these is amyloid β (A β), a pleotropic neurotoxin and neuropathologic hallmark of AD [46]. In addition to direct neurotoxicity, A β mediates increased cellular phospholipase activity [47, 48], the first step in prostanoid biosynthesis, in addition to stimulation of pro-inflammatory cytokine secretion.

Phospholipase A2 (PLA2) family members liberate fatty acid substrates, especially arachidonic acid, via hydrolysis of cellular membrane phospholipids, and thus initiate prostanoid signaling cascades (Figure 1). Interestingly, PLA2-independent sources of arachidonic acid also appear to contribute to the pool of readily available precursors for prostanoid biosynthesis [49, 50], especially in brain [51], suggesting a more complicated upstream signaling scheme *in vivo*. Free arachidonic acid is then converted to PGH₂ by COX enzymes in a two-step reaction that transiently forms the labile prostanoid intermediate PGG₂ via oxygenation, followed by the peroxidation of PGG₂ to yield more stable PGH₂ (Figure 1). In addition to COX enzymes, lipoxygenases and cytochrome P450s readily metabolize arachidonic acid, yielding leukotrienes and epoxyeicosatrienoic acids, respectively [52]. Two important COX isoforms exist, COX-1 and COX-2, each having distinct but overlapping tissue distributions and activity profiles. COX-1 is expressed in most tissues and cell types and is constitutively active, and as such has been historically considered a crucial player in the maintenance of general cell physiology and homeostasis. In contrast, COX-2 expression shows greater restriction and is uniquely inducible, collectively limiting its activity and delineating its role as a respondent to stress and insult. A variety of stimuli, including cell proliferation and differentiation, neoplasia, environmental stress, and inflammation, can induce COX-2 expression and increase prostanoid levels. COX-2 expression in all tissues is tightly controlled and is important in housekeeping roles, including regulation of systemic energy homeostasis [53], postnatal renal development [54], female fertility[55], and maintenance of cardiovascular homeostasis[56], as evidenced by the cardiovascular risks associated with chronic use of COX-2 selective inhibitors such as rofecoxib and celecoxib [39, 57]. COX-2 expression in brain is normally very low but is markedly increased in AD [58, 59]. COX-3, a novel splice variant of COX-1, has been identified and shows significant enrichment in human cerebral

cortex and heart [60]. While a link may exist between COX-3 and AD [61, 62], additional studies are needed to understand this relationship, especially given the fact that multiple COX-1 splice variants have been described and controversy remains as to the expression of COX-3 in humans [63].

COX activity has been repeatedly implicated in neuroinflammation associated with normal aging [64–66] and in the pathophysiology of experimental AD [29, 30, 67–73]. Isoform-specific COX expression changes are well documented in patients with AD [74, 75]. Thus, the epidemiological evidence supporting a therapeutic benefit of chronic NSAID administration in AD is presumed to derive from COX inhibition and modulation of neuroinflammation, although the effects may be more direct. For instance, many NSAIDs and structurally related compounds directly target gamma secretase [76–78], a membrane-associated multimeric protein complex that includes the aspartyl protease presenilin. Mutations in presenilin 1 and 2 are a well-known cause of familial AD. The gamma secretase complex differentially cleaves the transmembrane protein substrate amyloid precursor protein (APP), subsequently releasing A β . Select NSAIDs, in addition to several structural enantiomers, inhibit gamma secretase activity, and therefore reduce formation and accumulation of A β in animal models [76, 79, 80] and human trials [81, 82]. Nevertheless, NSAIDs appear to reduce risk of AD-related dementia independent of direct or indirect modulation of A β levels based on studies by Szekely [83], and identification of downstream effectors that specifically mediate this function has led to increased study of prostaglandin pathways as therapeutic targets for AD.

5. Prostaglandins

Transgenic animal models continue to support the therapeutic efficacy of NSAIDs for AD [26–32], and, while clinical trials have been variable, if not disappointing, some are working to identify patient subpopulations who might benefit from NSAID therapy, such as those in the ADAPT trial. However, in order to treat a broader AD population, a more targeted and efficacious pharmacotherapy is needed with a limited side effect profile. COX activation results in a cascade of prostanoid signaling with an abundance of potential downstream therapeutic targets, and COX inhibitors result in blanket suppression of prostanoid pathways. Teasing apart the COX-dependent neuroprotective pathways from the ones involved in cardiovascular toxicity or even neurotoxicity is an active area of research, since epidemiological and experimental studies continue to support the presence of a molecular target of NSAIDs in the development or progression of AD. COX activation through specific synthases results in the production of a number of biologically relevant prostaglandins (Figure 1): Prostaglandin I₂ (PGI₂), prostaglandin F₂ alpha (PGF_{2a}), prostaglandin D₂ (PGD₂), thromboxane (TXA₂), and prostaglandin E₂ (PGE₂). Each of these molecules has distinctive functional pathways and physiological consequences, such as immuno- or vaso-modulation, that can be beneficial or deleterious depending on the tissue substrate and clinical context.

6. Prostaglandin Pathways and AD

NSAIDs represent more of a pharmacological sledgehammer than a silver bullet in the therapeutic battle against AD. Yet their repeated efficacy in animal models and remarkable tale of epidemiology remain undeniable. While the answer may lie in appropriate temporal administration, it remains noteworthy that the site of NSAID anti-inflammatory action exists far upstream of a diverse prostaglandin signaling scheme. The question of therapeutic value may be better answered through directed targeting of the diverse downstream players, taking advantage of the high degree of receptor selectivity and responsiveness exhibited by this system.

In response to inflammatory stimuli, the prostaglandins are synthesized and then freely diffuse from cells into the extracellular compartment[84]. Clearance and recycling of extracellular prostaglandins is achieved by a family of organic anion-transporting polypeptide transporters[85, 86]. Prostaglandins act on cognate G protein-coupled receptors (GPCRs) to induce an inflammatory response (Figure 1), and numerous studies are under way targeting individual GPCRs in experimental AD as an effort to tease apart the neurotoxic and neuroprotective portions of the prostaglandin pathway. The GPCRs utilized by prostaglandin receptors subserve diverse cellular functions and their modulation may be associated with diverse cytotoxicities, so a more directed approach utilizing specific receptors is needed.

Of the five prostaglandins, PGE₂ is the major effector in the CNS based on synthase expression data and direct measurements [87], and is the most studied with regard to neuroinflammation. PGE₂ is synthesized in either the membrane by microsomal prostaglandin E synthase (mPGES) or in the cytosol by cytosolic PGES (cPGES). As the inducible form, much attention has been paid to the value of mPGES as a potential therapeutic target, and the efficacy of a variety of inhibitors has been investigated in relevant disease models [88]. However, it is important to note that the precision gained through targeted mPGES inhibition is only one level more selective than COX inhibitors. Instead, we propose that greater therapeutic value can be achieved by targeting prostaglandin receptors, the next level down. Indeed, PGE₂ can effect a multitude of functional outcomes, owing its diverse signaling repertoire to the activation of four cell-surface GPCR subtypes, EP1, EP2, EP3, and EP4 (Figure 1), in addition to several functionally relevant EP3 splice variants [89]. Of particular interest to this review, each of these receptors has been studied in relation to experimental AD [46, 90–94].

To initially test the relevance of various EP receptors in neurodegenerative disease, several groups developed genetic mouse models of AD that lacked specific PGE₂ receptor subtypes and then measured outcomes of cognition, amyloid plaque burden, proinflammatory cytokine expression, and oxidative stress [90, 92]. Amyloid plaque burden was significantly reduced in EP1 knockout mice expressing both the Swedish amyloid precursor protein (APP) and PS1 mutations, which were identified in human familial AD [90]. These mice, when exposed to either LPS or ischemia, were shown to have less neuronal injury and lower secretion of proinflammatory cytokines, TNF α and IL-6, than their WT counterparts [95, 96]. As with any genetic model, potential developmental differences temper interpretation of the data. WT mice exposed to ischemia by carotid occlusion and then treated with SC-51089, a highly specific EP1 antagonist, were shown to have similar neuroprotective phenotypes to EP1 knockout mice [96, 97]. These experiments have yet to be replicated in experimental AD *in vivo*, but SC-51089 showed highly reduced A β neurotoxicity in a neuroblastoma cell line (MC65) and in primary neuron cultures [98, 99]. These data support EP1 as a potential therapeutic target for AD, and a highly selective antagonist such as compound SC-51089, as a potential effector. However, to our knowledge, this drug or those like it have not been clinically tested in AD.

The other three PGE₂ receptors have been evaluated in a similar manner to EP1. EP2 receptor knockout AD mice showed reduced oxidative damage in comparison with controls, and, when given a bone marrow transplant of wild type macrophages, showed reduced A β plaque size [91, 100]. Interestingly, EP2 receptor knockout mice have cognitive deficits at baseline suggesting an important role for EP2 receptor signaling for neurodevelopment or normal cognitive functioning, and dampening enthusiasm for EP2 receptor clinical trials until the mechanism of this effect is better understood and can be effectively addressed [101]. EP3 receptor deficient AD mice demonstrated reduced proinflammatory gene expression, cytokine production, oxidative stress, and plaque production, as did EP4

receptor knockouts, which additionally demonstrated reduced atherosclerosis [46, 93, 102]. EP4 antagonist AE30208 acted to improve cognitive function and reduce A β plaques in an AD model [93]. All PGE₂ receptors show positive correlations with A β toxicity in culture and *in vivo*, and therefore represent a class of potential therapeutic targets with the potential to circumvent some of the toxic side effects of NSAIDs. In experimental AD, compounds SC-51089 and AE30208, which target EP1 and EP4, respectively, appear to have some efficacy. Availability of selective EP2 and EP3 receptor antagonists has been limited until recently, and therefore pharmacologic manipulation in experimental AD is less studied, but EP2 and EP3 receptor agonism has been shown to increase APP holoprotein concentrations and infarct size in ischemic insults in mice [103, 104].

7. Potential Prostaglandin Pathway Therapeutics

Understanding which receptor driven pathways are responsible for the neuroinflammation seen in AD requires additional PGE₂ receptor compounds to be tested in AD models. These drugs are available, have been used for diverse other studies, and may ultimately have therapeutic value for AD (Table 2). ONO-8713, ONO-8711, and SC-51089 are the most specific and favored EP1 antagonists and have been used effectively in models of colon/intestinal and urinary bladder inflammation [105–107]. SC-51089 was shown to be neuroprotective in AD [96, 97], while ONO-8713 and ONO-8711 have not been tested. EP1 agonists such as Iloprost and ONO-D1-004 might be expected to cause neurotoxicity in light of the neuroprotective phenotype of EP1 knockout mice, but these studies have not been done. PF-04418948 is a recently developed, highly selective EP2 antagonist created by Pfizer [108]. While the less specific AH-6809 (EP2 antagonist) has been shown to reduce levels of APP holoprotein in experimental AD, treatment with PF-04418948 has not been reported. Conversely, butaprost, the only EP2 agonist tested so far in experimental AD, was shown to increase levels of APP holoprotein [103]. Compounds AH-13205 and ONO-AE1-259 have been used in bronchodilation and airway smooth muscle research and remain strong candidates for testing in experimental AD [109, 110]. EP3 deficient mice were shown to have reduced proinflammatory gene expression, cytokine production, oxidative stress, and plaque production. ONO-AE3-240 and DG041 are widely used EP3 antagonists used in urinary system research and stroke models, but there is no *in vivo* testing reported to date with these drugs that corroborates results of EP3 deficiency in experimental AD [111, 112]. Of the EP3 effectors, the most specific agonists are ONO-AE-248 and SC-46275 and are currently primarily used for arterial vessel research [113, 114]. Treatment of AD mice with the highly specific EP4 antagonist, ONO-AE3-208, resulted in an increase in cognitive function and decrease in A β plaque [93]. In addition to ONO-AE3-208, GW627368 and L-161, 982 are highly specific EP4 antagonists that need to be evaluated. None of these drugs have been tested clinically.

Though PGE₂ is the principal prostaglandin in the CNS and is of primary interest, prostaglandin receptors to PGD₂, PGF_{2a}, and TXA₂ have all been shown to have biological relevance in AD (Table 2) [115–117]. Frontal cortical brain samples from later diagnosed AD patients had decreased microsomal PGD₂ and PGF_{2a} production [118]. In LOAD brain samples, PGD₂ synthase was found to be highly associated with A β plaques [119]. Additionally, PGD synthase/transferrin complex levels were found to be six times higher in LOAD and MCI patients than in controls [120]. Taken together, observational data indicates that PGD₂ is associated with AD clinical and neuropathological phenotype. Experimental studies suggest that A β plaques may modulate PGD₂ synthesis by interfering with PGD₂ synthase. In microglia/neuron co-cultures, BW245C and SQ27986, both DP (PGD₂ receptor) agonists, were shown to result in microglia-mediated neuronal toxicity. Conversely, neuroprotective properties have been ascribed to DP antagonist BWA868C, presenting a possible pathway for therapeutic drug intervention [121]. The role of PGF_{2a} and

TXA₂ in AD is less clear. Both molecules are elevated in urine samples from probable AD patients [122, 123], and administration of thromboxane receptor (TP) antagonists Daltroban and S18886 result in a reduction of A β . Conversely, TP receptor agonist I-BOP resulted in increased A β levels, further demonstrating the therapeutic potential of modulation of individual prostaglandin receptor effectors [124, 125]. Other non-PGE₂ receptors and drugs can be found in Table 2. It should be noted that there are currently no specific FP receptor antagonists.

8. Conclusion

Over 30 epidemiological studies have been reported on NSAIDs in AD, most indicating NSAID administration was associated with reduced incidence of AD [13], but NSAID toxicity has complicated efforts for long term prevention trials. Further studies are needed to identify downstream targets of COX cascades to deliver this therapeutic benefit whilst avoiding intolerable side effects. Chief among these COX-dependent pathways are the prostaglandins and PGE₂. While NSAIDs result in broad suppression of prostaglandin signaling through COX inhibition, selective prostaglandin receptor effectors have the potential advantage of targeting mechanisms specific to pathogenesis whilst sparing pathways critical for other aspects of normal neuro- and peripheral immunoregulation. There is much to be learned, but studies demonstrating improved cognitive function, reduced plaque burden, and suppressed free radical injury through antagonism of EP1, EP4, DP, and TP receptors hold promise for future targeted drug therapies. There are currently an abundance of prostaglandin receptor agonists and antagonists that are readily available and have been tested in diverse models of inflammatory disease. However, only a scant few of these effectors have ever been tested for efficacy in experimental AD. Future studies are needed to determine which molecular components of the prostaglandin pathway can be targeted for as preventive or therapeutic interventions for AD.

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Figure 1.

Generalized prostanoid signaling scheme. PLA₂-dependent hydrolysis of membrane phospholipids liberates AA, providing substrate for COX-1 and COX-2. Stepwise oxygenation and peroxidation reactions by COX enzymes yield PGH₂, which is then selectively converted to the various prostanoids by specific synthases. PGT then transports newly synthesized prostanoids to the extracellular compartment where they are free to act as autocrine or paracrine activators of cell-surface G protein-coupled prostanoid receptor subtypes. Preferred G_α subunit coupling is also denoted for each prostanoid receptor subtype. PLA₂ (phospholipase A₂); AA (arachidonic acid); COX (cyclooxygenase); PGG₂ (prostaglandin G₂); PGH₂ (prostaglandin H₂); PGE₂ (prostaglandin E₂); PGD₂ (prostaglandin D₂); PGF_{2α} (prostaglandin F_{2α}); PGI₂ (prostaglandin I₂); TXA₂ (thromboxane A₂); mPGES (microsomal PGE synthase); cPGES (cytosolic PGE synthase); PGDS (PGD synthase); PGFS (PGF synthase); PGIS (PGI synthase); TXS (TXA synthase); PGT (prostaglandin transporter); EP1 – 4 (PGE receptor 1 – 4); DP (PGD receptor); FP (PGF receptor); IP (PGI receptor); TP (TXA receptor).

Table 1

Results from randomized, double-blinded, placebo-controlled clinical trials using currently prescribed NSAIDs.

Drugs	No. of subjects	Primary outcome measure	Results	Pre-treatment state	References
Celecoxib	425	^a ADAS-cog and ^b CIBIC+	Did not slow the progression	Mild-to-moderate AD	[126]
Celecoxib or Naproxen	2528	Incidence of AD	Reduction in AD incidence among asymptomatic enrollees who were given naproxen. High incidence of adverse side effects for both drugs	Symptomatic AD	[37]
Ibuprofen	132	^a ADAS-cog	Did not slow the progression	Mild-to-moderate AD	[127]
Prednisone	138	^a ADAS-cog	Did not slow the progression	Probable AD	[128]
Rofecoxib	692	^a ADAS-cog and ^b CIBIC+	Did not slow the progression	Mild-to-moderate AD	[129]
Rofecoxib	1457	Percentage of patients with a clinical diagnosis of AD	Did not slow the progression	MCI	[130]
Rofecoxib or Naproxen	351	^a ADAS-cog	Did not slow the progression	Mild-to-moderate AD	[131]
Triflusal	257	^a ADAS-cog	Triflusal therapy was associated with a significant lower rate of conversion to dementia	MCI	[132]

ADAS-cog (Alzheimer Disease Assessment Scale- Cognitive); CIBIC+ (Clinician's Interview Based Impression of Change with caregiver input); AD (Alzheimer's Disease); MCI (mild cognitive impairment).

Table 2

Effect of prostanoid receptor subtype-specific agonists and antagonists on Alzheimer's disease-related outcomes *in vitro* and *in vivo*.

Receptor	Effect	Drug	AD outcome	Reference
EP1^a	Antagonist	SC-51089	↓Neuronal Injury	[96]
			↑ Neuroprotective	[97]
			↓ Aβ toxicity	[98]
EP2	Agonist	Butaprost	↑ APP holoprotein	[103]
EP2	Antagonist	AH-6809	↓ APP holoprotein	[103]
EP4^a	Antagonist	ONO-AE3-208	↑ Cognitive function	[93]
			↓ Aβ plaque	
DP^a	Agonist	BW245C	↑ Neuronal damage	[121]
DP^a	Agonist	SQ-27986	↑ Neuronal damage	[121]
DP^a	Antagonist	BWA868C	↑ Neuroprotective	[121]
TP	Agonist	I-BOP	↑ Aβ production	[124]
TP^a	Antagonist	Daltroban	↓ Aβ production	[124]
			↓ APP production	[125]
TP^a	Antagonist	S18886	↓ Aβ production	[124]
			↓ APP production	[125]

Aβ (amyloid beta); APP (amyloid precursor protein);

^a Highly specific effector.