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## PPAR $\gamma$ AGONISTS AS THERAPEUTICS FOR THE TREATMENT OF ALZHEIMER'S DISEASE

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### Abstract

Alzheimer's Disease is characterized by the deposition of  $\beta$ -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 microglial-mediated inflammatory response. The nuclear receptor PPAR $\gamma$  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 PPAR $\gamma$  agonists in ameliorating disease-related pathology and improved learning and memory in animal models of AD. Recent clinical trials of the PPAR $\gamma$  agonist rosiglitazone have shown significant improvement in memory and cognition in AD patients. Thus, PPAR $\gamma$  represents an important new therapeutic target in treating AD.

### Keywords

Peroxisome Proliferator-Activated Receptor gamma; Thiazolidinedione; Alzheimer's Disease; Amyloid Beta; Inflammation; Apolipoprotein E

### Introduction

The nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) 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 addresses some of the central issues which have arisen with the use of its agonists as a treatment of AD. Despite the fact that the thiazolidinedione (TZD) class of PPAR $\gamma$  agonists is widely prescribed for the treatment of Type II diabetes mellitus, comparatively little is known about PPAR $\gamma$  actions in the brain. Recently, agonists of PPAR $\gamma$  have been shown to be efficacious in a number of CNS disease models<sup>1</sup> and this has stimulated investigations examining the underlying biological actions of these receptors in the brain. The suggestion that PPAR $\gamma$  might

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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.<sup>2</sup> 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 PPAR $\gamma$  agonists in AD. There is presently no consensus on what is the dominant mode of PPAR $\gamma$  action, and it is probable that PPAR $\gamma$  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 ( $\alpha/\gamma/\delta$ ) 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.<sup>3</sup> The receptors act by mediating the body's response to dietary intake. PPAR $\gamma$  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.<sup>4</sup> The natural ligands of PPAR $\gamma$  include long-chain fatty acids, eicosanoids, oxidized lipoproteins and lipids, corresponding well to its function in regulating the metabolic response to dietary lipid intake.<sup>5</sup> Thus, PPAR $\gamma$  has been targeted for drug development for the treatment of Type II diabetes mellitus. Two thiazolidinedione (TZD) agonists of PPAR $\gamma$ , Actos<sup>TM</sup>, (pioglitazone) and Avandia<sup>TM</sup> (rosiglitazone) are FDA-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 does so poorly.<sup>6</sup> The BBB permeability of rosiglitazone has been controversial. Rosiglitazone was initially characterized as BBB impermeant;<sup>7</sup> however, Strum and colleagues<sup>8</sup> have recently reported that the drug can be found in the brain following oral administration. A 7-day oral treatment regimen resulted in brain levels of rosiglitazone in the submicromolar range (0.26–0.45  $\mu$ M).<sup>8</sup> It remains to be determined how rosiglitazone made its way into the brain, and whether this is also observed in humans.

## PPAR $\gamma$ regulation of gene expression

### Transactivation

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

PPAR $\gamma$  forms an obligate heterodimer with the retinoid X receptor. This receptor complex binds to PPAR responsive elements within the promoters of its target genes.<sup>10, 11</sup> In the absence of ligand, the transcriptional activity of PPAR $\gamma$  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. Upon binding of 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.<sup>12</sup>

### Anti-inflammatory actions of PPAR $\gamma$

PPAR $\gamma$  agonists robustly inhibit proinflammatory gene expression and this effect underlies many of the beneficial actions of these drugs.<sup>13</sup> The major anti-inflammatory effect of

PPAR $\gamma$  is to functionally inactivate NF $\kappa$ B-dependent promoters. Several mechanisms have been proposed to account for repression of gene expression.<sup>14,15</sup> However, Glass and colleagues<sup>16</sup> have recently provided compelling evidence that PPAR $\gamma$  blocks NF $\kappa$ B-dependent gene expression through corepressor interference. Inflammatory genes are normally repressed through the association of the co-repressors— NCoR with the  $\kappa$ BRE elements, present in the promoters of these genes. Upon ligand binding, a fraction of PPAR $\gamma$  in the nucleus becomes sumoylated and these modified receptors then bind to the  $\kappa$ BRE promoter element, preventing the dissociation of the repressor functionally inactivating the promoter and blocking gene expression. Agonists of PPAR $\gamma$  are attractive therapeutic agents owing to their ability to act broadly to inhibit inflammatory gene expression.

## Effects of PPAR $\gamma$ Agonists in Animal Models of AD

Several studies employing murine models of AD have been carried out to determine the therapeutic utility of PPAR $\gamma$  agonists in disease progression. Yan and colleagues<sup>17</sup> investigated the effects of a PPAR $\gamma$  agonist in Tg2576 mice. Aged (12-months old) Tg2576 mice 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.<sup>6</sup> The NSAID ibuprofen served as a positive control in these experiments since Lim and colleagues<sup>18</sup> had previously shown plaque reduction in this animal model following 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 levels of soluble A $\beta$  peptides. Ibuprofen-treated animals exhibited a dramatic reduction in soluble A $\beta_{42}$  levels. While 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 A $\beta$  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.<sup>19</sup> conducted a study using a dose of pioglitazone that was twofold higher (240 ppm; 40/mg/kg/day) in younger animals. They utilized a different mouse model that overexpresses human 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 20–25% reduction in A $\beta$  plaque burden and in A $\beta_{42}$  levels in the brain.<sup>19</sup> Additionally, there was a significant reduction in microglial activation. This study provided the first conclusive evidence that PPAR $\gamma$  agonists could suppress AD related pathology.

In another study, Pedersen and colleagues<sup>20</sup> examined the effect of the PPAR $\gamma$  agonist rosiglitazone in Tg2576 mice. An unappreciated phenotype 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<sup>20</sup> and lowered glucocorticoid levels. Importantly, rosiglitazone treatment rescued behavioral deficits displayed by these mice.<sup>7</sup> 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.<sup>21–23</sup> This study suggests that rosiglitazone could elicit its effects by acting on peripheral systems. Rosiglitazone treatment did not result in any changes in A $\beta$  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's actions in the Tg2576 mice arise from its effects on peripheral glucocorticoid levels is compelling. Interestingly, although PPAR $\gamma$  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.<sup>24–26</sup> However, the results of these studies are not conclusive<sup>27</sup> and the relevance of this mechanism to AD therapy warrants further investigation.

## Clinical trials

Two FDA-approved PPAR $\gamma$  agonists have been tested for their efficacy in AD patient populations. Watson et al.<sup>28</sup> 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 to placebo-treated control patients.<sup>28</sup> Geldmacher and colleagues<sup>29</sup> 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. PPAR $\gamma$  agonists have a generally favorable side effect profile, and are well tolerated and safe in the elderly.<sup>30</sup> Recently, however, rosiglitazone usage was found to be associated with an increased risk for cardiovascular side effects.<sup>31</sup> In contrast, pioglitazone has been found to be cardioprotective.<sup>32</sup>

The results of a phase II clinical trial, enrolling over 500 patients with mild to moderate AD, was recently reported by Risner et al.<sup>2</sup> These patients were treated with rosiglitazone (or placebo) for 6 months. Patients receiving rosiglitazone were found to have enhanced attention and memory, compared to those receiving placebo. Importantly, patients possessing an *ApoE4* allele did not respond to the therapy. This latter observation is consistent with previous studies by Craft and colleagues<sup>33–35</sup> demonstrating a functional interaction of ApoE isoforms with efficacy of insulin action on cognition. A large phase III trial of rosiglitazone in AD patients is currently underway.

## Mechanisms of PPAR $\gamma$ agonist action

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

### A $\beta$ homeostasis

PPAR $\gamma$  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 PPAR $\gamma$  regulates A $\beta$  metabolism. These studies have led to contradictory results. One mechanism through which PPAR $\gamma$  is able to accomplish this is by regulating A $\beta$  production. When neuroblastoma cells (stably transfected with human amyloid precursor protein) were stimulated with inflammatory cytokines, they activated the APP processing enzyme BACE1, resulting in an increase in A $\beta$  secretion. This was inhibited following PPAR $\gamma$  activation through its ability to suppress BACE1 transcription.<sup>36</sup> Indeed, there is a PPAR $\gamma$  response element in the promoter region of the BACE1 gene, and binding of PPAR $\gamma$  to this response element suppresses BACE1 expression and inhibits A $\beta$  production.<sup>37</sup>

A subsequent study by d'Abramo reported that PPAR $\gamma$  activation resulted in inhibition of APP expression. Moreover, overexpression of PPAR $\gamma$  in cultured cells decreased A $\beta$  secretion by promoting the increased ubiquitination of APP and subsequent degradation.<sup>38</sup>

Camacho et al.<sup>39</sup> have reported an alternative mechanism by which PPAR $\gamma$  may affect A $\beta$  homeostasis. They have shown that activation of endogenous PPAR $\gamma$  or overexpression of the receptor lead to the dramatically enhanced clearance of A $\beta$  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 involved 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.<sup>40</sup> Interestingly, several studies have also shown an *ApoE4* dose-dependent impairment in glucose utilization in brain regions affected by the disease.<sup>41–46</sup>

PPAR $\gamma$  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 the number of cristae they contain.<sup>47</sup> Roses et al.<sup>48</sup> have postulated that the PPAR $\gamma$  agonists act to improve mitochondrial function and this may be the basis of their beneficial effects on memory and cognition in AD patients.

PPAR $\gamma$  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.<sup>49</sup> A recent study has found analogous changes within the brain in response to oral rosiglitazone treatment.<sup>8</sup> Strum and colleagues have reported that PPAR $\gamma$  activation stimulated brain mitochondrial biogenesis and this stimulation was dependent on the ApoE isoforms.<sup>8</sup> PPAR $\gamma$  may elicit these changes through the peroxisome proliferator-activated receptor gamma coactivator 1 (PGC-1) family of proteins. These coactivators positively regulate mitochondrial function and metabolism.<sup>50</sup> PPAR $\gamma$  has been reported to stimulate the expression of PGC-1 $\alpha$ ,<sup>51</sup> which in turn, induces expression of the uncoupling proteins which stimulate mitochondrial biogenesis and respiration in muscle cells.<sup>52–54</sup> PGC-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.<sup>55, 56</sup> It should be noted that TZD agonists of PPAR $\gamma$  also have effects on mitochondrial metabolism that are receptor-independent.<sup>57</sup> The relationship between PPAR $\gamma$ , 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<sup>34, 58–61</sup> and individuals with Type II diabetes mellitus are twice as likely to develop AD when compared to gender-matched healthy subjects.<sup>62–67</sup> 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. PPAR $\gamma$  agonists have been widely prescribed for the treatment of Type II diabetes mellitus. An extensive body of evidence demonstrates a critical role for PPAR $\gamma$  in the regulation of insulin sensitivity. The ability to activate PPAR $\gamma$  is closely correlated with the antidiabetic actions of TZDs, suggesting that

receptor-dependent activation of PPAR $\gamma$  target genes may underlie the insulin sensitizing effect of this class of drugs.<sup>68, 69</sup>

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.<sup>70</sup> 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.<sup>71,72</sup> Craft and colleagues<sup>73</sup> 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 A $\beta$  peptides and inflammatory markers.<sup>74</sup> Diet-induced insulin resistance is also associated with enhanced A $\beta$  peptide levels and plaque formation, which was argued to arise from increased  $\gamma$ -secretase activity and lower IDE activity.<sup>75</sup>

It has been postulated that hyperinsulinemia in the brain may contribute to amyloid build-up due to inhibition of A $\beta$  degradation by IDE. IDE degrades both insulin and A $\beta$  peptides.<sup>76, 77</sup> 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.<sup>78</sup> Genetic ablation or partial loss of *Ide* leads to hyperinsulinemia and elevated A $\beta$  levels.<sup>79–81</sup> It has been postulated that inhibition of IDE proteolytic activity may impair A $\beta$  clearance, thereby initiating or accelerating the disease process. Recently, rosiglitazone has been shown to increase brain IDE levels in an animal model of AD.<sup>82</sup> 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.<sup>83, 84</sup> Consistent with this linkage, individuals on statin therapy exhibit a greatly reduced risk (~70%) for AD.<sup>85</sup> Several genes regulating cholesterol homeostasis have been reported to be associated with AD, including *ApoE*, *Lrp1*, *Abca1*, *Lxr $\beta$* , *Cyp46*, *Acat* and *Cetp*<sup>86, 87</sup> and even *Ppar $\gamma$*  itself.<sup>88,89</sup> Little is known about the role of PPAR $\gamma$  in regulating CNS lipid metabolism.

The *ApoE* gene is the best known bona fide risk factor for sporadic AD.<sup>86</sup> 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 HDL particles by astrocytes, and mediates the efficient transport and recycling of cholesterol within the CNS.<sup>90–92</sup> In humans, three naturally occurring variants of *ApoE*, E2, E3 and E4 have been demonstrated to modify the risk or age of onset of LOAD. The mechanism by which *ApoE4* modifies the risk remains unknown, but has been postulated to play a role in A $\beta$  clearance and deposition.

The lipidation of ApoE is carried out primarily by the ATP-binding cassette A1 (ABCA1). ABCA1 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.<sup>90,91</sup> Recently, three independent groups reported that, in four different animal models of AD, inactivation of the *Abca1* gene facilitates A $\beta$  fibrillogenesis and deposition within the brain.<sup>93–95</sup> Conversely, overexpression of human *Abca1* in mice resulted in reduced A $\beta$  levels and plaque burden.<sup>96</sup> Importantly, the expression

of the *Abca1* gene is transcriptionally regulated by the nuclear receptors, liver X receptors (LXR $\alpha$ ), PPAR $\gamma$  and RXR. The *Lxr $\beta$*  gene has recently been reported to be genetically associated with AD.<sup>97</sup> Genetic ablation of either LXR genes results in increased number and size of plaques in an animal model of AD.<sup>98</sup> Thus, regulation of the lipidation status of ApoE is an important determinant of A $\beta$  clearance and deposition.

A significant subset of the actions of PPAR $\gamma$  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.<sup>99</sup> 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.<sup>100–102</sup> 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.<sup>8</sup>

ApoE has been demonstrated to play essential roles in axonal growth<sup>103</sup> and synaptogenesis.<sup>104</sup> These effects of ApoE are isoform-dependent with ApoE3 promoting and ApoE4 inhibiting neurite outgrowth.<sup>105–109</sup> Interestingly, Brodbeck et al.<sup>110</sup> 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.<sup>110</sup>

## 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.<sup>111</sup> Microglia are the brain's tissue macrophages 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.<sup>112</sup> 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, proinflammatory phenotype accompanied by the elaboration of a wide range of proinflammatory 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.<sup>113–117</sup> The chronic activation of microglia and their production of proinflammatory 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.<sup>118</sup> 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.<sup>1</sup> There is extensive and compelling evidence that PPAR $\gamma$  agonists robustly suppress proinflammatory gene expression. PPAR $\gamma$  agonists have been reported to inhibit the expression of inflammatory cytokines, chemokines, MMPs, COX-2 and iNOS, each of which is reliant upon NF $\kappa$ B-dependent transcriptional effects.<sup>13</sup> There are now over nearly 30 studies showing microglial activation in response to inflammatory stimuli, including fibrillar A $\beta$ .<sup>119</sup> Heneka and colleagues<sup>120</sup> have shown that pioglitazone acts to suppress iNOS and COX2 expression in the brain of 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 IL-4 in the brain, which the authors suggest may underlie the anti-inflammatory actions of PPAR $\gamma$  agonists.<sup>121</sup>

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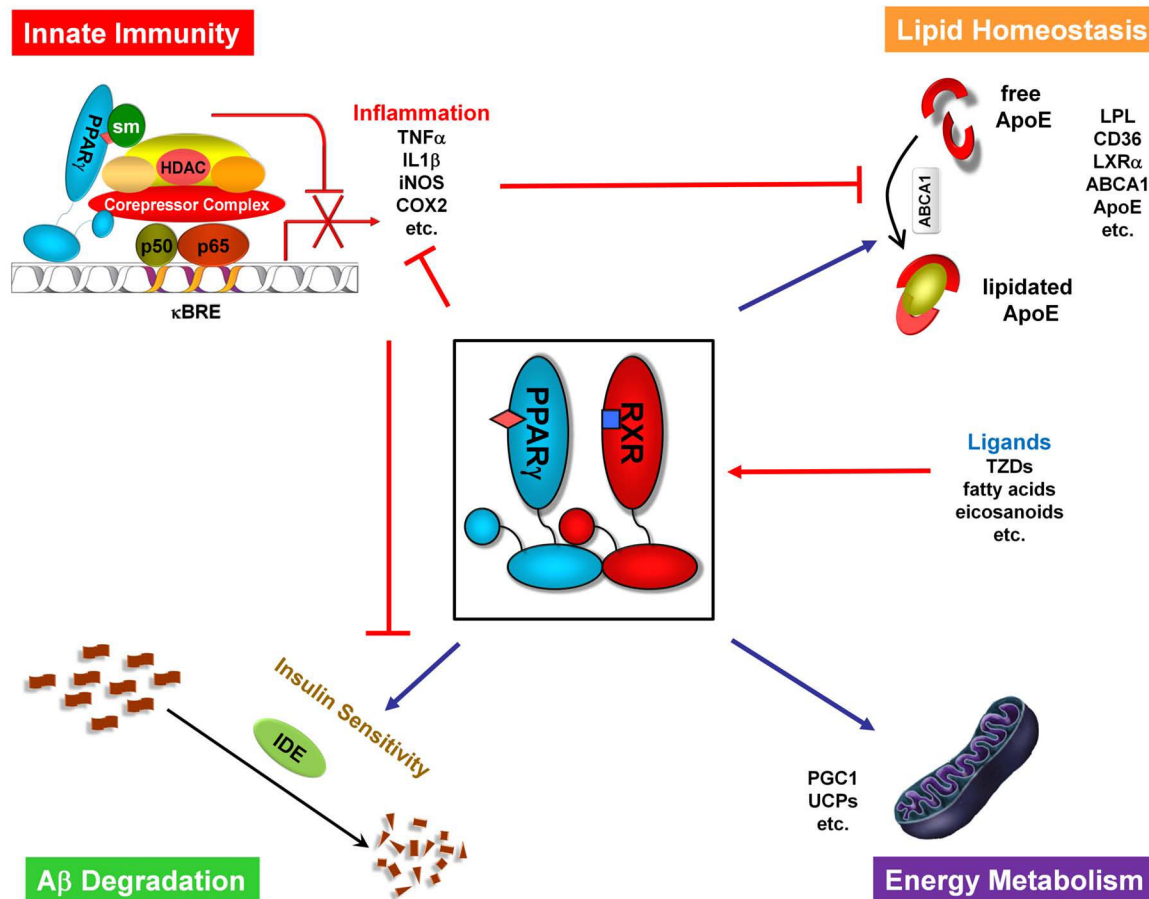
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**Fig. 1.** Potential mechanisms of PPAR $\gamma$  in the treatment of Alzheimer's Disease