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Anti-inflammatory actions of peroxisome proliferator-activated receptor gamma agonists in Alzheimer's disease

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Abstract

The role of inflammatory processes in the brains of Alzheimer's Disease (AD) patients has recently attracted considerable interest. Indeed, the only demonstrated effective therapy for AD patients is long-term treatment with non-steroidal anti-inflammatory drugs (NSAIDs). The mechanistic basis of the efficacy of NSAIDs in AD remains unclear. However, the recent recognition that NSAIDs can bind to and activate the nuclear receptor peroxisome proliferator-activated receptor gamma (PPARγ), has offered an explanation for the action of these drugs in AD. PPARγ activation leads to the inhibition of microglial activation and the expression of a broad range of proinflammatory molecules. The newly appreciated anti-inflammatory actions of PPARγ agonists may allow novel therapies for AD and other CNS indications with an inflammatory component. © 2001 Elsevier Science Inc. All rights reserved.

Keywords: Alzheimer's disease; NSAIDs; Inflammation; Microglia; Peroxisome proliferator-activated receptors; Cyclooxygenases

1. Introduction

The involvement of an inflammatory response in the etiology of Alzheimer's disease (AD) has recently received considerable attention. There is now a persuasive body of evidence describing a significant inflammatory component in this disease [31]. The recognition that a local inflammatory response within the brain contributes to the pathophysiology of the disease has resulted from the work over the past decade of a small and dedicated cadre of workers who have documented the presence of a large number of inflammatory molecules present at elevated levels in the AD brain [59]. These data have recently been comprehensively reviewed [1].

Abundant, activated microglia are invariably found to be associated with amyloid deposits in the AD brain [42,52], as well as in transgenic mouse models of AD that develop extensive plaque pathology [6]. Microglia interact with β-amyloid plaques through cell surface receptors linked to tyrosine-kinase based proinflammatory signal transduction cascades [3,16,40,41]. The interaction of microglia with the deposited fibrillar forms of β-amyloid leads to the conversion of the microglia into an activated phenotype and results in the synthesis and secretion of cytokines and other acute phase proteins which are neurotoxic [14]. The inflammatory activation of the microglia results in a feed-forward, fulminating activation of these cells as well as the surrounding astrocytes, culminating in the synthesis of proinflammatory products which are ultimately toxic to neurons.

An extensive body of epidemiologic evidence has convincingly demonstrated that inflammatory processes play a critical role in AD risk and progression [7]. It had been observed that patient populations treated with non-steroidal anti-inflammatory drugs (NSAIDs) exhibited a 55% decreased risk of AD [43]. AD patients receiving long-term NSAID therapy exhibited later onset of the disease, reduced symptomatic severity, and significantly slowed the rate of cognitive impairment [55]. In a recent prospective study, Stewart et al. reported that patients evaluated in the Baltimore Longitudinal Study of Aging had a 60% reduction in risk for AD if they were treated with NSAIDs for a two year period [63]. The putative target of NSAID action is thought to be microglia associated with the senile plaques. This view is supported by a compelling study by Mackenzie and Munoz documenting that patients receiving long term NSAIDs

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therapy exhibit a 65% reduction in plaque-associated reactive microglia [39].

The canonical targets of NSAID actions are the cyclooxygenases (COX), which are effectively inhibited by this class of drugs. However, a recent clinical trial found that a COX-2 selective inhibitor had no effect in disease progression in Alzheimer patients, suggesting that the protective effects of NSAIDs might be mediated through other mechanisms [61].

It is of particular importance that Lehmann et al. have identified a novel target of NSAID actions, the ligand-activated nuclear receptor peroxisome proliferator-activated receptor gamma (PPARγ) [35]. NSAIDs directly bind to PPARγ and activate its transcriptional regulatory activities. PPARγ has been shown to inhibit the expression of a wide range of proinflammatory genes [24,46,57]. These findings suggest that the anti-inflammatory effects of NSAIDs may not occur exclusively through their inhibition of cyclooxygenases, but rather may occur as a consequence of the ability of these drugs to directly activate PPARγ and inhibit proinflammatory gene expression [15,27,28,58]. The recognition that NSAIDs are PPARγ agonists has been argued to explain the discrepancy between clinically efficacious doses of NSAIDs which are typically achieved only at NSAIDs doses substantially greater than those required for inhibition of cyclooxygenases, but consistent with occupancy of PPARγ [30]. It is noteworthy that some studies examining the efficacy of NSAIDs in AD have shown that aspirin and acetaminophen are not linked to a reduction in AD risk, although they are very effective inhibitors of cyclooxygenases [7,63]. It remains controversial whether aspirin use confers a reduced risk of AD, as other studies have shown its use to be associated with a reduced occurrence of AD [2,8,9]. Aspirin acts through a cyclooxygenase-independent mechanism to inhibit the activation of proinflammatory gene expression through direct inhibition of the NFkB pathway [71]. Thus, there is a good correlation between epidemiologic studies that demonstrate a reduced risk of AD in the subset of NSAIDs that are PPARγ agonists [35].

There is a single report of PPARγ expression in the human brain. Kitamura and colleagues reported that PPARγ expression could be detected by Western analysis in the temporal cortex of the human brain [33]. Significantly, they found an approximate 50% increase in the amount of immunoreactive PPARγ protein in the brains of AD patients.

1.1. Peroxisome proliferator-activated receptors

The PPARs are a subclass of the the nuclear receptor superfamily of transcription factors. Ligand-activated nuclear receptors represent an important class of regulators of gene expression whose best recognized members include the steroid, thyroid, and retinoid receptors [5]. There are three PPAR genes, encoding the highly related receptor isoforms α, γ and β/δ (designated in the standardized nomenclature for nuclear receptors as: NR1C1, NR1C2 and NR1C3, respectively) that share a common structure and mechanism of regulation [69]. This nuclear receptor subfamily binds a diverse range of lipid ligands. Upon ligand binding, the transcriptional regulatory actions of the receptors are activated. The structure and biology of the PPARs have recently been reviewed [21,24,46,57,69,70].

PPARγ is the prinicipal isoform associated with the regulation of proinflammatory gene expression. PPARγ is expressed at highest levels in adipose tissue but is also found in the lymphocytes, vascular smooth muscle and myeloid cells. The best studied actions of PPARγ are its ability to regulate lipid metabolism and the differentiation of adipocytes. It has only recently been appreciated that PPARs also regulate proinflammatory gene expression [24, 46,57]. PPARγ acts to positively regulate the expression of a number of genes through transcriptional transactivation as well as to inhibit gene expression by transcriptional transrepression. These two distinct consequences of PPARγ activation are mediated through allied but mechanistically different processes.

PPARs are DNA binding proteins and are structurally similar to other members of the superfamily [48,67]. The PPARs possess a DNA binding domain positioned near the N-terminus of the molecule that is separated by a hinge region from the C-terminal ligand binding domain. The DNA binding domain has two zinc fingers which are highly conserved within this subfamily. The PPARs, like other members of the non-steroidal nuclear receptor superfamily, form heterodimers with the retinoid receptors (RXR) [5]. DNA binding requires paired PPAR-RXR recognition elements (termed PPREs) found in the promoters of target genes. Only one member of the heterodimeric receptor pair needs to bind ligand to elicit the transcriptional regulatory activity of the receptor. The ligand binding domain of the PPARs is characterized by a large binding pocket lined with a rather diverse range of putative interactive residues, accounting for the ability of the receptor to bind structurally distinct ligands [48,67]. Ligand binding induces a conformational change in the receptor, allowing its interaction with transcriptional co-activators.

1.2. PPARγ ligands

PPARγ can interact with a number of lipophilic ligands. Of particular interest is the ability of NSAIDs to bind to and activate PPARγ [35]. There is considerable controversy over the identity of the endogenous ligand for PPARγ [69]. A number of long chain polyunsaturated fatty acids and eicosanoids bind to PPARγ, including linoleic, eicosapentaenoic acid and docosahexanoic acid (DHA) [72]. It is not clear whether intracellular levels of these compounds are sufficient to activate PPARγ, and thus it remains uncertain if interactions with the endogenous fatty acids are biologically significant [69]. The cyclopentone prostaglandin, 15-deoxy$-\Delta$12,14 PGJ2 (PGJ2), binds to and activates PPARγ and there is a substantial literature suggesting that it is the

natural ligand for this receptor [23]. Indeed, PGJ2 exerts potent anti-inflammatory effects and inhibits cytokine expression. The interpretation of many of the studies on the anti-inflammatory effects of PGJ2 must be reevaluated in light of the recent reports that PGJ2 is a direct inhibitor of the IκB kinase, IKKα, and acts to inhibit NFκB activation [60,64]. Given the central role of NFκB in proinflammatory gene expression, many of the effects attributed to PPARγ may have arisen, at least in part, through the action of PGJ2 on the NFκB pathway. Recently, additional natural ligands have been identified that are components of oxidized low density lipoprotein. The modified oxidized lipids, 9-hydroxyoctadecadienoic acid (HODE) and 13-HODE, have been shown to bind and activate PPARγ [47].

The most prominent class of synthetic ligands that act as PPARγ agonists are the thiazolidinediones (TZDs) [69]. These compounds were developed as therapeutic agents for treatment of type II diabetes, as in adipose tissue PPARγ regulates fat cell differentiation, the expression of a number of enzymes of lipid metabolism and glucose uptake [50,62]. There are currently three members of the thiazolidinedione class (pioglitazone, Actos™; rosiglitazone, Advandia™; and troglitazone, Rezulin™) that have been approved by the FDA for treatment of type II diabetes [69].

Lehmann and colleagues found that a number of classic NSAIDs bind to PPARγ and activate its transcriptional acitivities [35]. Specifically, indomethacin, fenoprofen, flufenamic acid and ibuprofen act as PPARγ agonists. These findings suggest that the anti-inflammatory effects of NSAIDs may not occur exclusively through their inhibition of cyclooxygenases, but rather may occur as a consequence of the ability of these drugs to directly activate PPARγ and inhibit proinflammatory gene expression. Indeed, there is a poor correlation between therapeutically efficacious NSAID doses and COX inhibition [30]. Significantly, NSAIDs which act as PPARγ agonists have been linked to reduced risk of AD [7,63].

1.3. Mechanisms of transcriptional regulation by PPARγ

Transcriptional transactivation is mediated through the ligand-stimulated displacement of a transcriptional corepressor that is constitutively associated with the PPAR/RXR heterodimer. The transcriptionally inactive PPAR complex interacts in the nucleus with any of a number of corepressor molecules such as N-CoR or SMRT, suppressing its interaction with DNA and coactivators. The specific corepressor employed is likely to be distinct in different cell types. Upon ligand binding the corepressor is displaced, the receptor then associates with coactivator molecules and the complex then binds to the PPRE in the promoter of its target genes. The principal coactivators interacting with PPARγ are the ubiquitously expressed SRC-1 and functionally related molecules (e.g. PGC-1, PBP, TIF-2 and p/CIP). A second class of coactivators are the CREB binding protein (CBP) and its homolog p300. The transcriptionally active PPAR complex comprises a multimeric complex of SRC-1 and CBP/p300 assembled on the PPAR/RXR heterodimer [24]. The coactivators serve both to bridge the receptor complex to the basal transcriptional apparatus and to alter chromatin structure through their intrinsic histone acetylase activities. The assembly of these complexes on the promoter results in transcription of the target gene. In myeloid lineage cells, the B-class scavenger receptor CD36 is dramatically upregulated following PPARγ ligation. Recently, it has been suggested that the anti-inflammatory actions of the PPARs may also be mediated in part through the ability of this receptor class to induce the expression of IκB [20]. The presence of high levels of cytoplasmic IκB would serve to block the translocation of NFκB to the nucleus and act to inhibit proinflammatory gene expression.

1.4. Mechanisms of transcriptional transrepression by PPARγ

In myeloid lineage cells, the principal result of PPARγ activation is the inhibition of gene expression induced by inflammatory stimuli. PPARγ antagonizes the actions of the positively acting transcription factors AP-1, STAT and NFκB [58]. Dissection of the mechanism of PPARγ inhibition of the iNOS and COX-2 genes has led to the view that the transrepressive actions of PPARs do not involve the binding of the receptor to DNA, but rather through their capacity to bind and sequester coactivator molecules, preventing their association with the positively acting promoter elements [36,65]. PPARγ ligand binding results in dissociation of the corepressor from the nuclear PPAR/RXR complex and the subsequent association of the coactivator molecules SRC-1 in concert with CBP/p300. The amount of the coactivators is thought to be rate-limiting, thus, their sequestration by PPARγ arrests gene expression. PPARs are also thought to functionally inactivate the coactivator by conformationally constraining these molecules and thus inhibiting their interaction with the basal transcriptional apparatus [36]. The result of PPARγ agonist binding is the arrest of expression of a broad range of proinflammatory genes. The mechanism by which PPARs elicit transcription transrepression requires substantially higher levels of receptor occupancy, and thus higher ligand concentrations, since it involves sequestration of the bulk of the coactivators by the PPARγ-ligand complex. Indeed, the experimental data indicate that transrepression occurs at a higher drug concentration than that required for transactivation [58].

Several recent findings have suggested that PPARγ may also act to inhibit proinflammatory gene expression through its direct interaction with the transcription factors NFκB and c-jun. [19]. The data supporting this hypothesis is presently fragmentary. PPARγ has been shown to bind to both the p50 and p65 NFκB subunits in a ligand-independent manner and inhibit NFkB-dependent gene expression [12]. PPARγ has also been shown to block the action of the transcription factor AP-1 and it has been postulated that this effect is the

result of binding of PPARγ directly to c-jun, a mechanism similar to that recently demonstrated for PPARα [18]. PPAR ligands have recently been demonstrated to induce the expression of IkB [20] and repress the expression of c-jun [65]. These findings suggest that PPARγ may act through several distinct mechanisms to elicit its anti-inflammatory effects.

2. The role of PPARγ in inflammation

PPARγ plays a critical role in the regulation of inflammatory responses in a number of cell types. Of particular relevance to neuroinflammatory phenomena is the finding that activation of PPARγ by both synthetic and natural ligands blocked the phenotypic conversion of monocytes into reactive macrophages [15,56] and the activation of microglia [15].

2.1. Cytokines

There is now substantial evidence that PPARγ agonists have potent anti-inflammatory activity [21,24,46,57,69]. Ricote and Jiang and colleagues demonstrated that exposure of monocytes or macrophages to both synthetic and natural ligands of PPARγ resulted in the inhibition of expression of the proinflammatory cytokines IL-1β, IL-6, and TNFα [30, 58] and the chemokine MCP-1 gene [45].

2.2. iNOS

PPARγ agonists act in a broad fashion to suppress the expression of a number of genes which play critical roles in the proinflammatory response. PPARγ agonists inhibited inducible nitric oxide synthase (iNOS) expression in IFNγ-stimulated monocytes and macrophages [58]. Subsequently, PPARγ-mediated inhibition of iNOS expression has been described in a variety of cells such as macrophages, microglia, astrocytes, and neurons [13,27,32,58]. iNOS expression has been shown to provoke neuronal cell death. Importantly, a number of studies in rodent models of stroke, multiple sclerosis and neurodegeneration have demonstrated a neuroprotective action of iNOS inhibitors [26]. iNOS is found to be induced in neurons that undergo neurodegenerative changes in the brains of patients suffering from AD [68].

The induction of iNOS expression in neurons by IFNγ and LPS was antagonized by the PPARγ agonists troglitazone and PGJ2 both in vitro [27] and in vivo [28]. iNOS induction in response to LPS and various cytokines resulted in NO-dependent apoptotic cell death which was blocked by exposure of neurons to the PPARγ agonists and NSAIDs. Ogawa and colleagues reported that β-amyloid-induced iNOS expression in macrophages was inhibited by indomethacin and ibuprofen, but not aspirin [49]. Thus inhibition of both glial and neuronal iNOS by PPARγ-agonists may exert neuroprotective effects in a variety of CNS inflammatory disorders, including AD.

The molecular details of the mechanism of repression of iNOS gene transcription have recently been reported by Li et al. [36]. The inhibition of iNOS expression is due principally to the stable interaction of PPARγ with a complex of the coactivators, SRC-1 and CBP/p300. Competitive binding of PPARγ to limiting amounts of these coactivators prevented their association with AP-1 and NFκB elements in the iNOS promoter, thereby blocking promotor activity and the synthesis of iNOS [36].

2.3. Cyclooxygenase-2

The COX-2 gene is an immediate early gene that is rapidly induced in response to a variety of stimuli and in many cell types. The induction of COX-2 results in the acute upregulation of prostaglandin synthesis. The principal enzymatic product of COX-2 that has been postulated to have a role in proinflammatory responses is prostaglandin E2 and it has been argued that this proinflammatory product participates in the etiology of AD [51]. COX-2 levels in the AD cortex were reported to be elevated by 50% over age-matched control patients [33]. The argument that COX plays a role in the etiology of AD is derived principally from the epidemiologic studies demonstrating a protective effect of NSAIDs in AD, rather than compelling evidence that prostaglandins have deleterious actions in the CNS [15]. Combs et al. have recently demonstrated that β-amyloid stimulated COX-2 expression in primary microglia and in monocytes was inhibited by the PPARγ agonists troglitazone and PGJ2 [15]. In agreement with these studies, Kitamura et al. have reported that the NSAIDs indomethacin and PGJ2 inhibit COX-2 expression in mixed glial cultures [33], a finding similar to that reported in macrophages by Inoue et al. [29].

Subbaramaiah and colleagues have nicely dissected the mechanism by which PPARγ acts to inhibit COX-2 expression [65]. The induction of COX-2 in macrophages requires the binding of AP-1 (a c-fos and c-jun heterodimer) to the CRE element in the COX-2 promoter. PPARγ acts to prevent AP-1 binding to the promoter through two independent mechanisms. First, PPARγ ligands block the expression of the c-jun gene, thus preventing the formation of a functional AP-1 complex and resulting in the inhibition of promoters requiring AP-1 promoter elements for gene expression. In addition, the ligand-bound PPARγ associates with both CBP and p300, sequestering these coactivators and preventing their interaction with the promoter-associated AP1 complex (and presumably other transcription factors) in a fashion directly analogous to that reported for inhibition of iNOS expression [36]. These complementary mechanisms serve to silence the COX-2 gene.

The discussion of the action of COX 1 and 2 and their enzymatic products have been focused principally on the proinflammatory actions of these molecules; however, re-

cent evidence suggests that the cyclooxygenases are responsible for the production of anti-inflammatory compounds. It has recently been appreciated that COX-2 activation results in the production of the anti-inflammatory cyclopentenone prostaglandins, principally PGJ2. These prostanoids are produced during the later stages of an inflammatory response [25]. The cyclopentenone prostaglandins act to inhibit inflammatory gene expression through a direct inhibition of IκB kinases, and thus inhibition of NFκB activation, as well as through binding of PGJ2 and activation of PPARγ [25,60,64].

2.4. Other targets of PPARγ action

PPARγ inhibits the expression of other proinflammatory genes. Ricote et al. demonstrated that the synthesis of the metalloproteinase 9 (MMP9; also termed gelatinase B) that is induced upon macrophage activation was inhibited by PPARγ agonists [58]. This effect was shown to be a consequence of PPARγ acting directly on the promoter of the MMP9 gene through antagonism of positively acting AP-1 elements. Similarly, expression of the A class scavenger receptor, SRA, was blocked by PPARγ agonists [58].

2.5. Alternative mechanisms of action of PPARγ agonists

A criticism of the studies on the anti-inflammatory actions of PPARγ agonists, and TZDs in particular, has been that high levels of these agents are required to elicit anti-inflammatory effects. The anti-inflammatory actions are typically observed at concentrations that do not correspond well with the binding affinity of the receptor. Whether this is a reflection of the bioavailibility of the drug or that there are other mechanisms of drug action is presently controversial. It has been reported that some TZDs exhibit anti-diabetic actions while failing to significantly activate PPARγ [38,54]. Recent studies using macrophages in which the PPARγ gene was knocked out revealed that TZDs exhibited anti-inflammatory activity at high drug concentrations [11,44]. These findings demonstrate that the TZDs can operate through non-PPARγ dependent mechanisms, perhaps through binding of these drugs to the related PPARα isoform.

3. PPARγ actions in the CNS

3.1. Microglia

PPARγ is constitutively expressed in microglial cells and monocytes [4,14,34], and is upregulated following activation of the cells [58,66]. β-amyloid treatment of monocytes and microglia results in their proinflammatory activation and stimulation of the synthesis and secretion of neurotoxins. Combs et al. have reported that treatment of either microglia or monocytes with PPARγ agonists arrested the secretion of the neurotoxic factors [15]. This study also demonstrated that the PPARγ agonists inhibited the β-amyloid induced stimulation of IL-6 and TNFα expression. This effect was observed following treatment of the cells with the PPARγ agonists ciglitazone and troglitazone, the NSAIDs ibuprofen and indomethacin, as well as the natural PPARγ ligands PGJ2 and DHA. The phenotypic activation of monocytes by phorbol ester and microglia by β-amyloid was also blocked by PPARγ ligands, as was the expression of the complement receptor CR3/Mac1. Activation of PPARγ also resulted in the greatly reduced expression of β-amyloid-stimulated expression of COX-2 in both monocytes and microglia. This latter finding was also reported by Kitamura and colleagues using mixed glial cultures [33]. Bernardo et al. reported that activation of microglia with LPS or IFNγ resulted in the induction of iNOS, TNFα and MHC class II expression that was fully suppressed by treatment with PGJ2 [4]. Similarly, Van Eldik and colleagues reported that microglial activation resulted in the induction of iNOS expression that was effectively suppressed by PGJ2 [53]. The latter author's conclusion that PGJ2 may act through mechanisms independent of PPARγ has subsequently been substantiated by the demonstration that PGJ2 does indeed inhibit NFκB-stimulated gene expression through direct inhibition of IκB kinases [60,64].

Lim et al. have recently published a provocative study in which ibuprofen was administered to an animal model of AD [37]. In APP-overexpressing Tg2576 mice fed ibuprofen for 6 months, there was a reduction in the amount of IL-1β in the brain and reduced levels of activated microglia. The transgenic animals also exhibited a significant reduction in the amount of soluble β-amyloid in the brain and reduced the area occupied by amyloid plaques. It is not clear whether this is due to the action of ibuprofen on PPARγ or on the cyclooxygenases. The high levels of ibuprofen administered to the animals are likely to be sufficient to activate PPARγ. Indeed, Combs et al. have argued that the effects of NSAIDs is likely a consequence of their activation of PPARγ rather than acting on their canonical targets, the cyclooxygenases [15].

3.2. Astrocytes

There is only a small literature on the action of PPARγ agonists in astrocytes. Astrocytes from rat brain were reported to express all three PPAR isoforms [17] with those derived from adult cortex expressing PPARγ at higher levels than those from neonates. Kitamura and colleagues have reported that PPARγ agonists inhibit iNOS expression in mixed rodent glial cultures provoked by treatment of the cells with IFNγ and LPS [32]. These cultures are approximately 90% astrocytes, so it is likely that the iNOS inhibition by PPARγ activators observed in these studies reflects the effects of the drugs on this cell type. Microglial cells also respond to PPARγ agonists by suppression of iNOS expression however, and the mixed nature of the cultures

does not allow firm conclusions to be drawn as to the relative contribution of each cell type to the observed effects. These authors have also demonstrated that treatment of the mixed glial cultures with PPARγ agonists resulted in the induction of heme oxygenase-1 [32].

Chattopadhyay et al. reported that the PPARγ agonists ciglitazone and PGJ2 reduced the viability of primary human astrocytes within 4 h and induced apoptosis. The authors also reported that PPARγ agonists provoked apoptosis of the malignant human astrocytoma cell line T98G [10]. These latter findings are consistent with our observation that transformed astrocytic cell lines respond to PPARγ agonists by induction of apoptosis (Heneka et al., unpublished observations). However, we failed to observe this effect with primary rodent astrocytes under similar conditions [22]. The susceptibility of transformed or neoplastic cells to induction of apoptosis by PPARγ activation has been well documented in a number of cell types, although the molecular basis of this effect is presently unclear [24,46].

3.3. Neurons

There are only two reports of the actions of PPARγ agonists in neurons [27,28]. Treatment of primary cerebellar granule cell cultures with the proinflammatory activators LPS and IFNγ, resulted in the induction of iNOS expression and subsequent apoptotic death of the neurons arising from the action of NO and its immediate metabolites. If the cells were treated with the PPARγ agonists ciglitazone and PGJ2 iNOS expression was inhibited and enhanced neuronal survival was observed. A similar effect was observed following treatment with the NSAIDs ibuprofen and indomethacin, suggesting that NSAIDs exert their actions through their capacity to bind and activate PPARγ. These studies have been extended into an animal model in which LPS and IFNγ were injected into the cerebellum of rats resulting in the induction of neuronal iNOS expression and death of neurons at the site of injection [28]. If, however, PPARγ agonists troglitazone, ibuprofen or PGJ2 were injected simultaneously, the iNOS induction was suppressed and cell death was significantly attenuated.

4. Conclusions

The recent recognition that PPARγ plays important roles in the regulation of proinflammatory gene expression has provided new insight into the roles this transcription factor plays in the nervous system. It is of importance to determine if the efficacy of NSAIDs in reducing AD risk is a result of the action of these drugs on PPARγ. The discovery of the anti-inflammatory actions of PPARγ agonists argue that these compounds may be valuable in the treatment of other CNS inflammatory diseases. The availability of potent, FDA approved PPARγ agonists should facilitate the clinical evaluation of the efficacy of these compounds.

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