# Agonism of Peroxisome Proliferator Receptor–Gamma may have Therapeutic Potential for Neuroinflammation and Parkinson's Disease

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**Abstract:** Evidence suggests inflammation, mitochondria dysfunction, and oxidative stress play major roles in Parkinson's disease (PD), where the primary pathology is the significant loss of dopaminergic neurons in the substantia nigra (SN). Current methods used to treat PD focus mainly on replacing dopamine in the nigrostriatal system. However, with time these methods fail and worsen the symptoms of the disease. This implies there is more to the treatment of PD than just restoring dopamine or the dopaminergic neurons, and that a broader spectrum of factors must be changed in order to restore environmental homeostasis. Pharmacological agents that can protect against progressive neuronal degeneration, increase the level of dopamine in the nigrostriatal system, or restore the dopaminergic system offer various avenues for the treatment of PD. Drugs that reduce inflammation, restore mitochondrial function, or scavenge free radicals have also been shown to offer neuroprotection in various animal models of PD. The activation of peroxisome proliferator receptor–gamma **(**PPAR-γ) has been associated with altering insulin sensitivity, increasing dopamine, inhibiting inflammation, altering mitochondrial bioenergetics, and reducing oxidative stress - a variety of factors that are altered in PD. Therefore, PPAR-γ activation may offer a new clinically relevant treatment approach to neuroinflammation and PD related neurodegeneration. This review will summarize the current understanding of the role of PPAR-γ agonists in neuroinflammation and discuss their potential for the treatment of PD.

**Key Words:** PPAR-gamma, neuroinflammation, neurodegeneration, Parkinson's disease, pioglitazone.

## PARKINSON'S DISEASE

Parkinson's disease (PD) is a disorder that affects approximately 1-3% of the population in the US [7, 115] and currently has no known cure. The primary pathology of the disease is significant loss of the dopaminergic neurons in the substantia nigra (SN), which leads to a significant loss of striatal dopamine [96, 158]. This is because the cell bodies of the dopaminergic neurons are located in the SN and project their axons into the striatum, where they release the neurotransmitter dopamine. It is the loss of striatal dopamine that gives rise to some of the clinical signs of the disease [21]. Clinical motor related signs of PD include tremor, bradykinesia, rigidity, and postural instability [95]. Marked gliosis and the presence of Lewy body-like inclusions [70] are another hallmark of this disease. Cellular dysfunctions such as mitochondrial or proteasomal dysfunction, oxidative stress, and chronic inflammation have been hypothesized to play a role in PD [78, 94, 103, 130, 143, 193].

## THE CURRENT TREND IN PARKINSON'S DISEASE TREATMENT

The current non-invasive methods used to treat PD focus mainly on replacing dopamine in the nigrostriatal system with L-Dopa and its analogs. L-Dopa is the pre-cursor to dopamine and it restores striatal dopamine levels to alleviate some of the motor dysfunctions observed in PD patients. However, after a few years of treatment, the patients get worse [76], most likely as a result of only replacing or altering one factor in a multifactor environment. Thus, L-Dopa therapy is usually reserved for the treatment of late stage PD because of the toxic side effects that arise with its usage. Inhibition of monoamine oxidase activity, with drugs such as rasagiline, also increases dopamine levels by decreasing dopamine breakdown [27, 28]; however, these drugs only alter one factor like L-Dopa. Another method of trial employed to treat PD is grafting dopaminergic neurons into the striatum [142, 161]. These surgeries were successful to some degree as they restored the dopaminergic part of the nigrostriatal system; however, the new neurons died with time and the grafts failed [142, 161]. These studies imply that there is more to the treatment of PD then just increasing striatal dopamine or restoring the dopaminergic neurons of the SN because in PD the entire nigrostriatal environment has been altered. For example, chronic inflammation is present in the PD brain [129, 130, 133], and if the chronic inflammation in PD is not attenuated, then the neurotoxic inflammatory response will continue to damage cells, leading to the progressive neuronal loss associated with the duration of the disease. We propose that a broader spectrum of factors must be changed therapeutically in order to restore the environmental homeostasis required to allow life of the neurons and efficient treatment of PD. This concept was previously proposed by Hirsch *et al.* when they suggested that agents with a broader spectrum of action on inflammation would be more likely to protect dopaminergic neurons [93]. Support for using anti-inflammatory drugs for PD therapy comes from two studies showing that nonsteroidal anti-inflammatory drugs may reduce the risk of PD [25, 26]. Therefore, combinations of dopamine replacement therapies and anti-inflammatory drugs may alleviate the motor symptoms as well as slow the progression of the disease.

Restoration of the inflammatory environment is also crucial to therapies such as glial cell line-derived neurotrophic factor (GDNF), which has shown promise in humans and

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nonhuman primates [73, 80, 175]. This trophic factor enhances the function of the surviving dopaminergic neurons and allows compensation for those that were lost. However, as mentioned with the dopamine replacement therapies, there is no attenuation of the toxic inflammatory environment.

Pharmacological agents that can protect against progressive neuronal degeneration, increase the level of dopamine in the nigrostriatal system, or restore the dopaminergic system offer various avenues for the treatment of PD. Drugs that reduce inflammation, restore mitochondria function, or scavenge free radicals have shown neuroprotection in various animal models of PD [6, 61, 89, 100, 127, 183, 192]. Genetic evidence from specific knockout of inflammatory response related genes such as, cyclooxygenase - 2 (COX-2) [68, 192] or the inducible nitric oxide synthase (iNOS) [47, 102, 120] have also shown partial neuroprotection in PD animal models. However, since PD is considered to be of a multifactor origin [55], it would be logical that restoring multiple altered factors or deficits involved in the disease would produce a more optimal PD treatment. Since a trend in neurology is currently evolving for the role of inflammation in the pathology of several neurodegenerative diseases such as Alzheimer's disease, amyotrophic lateral sclerosis, and multiple sclerosis as well as in head trauma and stroke, researchers have extensively searched for new drugs to control or modify inflammation. As a result, several studies have pointed to the potential use of agonists of the peroxisome proliferator activated receptor-gamma (PPAR-γ).

## PEROXISOME PROLIFERATOR ACTIVATED RECEPTORS

Peroxisome proliferator activated receptors (PPARs) are members of the nuclear receptor superfamily, and they regulate gene expression using various ligand-dependent and -independent molecular processes. Three different isoforms of the PPARs exist and they are encoded by separate genes: PPAR-γ (NR1C3), PPAR-α (NR1C1), and PPAR-δ (NR1C2, β, or NUC-1) [60, 132, 186]. While these isoforms have similar protein sequence and structure, they differ in their ligand-binding domains and have different tissue distribution, ligand specificity, and biological actions [81]. Most of the biochemical functions that have been ascribed to the PPARs require that the receptor is part of a heterodimeric complex with a retinoid X receptor (RXR; also known as NR2B), which is another member of the nuclear-receptor superfamily (16). Therefore, these ligand-dependent transcription factors regulate target gene expression by heterodimerizing with RXR prior to binding to specific peroxisome proliferator response elements (PPREs) in the promoter region of regulated genes. This subsequently results in transcriptional regulation as agonist binding alters the PPAR conformation to allow the recruitment of transcriptional co-activators [52, 97, 160, 189, 205]. Several isoforms of RXRs also exist, have distinct tissue distribution [23, 124], and can be activated by 9-cis retinoic acid to synergizes PPAR activation; although, this binding is not required [113]. The RXRs may even heterodimerize with other nuclear receptors resulting in a decrease of PPAR-regulated transcriptional activation because of the competition among various RXR heterodimerization partners for the RXR [118].

While the PPAR:RXR heterodimer is crucial for determining specific gene transcription, transactivation of the target gene requires a large protein complex [14, 185]. Thus, the involvement of co-activators and co-repressors makes PPAR-regulated transcriptional activation more complex [204, 205]. Non-ligand bound PPARs are considered to be in an inactive state as they are bound with co-repressor proteins in what is known as the co-repressor complex (nuclear receptor co-repressor/silencing mediator for retinoid and thyroid hormone receptors, NCoR/SMRT), which because of its association with histone deacetylases, represses gene transcription [58, 88, 202]. It has recently been shown that SUMOylation of the PPAR-γ ligand-binding domain enables its direct interaction with the nuclear co-repressor complex, which prevents the degradation of the repressor complex and keeps gene transcription silenced [147]. Some cell types even have a cytoplasmic rather than a nuclear location for non-ligand bound PPARs [13, 31]; therefore, translocation to the nucleus is also important in these cells. Competitive inhibition for available PPRE sites can negatively regulate the agonist induced transactivation activities of both PPAR-α and PPAR-γ as both cannot bind to DNA while associated with the co-repressor complex, unlike the PPAR-δ/β [171]. This mechanism provides a unique role for the ubiquitously expressed PPAR-δ/β to act as a tonic suppressor of all PPAR-induced activities under physiological conditions. However, upon ligand activation, minor structural changes occur to the receptor causing the co-repressors to dissociate from PPARs as co-activators are recruited [204, 205]. The co-activator complexes, such as cAMP response element binding protein (CBP)/p300 and steroid receptor co-activator 1, reorganize chromatin to allow the transcriptional machinery to gain access to the promoter regions of the PPAR target genes, as a result of their histone-acetyltransferase activity [56, 57, 201, 204, 205]. Secondary complexes may also form with proteins such as the vitamin-D-receptor interacting protein/thyroid-hormone-receptor-associated protein (DRIP/TRAP) complex [201], as well as the protein complexes that are associated with the basal transcription machinery, so that transcription can be initiated.

Regulation of gene transcription by nuclear hormone receptors extends beyond their transactivation abilities as many members of the nuclear-hormone-receptor superfamily, once activated by an agonist, can interact physically with other types of transcription factors to influence their functional properties. PPARs can suppress the activities of many distinct families of transcription factors through various mechanisms; although, agonist-induced activation of the PPAR is required most of the time for effective transrepression to occur. There are at least three different ways in which ligand-activated PPAR–RXR heterodimers can negatively regulate the activities of other transcription factors. One mechanism, involves squelching of essential, shared co-activators by activated PPAR–RXR heterodimers, which occurs only when the levels of specific co-activators are rate limiting [119]. This co-activator competition, results in suppression of the other transcription factors dependent on the same co-activators. Another method of transrepression occurs through a process known as 'cross-coupling' or 'receptor mutual antagonism." This is a direct result of activated

PPAR–RXR heterodimers forming complexes with other types of activated transcription factors. For example, PPAR-γ plays regulates inflammation by attenuation of the inflammatory response, which is a result of antagonism of proinflammatory transcription pathways, such as nuclear factor-kappa B (NFκB), activator protein-1 (AP-1), signal transducer and activator of transcription (STAT), or nuclear factor of activated T Cells (NFAT) [12, 48, 146, 157]. This results in a functional cross-inhibition of transcription-factor activities of both participants. The third mechanism of transrepression involves regulation of the mitogen-activated protein kinase (MAPK) cascade, where activated PPAR–RXR heterodimers inhibit the phosphorylation and activation of certain members of the MAPK cascade. This was demonstrated when PPAR-γ agonists suppressed the activation of both c-Jun N-terminal kinase and p38 MAPK [51]. For a more detailed review of the structure and physiology of PPARs, see Ricote *et al.* 1999 [156] and for further information on transcriptional control see Devchand *et al.* 1999, Clark *et al.* 2002, Berger *et al.* 2002, and Blanquart *et al.* 2003 [9, 15, 32, 53]. However, for the remainder of this review we will focus on PPAR-γ, which has been shown to play a role in adipogenesis, cell cycle regulation, cell differentiation, insulin sensitivity, and of particular importance to this review, inflammation [19, 45, 52, 105, 121, 149, 157, 162, 196].

## PPAR-γ REGULATES INFLAMMATION

It has been hypothesized that PPARs are actively involved in immunoregulation, through their ability to regulate membrane lipid composition, cell proliferation, sensitivity to apoptosis, energy homeostasis, and various inflammatory related transcription factors. Overall, the general consensus is, PPARs play a role in controlling the inflammatory response, mainly through their transrepression capabilities; although, the transactivation of certain target genes can occur. Several inflammatory signaling systems maybe affected by PPAR-mediated transrepression such as NFκB, STAT, AP-1, or NFAT. These signal pathways are involved in various aspects of immunoregulation including: the functions of macrophages, endothelial cells (ECs), dendirtic cells (DCs), T cells, and B cells (for reviews see Daynes and Jones 2002 and Clark 2002) [32, 44].

Initial evidence for PPAR-γ expression and function in the immune system came from a study that showed a truncated PPAR-γ transcript in peripheral blood lymphocytes [79] and from a study that demonstrated PPAR-γ expression in the rat Peyer's patches and spleen [17]. Subsequent studies showed PPAR-γ is highly expressed in macrophage derived foam cells of atherosclerotic lesions [126, 155, 184]. PPAR-γ was also shown to be expressed in monocytes/macrophages as it plays a role in differentiation and activation as well as in the regulation of the inflammatory response [31, 105, 139, 155-157, 184]. In addition, many studies have demonstrated PPAR-γ ligands to inhibit the macrophage-inflammatory response [29, 156] as the secretion of pro-inflammatory mediators such as cytokines and the expression of iNOS and the transcription of the scavenger receptor-A gene are inhibited [105, 157]. Another study demonstrated, that PPAR-γ activation induced apoptosis in both activated and non-activated macrophages [31]. Others have suggested, that PPAR-γ ligands have a more complex pattern of macrophage-inflammatory responses as they stimulate the expression of the proinflammatory receptors and increase the expression of the class B scavenger receptor [30, 139, 184]. Therefore, the effects of PPAR-γ ligands on monocyte/macrophage inflammatory responses are not simple and appear to depend on the PPAR-γ agonist used, the mode of macrophage activation, and the inflammatory response parameters measured.

Another major cell type that relates PPAR-γ to inflammation and immunity are the ECs, which play role in homing the relevant immune cells and in localization of the inflammatory response. ECs express PPAR-γ and agonists mediate their effects on cell survival, surface-protein expression, and cytokine and chemokine expression. PPAR-γ agonism also induces EC apoptosis [13], and several studies have demonstrated anti-inflammatory effects with PPAR-γ agonism [116, 125]. However, as with the macrophages, a clear picture has not yet been determined for the role of PPAR-γ in modulation of the inflammatory response by the ECs.

PPARs also play an important immunomodulatory role in DCs, which primarily monitor the surrounding environment for potential pathogen infection [178]. DCs express PPAR-γ and agonist-induced activation of PPAR-γ influences DC maturation [77]. The PPAR-γ agonist, rosiglitazone, was shown to alter the membrane phenotype of DCs during maturation induced by lipopolysaccharide (LPS) or CD40 ligand [64, 77]. These studies suggested that activation of DC PPAR-γ influences effector T-cell differentiation as a result alterations in the DC cell-surface phenotype as well as by down-regulating the expression of the cytokines and chemokines required for T helper 1 (TH1)-cell development.

The expression of PPAR-γ by T cells [33, 42, 86, 87, 106, 144, 145, 194, 199] provided another possible role for PPAR-γ in the regulation of inflammation and immunity. Several studies have also shown that PPAR-γ is present at low levels in resting T cells and its expression is upregulated following T-cell activation [33, 42, 106]. In one study, PPAR-γ agonists inhibited the anti-CD3 antibody-stimulated proliferative response of T-cell clones and freshly isolated T-cell-enriched splenocytes as well as the antigen (BMBP)-stimulated response, where inhibition occurred at the level of the T cell [33]. PPAR-γ agonists also inhibited cytokine expression in human peripheral blood T cells, as a partial result of PPAR-γ effects on interleukin-2 (IL-2) promoter activity as well as from activated PPAR-γ physically associating with NFAT, which blocked the downstream effects of these transcription factors [199, 200]. This implies that PPAR-γ could have a suppressive effect on the development of an immune response. Another study demonstrated that PPAR-γ agonists mediate T-cell apoptosis [86]. PPAR-γ agonists can even inhibit the activation-induced production of several T-cell cytokines, such as interferon-gamma [42]. Furthermore, it was shown that the anti-inflammatoy cytokine, IL-4, can induce the upregulation of expression of PPAR-γ in T cells as well as provide a potential ligand for PPAR-γ [200]. Overall, T-cell studies agree on a functional role of PPAR-γ activation in inhibiting activated T-cell proliferation; although, the mechanism(s) are not totally clear.

Several studies have demonstrated PPAR-γ expression in B cells and that PPAR-γ agonists have antiproliferative and cytotoxic effects [144, 145]. The one study, suggested that PPAR-γ agonism induces apoptosis in normal murine B cells and B-cell lines [144]. In addition, a study using ppar-γ +/- mice demonstrated that B cells isolated from ppar-γ-+/-mice are hyperproliferative and have increased viability after exposure to LPS or after cross-linking their antigen receptors [170]. However, further study will be required to address the effects of PPAR-γ ligands on the normal B-cell immune response.

The role of PPAR-γ in inflammation has also been studied in PPAR-γ null macrophages as PPAR-γ-deficient animals are not available for study as a result of embryonic lethality. These studies have allowed new insights into the role of PPAR-γ in macrophage differentiation and function. One study, demonstrated that PPAR-γ is not essential for macrophage differentiation or for phagocytosis as well as cytokine production and expression of the scavenger receptor-A; however, PPAR-γ was required for basal expression of CD36 [136]. In the same study, the PPAR-γ-deficient macrophages showed no difference from wild-type macrophages in the expression of CD14 or other macrophage-specific surface markers and they also produced similar levels of proinflammatory cytokines when stimulated with LPS [136]. This suggested a lack of PPAR-γ ligand involvement in the normal regulation of macrophage-cytokine secretion. PPAR-γ is neither essential for nor substantially affects the development of the macrophage lineage *in vitro* and *in vivo*; however it is an important regulator of the scavenger receptor CD36 [24]. These results suggested that PPAR-γ agonists have anti-inflammatory effects independent of PPAR-γ as well as show that PPAR-γ is required for the positive effects of its ligands in modulating macrophage-lipid metabolism.

Overall, the role of PPAR-γ in the regulation of the inflammatory response is far from complete; however, a plethora of studies link agonism of PPAR-γ to the attenuation of inflammation [59, 105, 157]. Therefore, PPAR-γ activation can influence the development and intensity of the inflammatory response, where it is generally accepted that PPAR-γ activation negatively regulates the inflammatory response (see Fig. **1**). However, in the studies using the natural ligand of PPAR-γ, 15d-PGJ2 [69, 112], or the synthetic ligand, thiazolidinediones, [8, 117] anti-inflammatory activities have been shown to occur in a PPAR-γ dependent and –independent manner [24, 32]. And, the recent suggestion that 15d-PGJ2 is not a biologically relevant PPAR-γ agonist [75] makes the specific immunomodulatory role for PPAR-γ even less clear and more complex. Therefore, caution should be used in interpreting results in which 15d- PGJ2 or the thiazolidinediones were used as PPARγ- specific agonists. However, as a result of numerous reports showing beneficial effects of PPAR agonists in animal models of inflammation, several clinical trials using synthetic PPAR agonists have begun in the treatment of diseases involving aberrant or chronic immune/inflammatory responses [150, 159].

## PPAR-γ IN NEURODEGENERATION

With the realization that inflammation plays a role in several neurodegenerative diseases, researchers have begun to search for a role of PPAR-γ in neurodegeneration. This is because PPAR-γ activation can regulate the inflammatory response and decrease the expression of a variety of pro-inflammatory genes such as COX-2, iNOS, and various cytokines [11, 105, 110, 157], all of which have been associated with inflammation induced neurodegeneration [4, 5, 91, 120, 134, 152, 192]. Since evidence shows that PPAR-γ is expressed in certain areas of the brain [137] such as neurons [17] and glia [11, 40, 41, 90], it is possible that PPAR-γ agonism could potentially inhibit neuroinflammation and subsequently neurodegeneration. It is hypothesized, that this may partially occur through the abilities of agonist bound PPAR-RXR heterodimers to antagonize NFκB mediated gene transcription of several inflammatory mediators such as COX-2, iNOS, and various proinflammatory cytokines [11, 49, 63, 91, 92, 105, 109, 110, 169, 173, 179]. Although, transrepression of other signal pathways may also play a role in the anti-inflammatory effects of PPAR-γ agonism [48, 146, 157]. These data suggest, that PPAR-γ agonists may be used to suppress inflammatory molecules, which are involved in the perpetuation the inflammatory response that is known to produce secondary neurodegeneration.

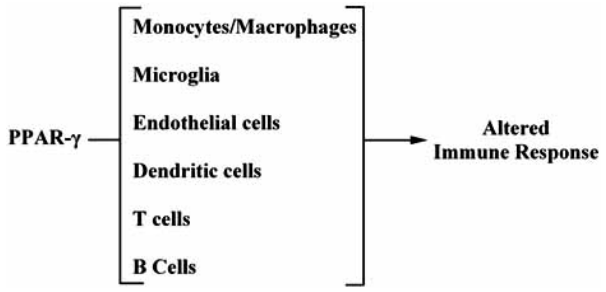


**Fig. (1).** PPAR-γ plays a role in immunomodulation. PPAR-γ is expressed in monocytes/macrophages, microglia, endothelial cells, dendritic cells, T cells, and B cells; and numerous studies have demonstrated that PPAR-γ agonism has immunomodulatory effects in these cells, which can alter the immune response.

Studies showing increased PPAR-γ in the temporal cortex of patients with Alzheimer's disease [111] as well as within the ischemic brain [181] support a role for PPAR-γ in neuroinflammation and neurodegeneration. Since these discoveries, agonists of PPAR-γ, have been used to demonstrate anti-inflammatory effects within the CNS as they inhibit inflammatory molecule production by the glia [11, 12, 15, 39, 91, 109, 110]. For a more detailed review of PPAR-γ in microglia (the macrophages of the brain) mediating the inflammatory response, see Bernardo and Minghetti 2006 [12]. The PPAR-γ agonists also yield protection in models of multiple sclerosis [1, 66, 140, 168, 169] by exerting anti-inflammatory effects on glial cells, by reducing T cell activation and proliferation, and by induction of T cell apoptosis. The PPAR-γ agonist, pioglitazone, has even been used to successfully treat multiple sclerosis [150]. PPAR-γ agonists also offer neuroprotection in ischemia [172, 179, 181, 191, 203] where they decrease microglial activation and the production of pro-inflammatory molecules. They protect in models of amyotrophic lateral sclerosis [108, 169] by decreasing microglial activation as well as COX-2 and iNOS expression. The PPAR-γ agonist also show potential in Alz-

heimer's disease research [39, 43, 72, 92, 101, 114, 148, 197] by decreasing glucocorticoids, beta-secretase, glial activation, proinflammatory molecule production, and amyloid-beta secretion as well as attenuating the decrease in insulin degradation enzyme and through the modulation of the wnt signal cascade. Agonists of PPAR-γ are even being tested in Alzheimer's disease clinical trails where patients receiving a PPAR-γ agonist exhibit cognitive and functional improvements, such as better delayed recall and selective attention [65, 159, 195]. However, in the study by Watson *et al.* the PPAR-γ agonist, rosiglitazone, did not cross the blood-brain barrier [195], which implies that the protective effects of this PPAR-γ agonist are not mediated by local CNS PPAR-γ activation. For a more extensive review on PPAR-γ agonist effects in various neurodegenerative diseases see Sundararajan *et al.* [180]. While these studies offer various explanations for the attenuation of inflammation or neuroprotection that are both PPAR-γ dependent [101, 122, 166] and –independent [66, 67], they all support the use of PPAR-γ agonism to treat neurodegeneration *via* the attenuation of the inflammatory response.

Other evidence to support a role for PPAR-γ agonists in protection against neuroinflammation and neurodegeneration comes from a study using intracerabellar LPS, where PPAR-γ agonists attenuated increased iNOS and cell death [91]. Another study, showed that PPAR-γ agonists induce motorneuron survival through a PI3 kinase mechanism independent of PPAR-γ [75, 141]. In addition, it has been demonstrated that PPAR-γ agonism promotes neurite extension [167]; although, a caveat to this was the use of 15d-PGJ2 as a PPAR-γ agonist, which has recently been shown not to be a biologically active PPAR-γ agonist [75]. The overall consensus, from these studies, supports the use of PPAR-γ agonism to treat neuroinflammation and neurodegeneration.

## PPAR-γ ACTIVATION MAY HAVE POTENTIAL USE FOR PD TREATMENT

Since PPAR-γ agonism has proven successful in various forms of neuroinflammation and neurodegeneration, it is hypothesized that the PPAR-γ agonist, pioglitazone, could be used as a novel treatment approach to controlling the neuroinflammation observed in PD. As a result, pioglitazone treatment was shown to be neuroprotective in the 1-methy-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of PD [18, 46]. In the first study by Breidert *et al.* using an acute MPTP model, pioglitazone attenuated SN inflammation and dopaminergic cell loss but it did not attenuate striatal microglial activation or the loss of striatal tyrosine hydroxylase immunoreactivity, nor did it restore the dopamine levels [18]. Therefore, the authors concluded that PPAR-γ agonism with pioglitazone affects primarily the SN in the MPTP model of PD as a result of attenuating SN inflammation. At best, this study suggests a very weak therapeutic effect.

In a more chronic MPTP dosing study by Dehmer *et al.* pioglitazone had a modest protective effect as it reduced glial activation and iNOS expression in both the SN and striatum as well as attenuated the oxidative stress marker, 3-nitrotyrosine, in the remaining dopamine neurons. This lead to dopaminergic neuroprotection and a partial restoration of striatal dopamine [46]. This study implied that PPAR-γ agonism with pioglitazone has both an anti-inflammatory and antioxidant effect, which may account for the attenuation of dopaminergic cell loss. It was also suggested that these effects were due to PPAR-γ activation, increased IκB expression, and inhibition of p65 nuclear translocation in both the dopaminergic neurons and glia [46]. This is important because the NFκB signaling pathway has been implicated in the pathogenesis of PD [98, 99] as inflammation [93, 129-131] and oxidative stress have been implicated in PD [2, 54, 74, 104] as well as in MPTP-induced PD [3, 151].

While only a modest effect was seen in the MPTP studies, it is important to note two things: (1) most PD cases are not induced by MPTP exposure and (2) MPTP is a dopaminergic specific neurotoxin; therefore, the effects of pioglitazone take place after significant dopaminergic cell damage occurs. This implies that pioglitazone can offer protective properties to an already damaged nigrostriatal environment, which is important to think about when attempting to translate into a clinical application where this environment is already damaged.

Recently, our own lab studies suggested that pioglitazone offers neuroprotective properties in the LPS-induced inflammation model of PD because of its anti-inflammatory and anti-oxidative stress properties, which resulted in restored striatal dopamine, mitochondria function, and significant dopaminergic neuroprotection [100]. Therefore, offering support to the hypothesis that pioglitazone, as well as other agonists of PPAR-γ, may offer a new clinically relevant treatment approach to neuroinflammation and PD related neurodegeneration. Several other studies that have demonstrated an ability for PPAR-γ agonists to protect against LPS toxicity support our data [36, 37, 62, 109], where in these studies, the protection appears to be mediated in part by PPAR-γ activation.

As previously, mentioned, our study and the one by Dehmer *et al.* also supports the idea that pioglitazone offers what appears to be an antioxidant effect [46, 100] as both demonstrated the attenuation of oxidative stress markers. This concept of an antioxidant property, is supported by others who have demonstrated that PPAR-γ agonists decrease 3-nitrotyrosine and increase CuZn superoxide dismutase, as well as by the fact that troglitazone, a PPAR-γ agonist, has an antioxidant chromanol moiety [82, 83, 108, 141, 172]. However, one study argues against antioxidant properties of PPAR-γ agonism because superoxide dismutase levels were not altered [169].

We also demonstrated that pioglitazone restores mitochondria function [100], which is supported by studies showing that thiazolidinediones alter mitochondria bioenergetics [16, 50] as well as directly inhibit mitochondrial fatty acid metabolism [20, 71] and alter mitochondrial uncoupling protein expression [84, 85, 107, 153]. Therefore, since PPAR-γ agonism also affects mitochondria bioenergetics [16, 50, 100], induces a heat shock response [38], and regulates insulin sensitivity [9, 135, 177], some of the protective properties may result from insulin sensitization or alterations in mitochondria function. In other words, PPAR-γ agonists may be altering glucose metabolism, lactate production, or mitochondrial bioenergetics to provide their protective effects,

and several studies have demonstrated these properties [8, 50, 67, 162].

One mechanism that appears to be of relevance is that PPAR-γ agonism regulates insulin sensitivity, which is of particular interest because epidemiological evidence shows 7% of PD patients have type-II diabetes or insulin desensitization [22]. In fact, insulin receptors and dopaminergic neurons are densely represented in the SN [115, 187] and there is a significant decrease in the insulin receptor in the SN of PD patients [138, 182]. There is also reduced insulin-mediate glucose uptake in newly diagnosed and untreated PD patients [188], where a high prevalence of insulin resistance typically occurs [164]. It has even been suggested that diabetes accelerates the progression of the motor and cognitive symptoms of PD [165], and drugs used to treat PD such as L-dopa or bromocriptine alter insulin signaling and sensitivity [174, 188]. Therefore, a potential role of insulin or insulin desensitization in the nigrostriatal system exists in relation to PD. The fact that pioglitazone is used to treat type-II diabetes mellitus by its regulation of insulin sensitivity [176] causes the speculation that some of the protective effects seen with pioglitazone in the PD models may be because of its ability to regulate insulin signaling, glucose metabolism, or lactate production. In our intrastriatal LPS study, pioglitazone attenuated the LPS-induced decrease in the insulin receptor beta subunit [100], which may imply that PPAR-γ agonism altered insulin signal transduction. This is important because control or modulation of insulin is beneficial in sepsis and inflammation [34, 163, 190]. Support for changes related to insulin and neurodegeneration comes from a review that links insulin or hyperinsulinaemia with Alzheimer's disease [154]. Therefore, the anti-inflammatory, anti-oxidative stress, and the insulin sensitizing properties of PPAR-γ activation may allow the neuroprotection seen with PPAR-γ agonism.

Changes in mitochondrial uncoupling protein expression could also provide partial protection in these PD models since PPAR-γ agonism is know to regulate the expression of the uncoupling proteins [84, 107, 153] and these proteins have demonstrated neuroprotective properties [128]. While this has not yet been determined, it seems likely that uncoupling protein expression could potentially play a role in the LPS PD model as pioglitazone demonstrated protective properties related to mitochondrial bioenergetics [100].

In these PD studies, pioglitazone may also afford neuroprotection by a method completely unrelated to its ability to bind and activate PPAR-γ because the dose administered was much higher then the max clinical dose. So the question is, what are the molecular targets being affected when administered high doses of pioglitazone? Recently, it was shown that photoprobe pioglitazone binds a novel mitochondrial protein termed "mitoNeet" with a high affinity, and mitoNEET is found in brain mitochondria [35]. This means it is possible that pioglitazone may be binding and modifying the function of the mitochondrial target protein to contribute to the protective actions of the drug without the activation of PPAR-γ [67]. However, when taking into account the fact that mitoNEET showed specificity in thiazolidinedione binding [35] there appears to be a role for at least some of the protective properties being mediated by PPAR-γ agonism. However, this does not rule out the potential for binding mitoNEET in our LPS model of PD where mitochondrial bioenergetics were altered by LPS and were restored by pioglitazone [100] or in the MPTP studies that used pioglitazone [18, 46]. Thus, the mitoNEET issue, in these studies, remains unsolved.

## CONCLUSIONS

It is clear that agonists of PPAR-γ may have therapeutic potential for the treatment of neuroinflammation and neurodegeneration, with an emphasis on PD related degeneration. However, the exact mechanisms of protection are not clear. Therefore, more studies with these agonists will need to be run not only to test their effectiveness but also to determine and validate their mechanisms of action. Regardless of the exact mechanisms, the PPAR-γ agonist, pioglitazone, seems to offer a broad range of potentially protective proper-

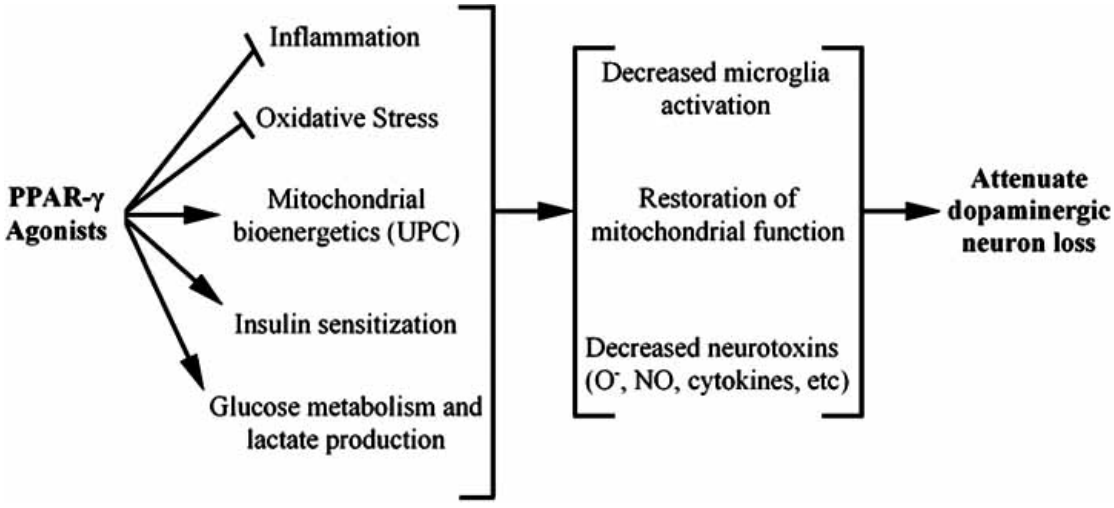


**Fig. (2).** PPAR-γ agonism offers protective properties to dopaminergic neurons. PPAR-γ agonists inhibit inflammation and oxidative stress, alter mitochondrial bioenergetics, and potentially regulate insulin sensitivity, glucose metabolism, and lactate production. The attenuated microglial activation and toxic molecule production results in improved mitochondrial function, which subsequently leads to the attenuation of dopaminergic neuronal loss.

ties that may be important in attenuating the chronic neuroinflammation and oxidative stress that is responsible for the progression of dopaminergic neurodegeneration in PD. This is because pioglitazone will decrease microglia activation and the subsequent release of potential neurotoxins, which attenuates oxidative stress and allows restoration of mitochondria function. This will subsequently attenuate dopaminergic cell loss and the depletion of striatal dopamine (see Fig. **2**). Therefore, pioglitazone could easily be used to treat PD because (1) it is already FDA approved, (2) it has proven to be safe for long term use when prescribed as a diabetes medication, (3) because it crosses the blood brain barrier [123], (4) PPAR-γ is expressed in the region of the brain that is affected in PD [137], and (5) because pioglitazone has shown neuroprotection in the MPTP and LPS models of PD [18, 46]. Further testing of the PPAR-γ agonists should continue in various models of PD as well as in graft transplant studies, stem cell research, in clinical trials, in combination with deep brain stimulation, or with trophic factors, such as GDNF, to see if PPAR-γ activation can help restore some of the diseased environment in the PD nigrostriatal system. However, some concern and caution should be used with the administration of PPAR-γ ligands as some of the agonists promote carcinogenesis, weight gain, hemodilution, edema, plasma-volume expansion, increased adiposity, and cardiomegaly, which may limit their clinical applications [10, 198]. Work should also continue to identify novel PPAR-γ agonists with improved tolerance, efficacy, and targeting.

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