# PPARγ Agonists as Therapeutics for the Treatment of Alzheimer's Disease

Gary Landreth,* Qingguang Jiang,* Shweta Mandrekar,* and Michael Heneka†

*Alzheimer Research Laboratory, Department of Neurosciences, Case Western Reserve University School of Medicine, Cleveland, Ohio 44106; †Department of Neurology, Molecular Neurobiology Unit, University of Munster, Munster, 48149, Germany

**Summary:** Alzheimer's disease (AD) is characterized by the deposition of β-amyloid within the brain parenchyma and is accompanied by the impairment of neuronal metabolism and function, leading to extensive neuronal loss. The disease involves the perturbation of synaptic function, energy, and lipid metabolism. The development of amyloid plaques results in the induction of a microglial-mediated inflammatory response. The nuclear receptor peroxisome proliferator-activated receptor gamma (PPARγ) is a ligand-activated transcription factor whose biological actions are to regulate glucose and lipid metabolism and suppress inflammatory gene expression. Thus, agonists of this receptor represent an attractive therapeutic target for AD. There is now an extensive body of evidence that has demonstrated the efficacy of PPARγ agonists in ameliorating disease-related pathology and improved learning and memory in animal models of AD. Recent clinical trials of the PPARγ agonist rosiglitazone have shown significant improvement in memory and cognition in AD patients. Thus, PPARγ represents an important new therapeutic target in treating AD.
**Key Words:** Peroxisome proliferator-activated receptor gamma, thiazolidinedione, Alzheimer's disease, amyloid beta, inflammation, apolipoprotein E.

## INTRODUCTION

The nuclear receptor peroxisome proliferator-activated receptor gamma (PPARγ) is a newly recognized therapeutic target for the treatment of Alzheimer's disease (AD). This review provides an overview of the biological actions of this ligand-activated transcription factor, and it addresses some of the central issues that have arisen with the use of its agonists as a treatment of AD. Despite the fact that the thiazolidinedione (TZD) class of PPARγ agonists is widely prescribed for the treatment of type II diabetes mellitus, comparatively little is known about PPARγ actions in the brain. Recently, agonists of PPARγ have been shown to be efficacious in a number of CNS disease models[1], and this has stimulated investigations examining the underlying biological actions of these receptors in the brain. The suggestion that PPARγ might be of utility in treatment for AD arose from consideration of its effects on insulin action, energy metabolism, lipid metabolism, and inflammation. This discussion is particularly timely as the outcomes of the first clinical trials of these drugs are being reported.[2] The mechanisms subserving their actions in AD are presently unclear. Thus, an active debate of these issues is needed as these agents are being advanced into phase III clinical trials for the treatment of AD. Several potential mechanisms have been proposed as rationales for the therapeutic use of PPARγ agonists in AD. There is presently no consensus on what is the dominant mode of PPARγ action, and it is probable that PPARγ agonists act through multiple parallel pathways to affect disease pathophysiology in both humans and animal models of the disease.

The PPARs are a family of three (α/γ/δ) related nuclear receptors that act as whole body lipid sensors, and each member functions to regulate a unique subset of genes responsible for lipid and energy metabolism.[3] The receptors act by mediating the body's response to dietary intake. PPARγ is of particular importance as this nuclear receptor acts to regulate both lipid and carbohydrate metabolism and participates in the regulation of serum glucose levels, as well as regulating insulin sensitivity.[4] The natural ligands of PPARγ include long-chain fatty acids, eicosanoids, oxidized lipoproteins, and lipids, cor-

Address Correspondence to: Gary Landreth, M.D., Department of Neurosciences, Alzheimer Research Laboratory, School of Medicine, Case Western Reserve University, 10900 Euclid Avenue, Cleveland, OH 44106. E-mail: gel2@case.edu.

responding well to its function in regulating the metabolic response to dietary lipid intake.[5] Thus, PPARγ has been targeted for drug development for the treatment of type II diabetes mellitus. Two thiazolidinedione (TZD) agonists of PPARγ, Actos (pioglitazone) (Takeda Pharmaceuticals North America, Inc., Deerfield, IL), and Avandia (rosiglitazone) (GlaxoSmithKline, Research Triangle Park, NC) are Food and Drug Administration-approved and widely prescribed for this disease. However, the use of these drugs for CNS treatments is under close scrutiny due to their poor blood-brain-barrier (BBB) permeability. Pioglitazone does pass the BBB, but it does so poorly.[6] The BBB permeability of rosiglitazone has been controversial. Rosiglitazone was initially characterized as BBB impermeant;[7] however, Strum et al.[8] have recently reported that the drug can be found in the brain after oral administration. A 7-day oral treatment regimen resulted in brain levels of rosiglitazone in the submicromolar range (0.26–0.45 μM).[8] It remains to be determined how rosiglitazone made its way into the brain, and whether this is also observed in humans.

## PPARγ regulation of gene expression

**Transactivation.** PPARγ is a ligand-activated transcription factor that binds to sequence-specific promoter elements of its target genes and directly regulates their expression.[9] The PPAR subfamily of nuclear receptors acts as dominant regulators of lipid metabolism.[3] These receptors rapidly transcriptionally transactivate gene expression in response to ligands that are directly obtained from the diet or generated through normal metabolic processes. PPARγ regulates a specific subset of genes, most prominently those responsible for lipid metabolism and storage.

PPARγ forms an obligate heterodimer with the retinoid X receptor. This receptor complex binds to PPAR responsive elements within the promoters of its target genes.[10,11] In the absence of ligand, the transcriptional activity of PPARγ is suppressed through its constitutive association with a nuclear corepressor complex, comprised of NCoR/SMRT and histone deacetylases. The corepressor complex maintains chromatin in a condensed state and prevents recruitment of coactivator complexes and transcriptional initiation. With binding of the ligand to the receptor, the corepressor complex is dismissed and the transcriptional coactivators are recruited to the promoter, initiating the formation of active transcription complex that is coupled to the basal transcriptional apparatus.[12]

## Anti-inflammatory actions of PPARγ

PPARγ agonists robustly inhibit pro-inflammatory gene expression and this effect underlies many of the beneficial actions of these drugs.[13] The major anti-inflammatory effect of PPARγ is to functionally inactivate NFκB-dependent promoters. Several mechanisms have been proposed to account for repression of gene expression.[14,15] However, Pascual et al.[16] have recently provided compelling evidence that PPARγ blocks NFκB-dependent gene expression through corepressor interference. Inflammatory genes are normally repressed through the association of the co-repressors—NCoR with the κBRE elements, present in the promoters of these genes. With ligand binding, a fraction of PPARγ in the nucleus becomes sumoylated, and these modified receptors then bind to the κBRE promoter element, preventing the dissociation of the repressor functionally inactivating the promoter and blocking gene expression. Agonists of PPARγ are attractive therapeutic agents owing to their ability to act broadly to inhibit inflammatory gene expression.

## Effects of PPARγ agonists in animal models of AD

Several studies using murine models of AD have been carried out to determine the therapeutic utility of PPARγ agonists in disease progression. Yan et al.[17] investigated the effects of a PPARγ agonist in Tg2576 mice. Aged Tg2576 mice (12-months old) with established plaque pathology were treated orally with pioglitazone (120 ppm, 20 mg/kg/day) for 4 months. Pioglitazone was used in these studies due to its ability to pass the BBB, albeit poorly.[6] The nonsteroidal anti-inflammatory drug, ibuprofen, served as a positive control in these experiments since Lim et al.[18] had previously shown plaque reduction in this animal model after oral ibuprofen therapy. Ibuprofen treatment resulted in approximately 60% reduction in plaque number. However, pioglitazone-treated animals did not exhibit a statistically significant change in plaque pathology. Both ibuprofen and pioglitazone treatment resulted in a small, but significant, reduction in the levels of soluble Aβ peptides. Ibuprofen-treated animals exhibited a dramatic reduction in soluble $A\beta_{42}$ levels. Although soluble $A\beta_{42}$ levels in pioglitazone-treated animals were lower, they did not reach statistical significance. In addition, pioglitazone had no effect on the number of activated microglia. This experiment demonstrated that pioglitazone exhibited effects on soluble Aβ levels in the brain; however, it did not significantly affect AD-related pathology or microglial-mediated inflammation. These findings were interpreted as evidence that the poor penetration of pioglitazone into the brain, due to its poor BBB permeability, limited its efficacy.

Heneka et al.[19] conducted a study using a dose of pioglitazone that was twofold higher (240 ppm; 40/mg/kg/day) in younger animals. They used a different mouse model that overexpresses human amyloid precursor protein (APP) with London mutation (V717I). These animals were treated at 10 months of age (just as they are beginning to exhibit plaque pathology) for only 7 days. Ibuprofen-treated animals comprised the controls for this study. The higher dosage of pioglitazone resulted in an

approximate 20 to 25% reduction in Aβ plaque burden and in $A\beta_{42}$ levels in the brain.[19] In addition, there was a significant reduction in microglial activation. This study provided the first conclusive evidence that PPARγ agonists could suppress AD-related pathology.

In another study, Pedersen and Flynn[20] examined the effect of the PPARγ agonist rosiglitazone in Tg2576 mice. An unappreciated phenotype that these mice display is metabolic abnormality, including increased fasting serum glucocorticoid levels and insulin resistance. A 6- week treatment of rosiglitazone restored insulin responsiveness in these mice[20] and lowered glucocorticoid levels. Importantly, rosiglitazone treatment rescued behavioral deficits displayed by these mice.[7] The authors have argued that the improved behavior may result from suppression of glucocorticoid levels, as glucocorticoids have been well described to have negative effects on learning and memory and act to impair insulin receptor function.[21–23] This study suggests that rosiglitazone could elicit its effects by acting on peripheral systems. Rosiglitazone treatment did not result in any changes in Aβ plaque pathology, but selectively reduced brain $A\beta_{42}$ levels. This study noted that AD patients also exhibit elevated levels of plasma cortisol. The hypothesis that rosiglitazone reactions in the Tg2576 mice arise from its effects on peripheral glucocorticoid levels is compelling. Interestingly, although PPARγ agonists have not been previously reported to have analogous effects on glucocorticoids in humans, recent studies have suggested that rosiglitazone may be a short-term treatment option for hypercortisolemia in Cushing's patients.[24–26] However, the results of these studies are not conclusive[27] and the relevance of this mechanism to AD therapy warrants further investigation.

## Clinical trials

Two Food and Drug Administration-approved PPARγ agonists have been tested for their efficacy in AD patient populations. Watson et al.[28] have reported the results of a small clinical study examining the effects of rosiglitazone in patients with mild AD. They found that 6 months of drug treatment resulted in enhanced memory and cognitive function compared with placebo-treated control patients.[28] Geldmacher et al.[29] have studied of the actions of pioglitazone in mild to moderate AD cases. This study, designed primarily as a safety trial, demonstrated a small but statistically insignificant improvement in memory. PPARγ agonists have a generally favorable side effect profile, and are well tolerated and safe in the elderly.[30] Recently, however, rosiglitazone usage was found to be associated with an increased risk for cardiovascular side effects.[31] In contrast, pioglitazone has been found to be cardioprotective.[32]

The results of a phase II clinical trial, enrolling over 500 patients with mild to moderate AD, was recently reported by Risner et al.[2] These patients were treated with rosiglitazone (or placebo) for 6 months. Patients receiving rosiglitazone were found to have enhanced attention and memory, compared with those receiving the placebo. Importantly, patients possessing an *apolipoprotein E4* (*APOE4*) allele did not respond to the therapy. This latter observation is consistent with previous studies by Craft et al.[33–35] demonstrating a functional interaction of apolipoprotein E (ApoE) isoforms with efficacy of insulin action on cognition. A large phase III trial of rosiglitazone in AD patients is currently underway.

## Mechanisms of PPARγ agonist action

AD is a complex neurodegenerative disorder. The etiology of the disease has proven to be divergent with contributions from genetics, the environment as well as the normal aging process. There is ample evidence that multiple physiological functions are altered in AD. PPARγ exhibits pleiotropic physiological functions in multiple systems. Therefore, PPARγ agonists could exert their salutary effects in treating AD by regulating multiple aspects involved in AD, including Aβ homeostasis, insulin sensitivity, energy metabolism, lipid metabolism, and inflammation (FIG. 1).

**Aβ homeostasis.** PPARγ involvement in ameliorating AD-related pathology has been the focus of a number of recent studies that have been directed at dissecting the mechanisms through which PPARγ regulates Aβ metabolism. These studies have led to contradictory results. One mechanism through which PPARγ is able to accomplish this is by regulating Aβ production. When neuroblastoma cells (stably transfected with human APP) were stimulated with inflammatory cytokines, they activated the APP processing enzyme beta-secretase (BACE1), resulting in an increase in Aβ secretion. This was inhibited after PPARγ activation through its ability to suppress BACE1 transcription.[36] Indeed, there is a PPARγ response element in the promoter region of the BACE1 gene, and binding of PPARγ to this response element suppresses BACE1 expression and inhibits Aβ production.[37]

A subsequent study by d'Abramo et al.[38] reported that PPARγ activation resulted in inhibition of APP expression. Moreover, overexpression of PPARγ in cultured cells decreased Aβ secretion by promoting the increased ubiquitination of APP and subsequent degradation.

Camacho et al.[39] have reported an alternative mechanism by which PPARγ may affect Aβ homeostasis. They have shown that activation of endogenous PPARγ or overexpression of the receptor lead to the dramatically enhanced clearance of Aβ from the media of both neuronal and non-neuronal cells. The mechanism subserving this effect is unknown.

**Energy metabolism.** There is ample documentation that glucose utilization is impaired in brain regions in-

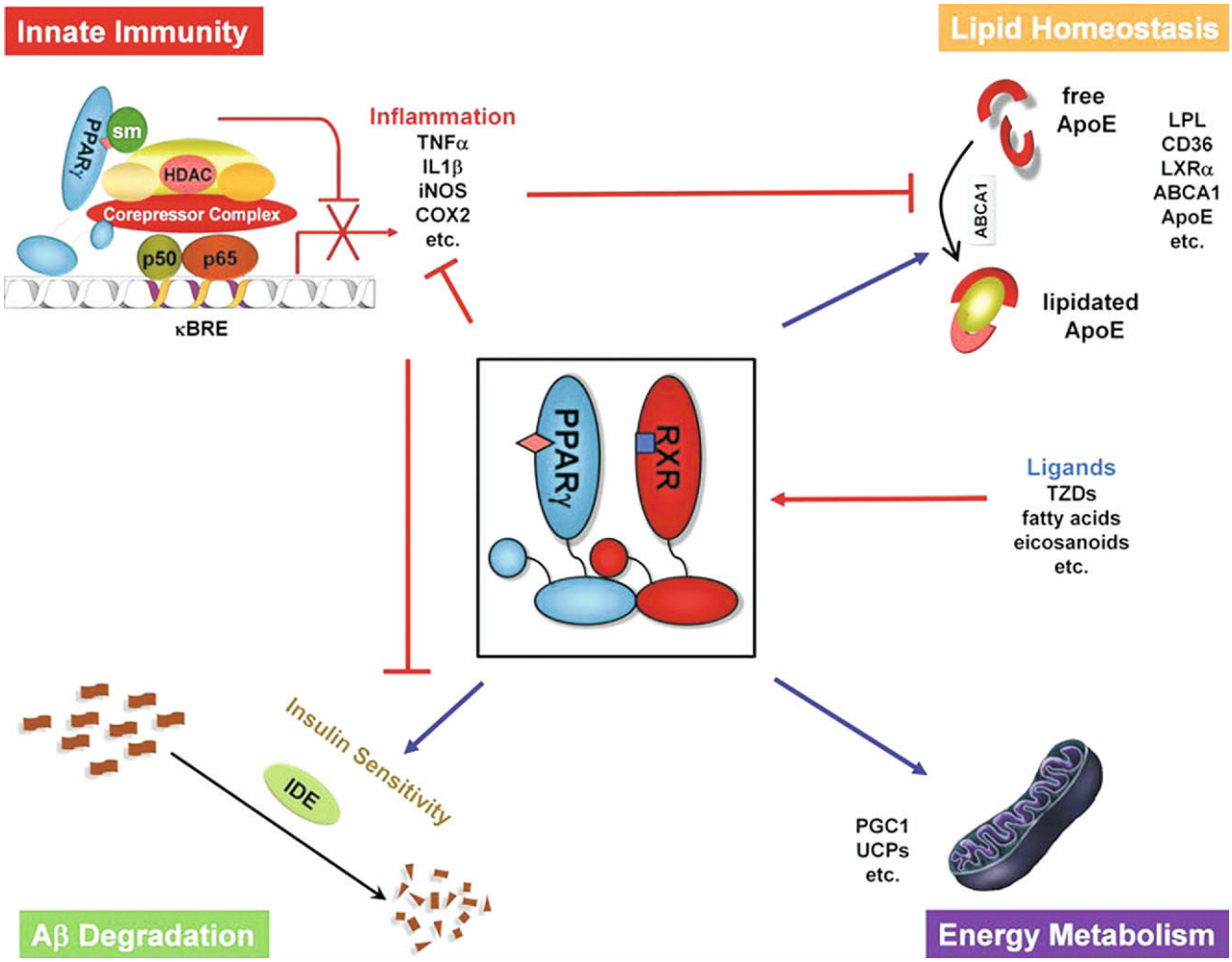


**FIG. 1.** Potential mechanisms of PPARγ in the treatment of Alzheimer's disease. ABCA1 = ATP-binding cassette A1; ApoE = apolipoprotein E; κBRE = kappa B response element; COX2 = cyclooxygenase 2; HDAC = histone deacetylase; IDE = insulin degrading enzyme; IL1β = interleukin 1 beta; iNOS = inducible nitric oxide synthase; LPL = lipoprotein lipase; LXRα = liver X receptor alpha; PGC1 = peroxisome proliferator-activated receptor gamma coactivator 1; RXR = retinoid X receptor; sm = small ubiquitin-related modifier; TNFα = tumor necrosis factor alpha; TZDs = thiazolidinediones; UCPs = uncoupling proteins.

volved in memory and cognition in AD patients. Significantly, AD patients exhibit impaired cerebral glucose metabolism before the symptomatic onset of the disease and in the absence of detectable structural changes in the brain.[40] Interestingly, several studies have also shown an *APOE4* dose-dependent impairment in glucose utilization in brain regions affected by the disease.[41–46]

PPARγ plays critical roles in energy metabolism due to its direct effects on mitochondrial function and ultimately ATP production. Mitochondria may be key players in the cerebral hypometabolism observed in AD, as this organelle plays critical roles in both energy metabolism as well as neuronal apoptosis. In the diseased brain, the numbers of neuronal mitochondria are greatly reduced and those remaining have very distinct morphological changes in their size and in the number of cristae they contain.[47] Roses et al.[48] have postulated that the PPARγ agonists act to improve mitochondrial function and this may be the basis of their beneficial effects on memory and cognition in AD patients.

PPARγ activation by pioglitazone resulted in a significant increase in mitochondrial DNA copy number as well as the expression of genes involved in mitochondrial biogenesis in fat tissue.[49] A recent study has found analogous changes within the brain in response to oral rosiglitazone treatment.[8] Strum et al.[8] have reported that PPARγ activation stimulated brain mitochondrial biogenesis and this stimulation was dependent on the ApoE isoforms. PPARγ may elicit these changes through the peroxisome proliferator-activated receptor gamma coactivator 1 (PGC1) family of proteins. These coactivators positively regulate mitochondrial function and metabolism.[50] PPARγ has been reported to stimulate the expression of PGC-1α,[51] which in turn, induces expression of the uncoupling proteins that stimulate mitochondrial biogenesis and respiration in muscle cells.[52–54] Proliferator-

activated receptor gamma coactivator 1 also stimulates the expression of a variety of genes that are vital for the mitochondrial oxidative phosphorylation pathway, as well as duplication of mitochondrial DNA content.[55,56] It should be noted that TZD agonists of PPARγ also have effects on mitochondrial metabolism that are receptor-independent.[57] The relationship between PPARγ, ApoE, and energy metabolism is not clear and warrants further investigation.

**Insulin sensitivity.** A number of studies have suggested that perturbation of insulin metabolism is associated with AD,[34,58–61] and individuals with type II diabetes mellitus are twice as likely to develop AD when compared with gender-matched healthy subjects.[62–67] Insulin resistance and hyperinsulinemia, two characteristics of type II diabetes mellitus, have been shown to have a high correlation with memory impairment and risk for AD. PPARγ agonists are widely prescribed for the treatment of type II diabetes mellitus. An extensive body of evidence demonstrates a critical role for PPARγ in the regulation of insulin sensitivity. The ability to activate PPARγ is closely correlated with the antidiabetic actions of TZDs, suggesting that receptor-dependent activation of PPARγ target genes may underlie the insulin sensitizing effect of this class of drugs.[68,69]

There is substantial evidence establishing a role of insulin in cognition. Insulin can pass across the BBB and enter the CNS via a receptor-mediated transport process. An acute increase in peripheral insulin concentrations results in the rapid elevation of CSF and brain insulin levels.[70] Insulin receptors in the mammalian brain have a very specific pattern of expression and are localized to the hippocampus and medial temporal cortex, both of which are areas associated with memory. In addition, brain insulin receptor signaling has been reported to be significantly reduced in AD, an indication of insulin resistance.[71,72] Craft et al.[73] have found that insulin administration improves memory. In addition, raising plasma insulin levels to those characteristic in insulin resistance is accompanied by parallel increases in plasma and brain levels of Aβ peptides and inflammatory markers.[74] Diet-induced insulin resistance is also associated with enhanced Aβ peptide levels and plaque formation, which was argued to arise from increased γ-secretase activity and lower IDE activity.[75]

It has been postulated that hyperinsulinemia in the brain may contribute to amyloid build-up due to inhibition of Aβ degradation by IDE, which degrades both insulin and Aβ peptides.[76,77] IDE levels have been shown to be reduced in the brains of AD patients and are further reduced by 50% in brains of AD patients homozygous for the *APOE4* allele.[78] Genetic ablation or partial loss of *Ide* leads to hyperinsulinemia and elevated Aβ levels.[79–81] It has been postulated that inhibition of IDE proteolytic activity may impair Aβ clearance, thereby initiating or accelerating the disease process. Recently, rosiglitazone has been shown to increase brain IDE levels in an animal model of AD.[82] Thus, *Ide* could potentially be responsible for the association between hyperinsulinemia and AD. However, it remains controversial whether this relationship is physiologically relevant, owing to the low levels of insulin in the brain.

**Dyslipidemia.** Genetic studies and epidemiological observations strongly suggest a relationship between dyslipidemia and AD. Elevated serum cholesterol levels have been reported to correlate with an increased incidence of AD.[83,84] Consistent with this linkage, individuals on statin therapy exhibit a greatly reduced risk (~70%) for AD.[85] Several genes regulating cholesterol homeostasis have been reported to be associated with AD, including *APOE*, *LRP1*, *ABCA1*, *NR1H2* + (*LXRβ*), *CYP46*, *ACAT*, and *CETP*,[86,87] and even PPARγ itself.[88,89] Little is known about the role of PPARγ in regulating CNS lipid metabolism.

The *APOE* gene is the best known bona fide risk factor for sporadic AD.[86] ApoE plays an important role in lipid transport throughout the body. It participates in lipoprotein metabolism, cholesterol homeostasis, and local lipid transport processes. In the brain, it is primarily synthesized and secreted within high-density lipoprotein (HDL) particles by astrocytes, and mediates the efficient transport and recycling of cholesterol within the CNS.[90–92] In humans, three naturally occurring variants of *APOE*, E2, E3, and E4 have been demonstrated to modify the risk or age of onset of late-onset AD (LOAD). The mechanism by which *APOE4* modifies the risk remains unknown, but has been postulated to play a role in Aβ clearance and deposition.

The lipidation of ApoE is carried out primarily by the ATP-binding cassette A1, which is a lipid transporter that mediates the loading of ApoE with phospholipids and cholesterol. ApoE acts as a structural scaffold for the formation of HDL particles. ABCA1 acts to regulate ApoE function in the CNS.[90,91] Recently, three independent groups, in four different animal models of AD, reported that inactivation of the *Abca1* gene facilitates Aβ fibrillogenesis and deposition within the brain.[93–95] Conversely, overexpression of human *Abca1* in mice resulted in reduced Aβ levels and plaque burden.[96] Importantly, the expression of the *Abca1* gene is transcriptionally regulated by the nuclear receptors, liver X receptors (LXRs), PPARγ, and RXR. The *NR1H2* gene has recently been reported to be genetically associated with AD.[97] Genetic ablation of either LXR genes results in increased number and size of plaques in an animal model of AD.[98] Thus, regulation of the lipidation status of ApoE is an important determinant of Aβ clearance and deposition.

A significant subset of the actions of PPARγ activation arises from its ability to induce the expression of a

related nuclear receptor, LXR$\alpha$. LXR$\alpha$ regulates genes that are involved in lipid metabolism and reverse cholesterol transport, including *Apoe* and *Abca1*, among others. It has been demonstrated that there is a reciprocal positive regulation of both receptors that comprises a feed-forward mechanism to orchestrate the expression of both classes of receptors. PPAR$\gamma$ activation stimulates LXR$\alpha$ expression and vice versa. Recent evidence suggests that this results in synergistic induction of both PPAR$\gamma$ and LXR target gene expression.[99] PPAR$\gamma$ agonists have been shown to increase both ABCA1 and ApoE mRNA and protein levels and this effect is believed to be secondary to its induction of LXR$\alpha$ expression.[100–102] Significantly, it has recently been reported that rosiglitazone treatment of mice expressing the human *APOE4* allele induces a two-fold increase in brain ApoE4 mRNA.[8]

ApoE has been demonstrated to play essential roles in axonal growth[103] and synaptogenesis.[104] These effects of ApoE are isoform-dependent with ApoE3 promoting and ApoE4 inhibiting neurite outgrowth.[105–109] Interestingly, Brodbeck et al.[110] have recently reported that ApoE4 exposure is associated with decreased dendritic spine density of cortical neurons and this effect could be ameliorated by treatment of cultured cortical neurons with rosiglitazone.[110]

**Inflammation.** The AD brain is characterized by a significant microglial-mediated inflammatory response. A$\beta$ plaque deposition results in the accumulation of microglia that become physically associated with deposited amyloid.[111] Microglia are the tissue macrophages of the brain and are derived from a myeloid lineage. The formation of A$\beta$ fibrils and their deposition in the parenchyma of the brain elicits the phenotypic activation of microglia.[112] The persistent activation of abundant plaque-associated microglia typifies the human disease and its murine models. The activation of A$\beta$-stimulated signaling pathways mediates the acquisition of a reactive, pro-inflammatory phenotype accompanied by the elaboration of a wide range of pro-inflammatory cytokines, chemokines, acute phase proteins, as well as reactive nitrogen and oxygen species. A number of inflammatory cytokines, chemokines, and activated glial markers have also been found at elevated levels in the AD brain.[113–117] The chronic activation of microglia and their production of pro-inflammatory molecules is postulated to accelerate the disease progress, culminating in neuronal death. Inflammation has been proposed to exacerbate amyloid deposition and disease progression, whereas anti-inflammatory therapies inhibit A$\beta$ generation and slow disease progress.

The role of PPAR$\gamma$ in regulating the microglial inflammatory responses has attracted substantial attention.[118] The anti-inflammatory actions of PPAR$\gamma$ agonists have been proposed to account for their positive effects in a number of animal models of CNS disease including AD.[1] There is extensive and compelling evidence that PPAR$\gamma$ agonists robustly suppress pro-inflammatory gene expression. PPAR$\gamma$ agonists have been reported to inhibit the expression of inflammatory cytokines, chemokines, matrix metallopeptidases (MMPs), cyclooxygenase 2 (COX-2) and inducible nitric oxide synthase (iNOS), each of which is reliant upon NF$\kappa$B-dependent transcriptional effects.[13] There are now over nearly 30 studies showing microglial activation in response to inflammatory stimuli, including fibrillar A$\beta$.[119] Heneka et al.[120] have shown that pioglitazone acts to suppress iNOS and COX2 expression in the brain of the murine model of AD. A recent study in aged mice has provided compelling evidence that rosiglitazone treatment is associated with elevated levels of the anti-inflammatory cytokine interleukin-4 in the brain, which the authors suggest may underlie the anti-inflammatory actions of PPAR$\gamma$ agonists.[121]

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