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Review Article

PPAR Regulation of Inflammatory Signaling in CNS Diseases

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Central nervous system (CNS) is an immune privileged site, nevertheless inflammation associates with many CNS diseases. Peroxisome proliferator-activated receptors (PPARs) are a family of nuclear hormone receptors that regulate immune and inflammatory responses. Specific ligands for PPARα, γ, and δ isoforms have proven effective in the animal models of multiple sclerosis (MS), Alzheimer's disease, Parkinson's disease, and trauma/stroke, suggesting their use in the treatment of neuroinflammatory diseases. The activation of NF-κB and Jak-Stat signaling pathways and secretion of inflammatory cytokines are critical in the pathogenesis of CNS diseases. Interestingly, PPAR agonists mitigate CNS disease by modulating inflammatory signaling network in immune cells. In this manuscript, we review the current knowledge on how PPARs regulate neuroinflammatory signaling networks in CNS diseases.

1. INTRODUCTION

The central nervous system (CNS) was thought to be an immune privileged site due to the ability of blood-brain-barrier (BBB) to shield immune cell entry and protect from the constantly changing circulatory milieu. Nevertheless, activated immune cells readily traverse the BBB, secrete inflammatory cytokines, and mediate many CNS diseases. Neuroinflammatory diseases present major challenges to the health care system and impose substantial economic costs around the world. Current treatments targeting clinical symptoms of CNS diseases have modest therapeutic values in patients. Significant progress has been made in recent years in developing therapeutic strategies for the treatment of neuroinflammatory diseases.

2. NEUROINFLAMMATORY DISEASES

The innate and adaptive immunity evoked during infection in the CNS often leads to the development of neuroinflammatory diseases [1–3]. The mounting evidence suggests that neuroinflammatory diseases such as multiple sclerosis (MS), Alzheimer's disease (AD), trauma, and ischemia/stroke can occur in the absence of infection. MS is an inflammatory demyelinating disease of the CNS with clinical symptoms ranging from pain to paralysis and the patients becoming wheel-chair bound for rest of their lives [4]. Although the etiology of MS is not known, it is generally viewed as a neural antigen-specific T cell-mediated autoimmune disease [4–6]. Experimental allergic encephalomyelitis (EAE) is an autoimmune disease model of MS, commonly used to study the mechanism of disease pathogenesis and to test the efficacy of potential therapeutic agents for the treatment of MS. In AD, the deposition of beta-amyloid (Aβ) and plaque formation in the CNS associate with inflammation resulting in neuronal death, progressive deterioration of cognitive functions, and memory loss [7, 8]. Traumatic brain injury (TBI), spinal cord injury, and ischemic stroke also display neuroinflammation associated secondary tissue damage in the CNS [9, 10]. The pathogenesis of neuroinflammatory diseases involves the orchestrated interaction of immune cells resulting in tissue injury to the CNS [6, 11]. Although the exact mechanisms are not known, recent evidence suggests the use of peroxisome proliferator-activated receptor (PPAR) agonists in the treatment of neuroinflammatory diseases.

3. PPAR ISOFORMS AND THEIR LIGANDS

PPAR is a family of ligand-dependent nuclear hormone receptor transcription factors that play key roles in the

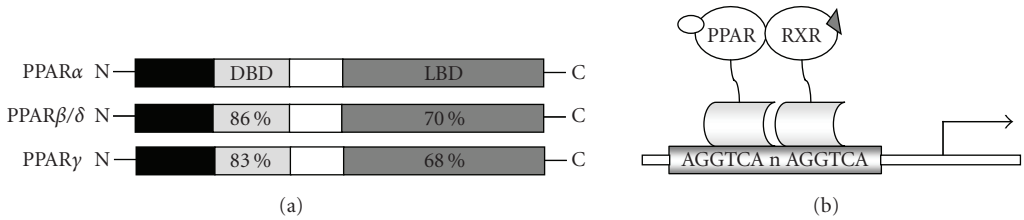

Figure 1: (a) Functional domains of PPAR isoforms. N, N-terminus; DBD: DNA-binding domain; LBD: ligand-binding domain. The numbers represent percentage identity to human PPARα. (b) PPAR/RXR binds to PPREDR-1 promoter regions. Binding of agonists leads to heterodimerization, recruitment of coactivator and transcriptional activation of target genes.

regulation of immune and inflammatory responses [12]. Structure-function analyses revealed that PPARs are composed of a DNA-binding domain (DBD) linked to the C-terminal ligand-binding domain (LBD) by a hinge region (Figure 1) [13, 14]. PPARs stimulate gene expression through binding to peroxisome-proliferator response elements (PPREs), present in the promoter regions of the target genes. In the absence of ligands, the heterodimers physically associate with corepressors and suppress gene transcription [14, 15]. Upon ligand binding, the coactivators replace corepressors and activate gene expression [16, 17]. PPARα, PPARβ/δ, and PPARγ are three structurally homologous isotypes found in various species which display distinct physiological and pharmacological functions [18]. The PPARα is expressed in liver, kidney, intestine, heart, skeletal muscle, adrenal gland, pancreas, and brain. PPARα is involved in acetylcholine metabolism, excitatory neurotransmission, and oxidative stress defense [19]. PPARα also regulates lipid metabolism and energy homeostasis through its ability to stimulate the breakdown of fatty acids and cholesterol, driving gluconeogenesis and reduction in serum triglyceride levels [19]. While polyunsaturated fatty acids activate all three isoforms of PPARs with different affinities, each isotype has its own ligand binding property [20]. Fibrates, WY14643, and GW7647 are PPARα agonists commonly used for the treatment of hypertriglyceridemia [19].

PPARβ/δ is ubiquitously expressed in all cell types including immature oligodendrocytes and promotes differentiation and myelination in the CNS [21–23]. PPARβ/δ null mice show an altered myelination of corpus callosum, suggesting its role in brain function [24]. PPARβ/δ regulates transcriptional activation of Acyl-CoA synthetase 2, a key enzyme in fatty acid utilization, suggesting its role in lipid metabolism in the brain. Prostagladin I_2, GW0742, GW501516, and GW7842 are PPARβ/δ agonists which induce fatty acid oxidation in muscle [25]. PPARγ expression is detected in adipose tissue intestinal mucosa, retina, skeletal muscle, heart, liver, and lymphoid organs [26]. PPARγ is expressed in microglia and astrocytes and regulates inflammation in the CNS [27, 28]. Eicosanoids and prostaglandin J2 (15d-PGJ2) are the naturally occurring PPARγ ligands, and thiazolidinedones (TZDs) including pioglitazone (Actos) and rosiglitazone (Avandia) are Food and Drug Administration (FDA) approved synthetic drugs for the treatment of type II diabetes [29]. Recent studies have shown the use of PPAR agonists in the treatment of many neuroinflammatory diseases.

4. THERAPEUTIC EFFECTS OF PPAR AGONISTS IN CNS DISEASES

The therapeutic effects of PPAR agonists have been tested in many different neuroinflammatory diseases (Table 1). The use of PPARγ agonists in the treatment of MS has been tested in EAE model by different groups [30–33]. In vivo treatment with synthetic PPARγ ligand, troglitazone, ameliorates EAE by reducing the infiltration of leukocytes in the CNS [34]. Two other studies also showed that in vivo treatment with PPARγ ligands, 15d-PGJ_2 and ciglitazone, ameliorates EAE [30, 31]. Oral treatment with pioglitazone inhibits chronic progressive and relapsing forms of EAE even when administered at the peak of disease [35, 36], suggesting their use of PPARγ agonists in the treatment of MS. PPARγ-deficient heterozygous mice develop an exacerbated EAE with increased CNS inflammation and demyelination [37]. A recent report also showed that PPARγ antagonists, bisphenol A diglycidyl ether (BADGE), and 2-chloro-5 nitro-N-(4 pyridyl) benzamide (T007) reversed the inhibition of EAE by PPARγ agonists, further suggesting the physiological role of PPARγ in the pathogenesis of EAE [38].

Epidemiological studies suggest a reduced risk of AD among the users of nonsteroidal anti-inflammatory drugs (NSAID) [39, 40]. Treatment with pioglitazone and rosiglitazone significantly reduced the lesion size, motor neuron loss, myelin loss, astrogliosis, microglial activation, and chronic thermal hyperalgesia in spinal cord injury [41]. In a rat model of AD induced by cortical Aβ injection, ciglitazone and pioglitazone suppressed the clinical symptoms significantly. In the amyloid precursor protein (APP) transgenic model of AD, treatment with pioglitazone reduced the plaque burden by affecting the production, clearance, and homeostasis of Aβ in the CNS [42]. A clinical trial involving 500 AD patients showed significant improvement in cognition following treatment with rosiglitazone for 6 months, suggesting its use in the treatment of AD [43]. Recent evidence also suggests that NSAIDs such as ibuprofen may delay or prevent the development of Parkinson's disease (PD) [44, 45]. Moreover, PPARγ is expressed in the CNS of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced model of PD [24] and treatment with pioglitazone protected the animals from neuronal cell death [46]. Similar results

Table 1: Role of PPARs in the regulation of neuroinflammatory diseases.

CNS disease	Inflammatory response	Effect of PPAR agonists
Multiple sclerosis	Activation of macrophage, microglia and dendritic cells; infiltration of Th1/Th17 cells in the CNS; induction of NF-κB and Jak-Stat pathway and release of IL-12, IFNγ, IL-17 and other cytokines in the CNS	PPARα, δ and γ agonists ameliorate EAE by inhibiting inflammation
Alzheimer's disease	Beta-amyloid (Aβ) accumulation leads to CNS inflammation via TNFα and NF-κB pathway and secretion of inflammatory cytokines	PPARγ ligands reduce neuronal loss in animal models of AD
Infection	During bacterial, viral, fungal and parasitic infection, activated APC and T cells release TNFα, IFNγ, iNOS, IL-2, IL-6 and induce inflammation via NF-κB, Stat and AP-1 signaling pathways	PPAR agonists regulate infection associated inflammation
Trauma	CNS injury results in the activation of resident microglia and astrocytes resulting inflammation through secretion of TNFα, prostaglandin and COX-2 and mediate inflammation via NF-κB, Stat1 and AP-1 pathways	PPARα, δ and γ ligands regulate inflammatory response in trauma
Ischemia/stroke	Ischemic stroke associates with recruitment and activation of macrophages and neutrophils via increased expression of VCAM-1, ICAM-1, IL-6, IL-8 and COX-2 through Stat-1	PPARγ ligands reduce the infarct size in animal models

were also generated using lipopolysaccharide (LPS)-induced inflammation model of dopaminergic neurodegeneration in rat, where pioglitazone treatment effectively reduced inflammation, oxidative stress, and restored mitochondrial function [47]. Treatment with pioglitazone also extends the survival of superoxide dismutase-1 (SOD1-G93A) transgenic animal model of amylotrophic lateral sclerosis (ALS) [36, 48–51].

The effects of PPAR agonists in reducing deleterious inflammatory responses suggest their use in the treatment of trauma, spinal cord injury, and stroke. Experimental evidence suggests that the Pro12Ala polymorphism of PPARγ2 is associated with a reduced risk for ischemic stroke [52] and treatment with TZDs and 15d-PGJ2 cause neuroprotection in animal models of stroke. Treatment with PPARγ agonists also reduce the infarct volumes and improve sensorimotor function in a rodent model of middle cerebral artery occlusion (MCAO) [53, 54]. Similar effects were observed following oral or intracerebrovascular administration of PPARγ agonists [55, 56]. TZD-unrelated PPARγ agonist L-796,449 decreases infarct size and improves neurological scores after MCAO in the rat brain [57]. Treatment with PPARγ antagonist T0070907 increased the infarct size and reversed rosiglitazone-induced protection after stroke. A small clinical trial has revealed improved functional recovery after stroke in diabetic patients receiving pioglitazone or rosiglitazone compared to patients not receiving TZD therapy [58]. A recent clinical trial demonstrated that pioglitazone significantly reduced the combined risk of myocardial infarction and stroke-associated death in high-risk patients with type 2 diabetes [59].

Recent studies have demonstrated the beneficial effects of PPARα agonists in the treatment of neuroinflammatory diseases. Oral treatment with gemfibrozil protects mice from EAE [60]. The tyrosine hydroxylase (TH)-positive SNpc cells express PPARα and in vivo treatment with PPARα agonist, fenofibrate, protects mice from MPTP-induced inflammation and neuronal loss. In vivo treatment with PPARα agonist, fenofibrate and WY-14643, reduced the infarct size in mouse models of stroke [61, 62]. This effect was absent in PPARα deficient mice, reinforcing receptor dependency of the observed effects . Treatment with PPARα agonist, fenofibrate, decreases the neurological deficit induced by traumatic brain injury (TBI) caused by lateral fluid percussion of brain in rats [63]. Fenofibrate also reduces brain edema and ICAM-1 expression and induces neurological recovery associated with a reduction of the brain lesion. Anti-inflammatory therapies showed neuroprotective effects after spinal cord injury in rodents [64, 65]. Moreover, oral treatment with selective PPARβ/δ agonist GW0742 exerted beneficial effects in the MOGp35-55-induced EAE model [66]. GW0742 reduced the severity of EAE even when administered at the peak of clinical disease [66]. PPAR β/δ null mice exhibit significantly greater infarct sizes than wild type animals suggesting its role in stroke [67].

5. PPAR AGONISTS REGULATE INFLAMMATORY CYTOKINES IN CNS DISEASES

The anti-inflammatory effects of PPARγ agonists have been extensively studied in CNS diseases (Table 2). While the inflammatory cytokines, IL-1β, IL-6, TNFα, IL-12, IL-23, IL-27, IFNγ, and IL-17, mediate the pathogenesis of CNS diseases, anti-inflammatory cytokines, IL-4, IFNβ, TGFβ, and IL-10, confer recovery in MS and its animal model, EAE [68–70]. In EAE model of MS, PPARγ agonists decrease

Table 2: Role of PPARs in the regulation of inflammatory signaling pathways in CNS diseases.

Tissue Distribution	PPAR Agonists	Effect and Mode of Action in CNS diseases
PPARα Expressed in liver, heart, kidney, large intestine, skeletal muscle and astrocytes. PPARα knockout mice develop severe LPS-induced inflammation	Palmitic acid, linoleic acid, stearic acid, palmitoleic acid, oleic acid, 8-HETE, Wy-14643, clofibrate, nafenopin, bezafibrate, fenofibrate	PPARα agonists inhibit Aβ induced expression of TNFα, IL-6, IL-4 and infiltration of $CD4^+$ T cells in the CNS of AD; reduce ICAM-1 expression and oxidative damage in stroke; protect MPTP-induced loss of neurons in PD; protect mice from EAE by inhibiting IFNγ, TNFα and IL-6 production in stroke, cerebral ischemia and MS models
PPARβ/δ Expressed ubiquitously in brain, adipose tissue and skin. PPARβ/δ knockout mice show reduced fat deposition	Prostacyclin, PGI2, GW0742, GW501516, GW7842, L165041	PPARβ/δ agonists reduce the severity of EAE and stroke by inhibiting NF-κB and Jak-Stat signaling pathways in immune cells from MS and stroke models
PPARγ Expressed in heart, muscle, colon, kidney, pancreas, spleen, macrophage, intestine, adipose tissue and liver. PPARγ knockouts are embryonically lethal	Prostaglandin J2, thiazolidinediones, pioglitazone, rosiglitazone, GW78456, WY14,643, GW7647	PPARγ agonists inhibit T-cell proliferation, IFNγ, IL-10 and IL-4 production through blocking NF-κB, AP-1 and Jak-Stat pathways in CNS diseases models of AD, PD, Trauma, MS, ALS, stroke and ischemia

the TNFα mRNA expression in antigen-specific T cell in vitro [71]. Other studies have shown that 15d-PGJ_2 inhibits EAE in association with inhibition of T-cell proliferation and secretion of inflammatory cytokines including IFNγ, IL-10, and IL-4 in culture [31–34]. PPARγ agonists, 15d-PGJ2 and ciglitazone, block IL-12 signaling through Jak-Stat pathway leading to Th1 differentiation in T cells. Pioglitazone also suppresses IFNγ secretion in spleen T cells following stimulation with MOGp35-55 in vitro [30]. The activation of resident glial cells and infiltration of leukocytes contribute to demyelination in EAE and MS. The chemokines and chemokine receptors promote the trafficking and entry of immune cells across blood-brain barrier into the CNS in EAE and MS [71–74]. Whereas, PPARγ agonists, troglitazone and pioglitazone, reduce the expression of MCP1 [33], IP-10 (CXCL3), MIG, I-TAC, MIP1α, and RANTES [27] that contribute to reduced infiltration of immune cells in the MOG-induced EAE [73, 74]. Moreover, the surface molecules such as MHC class II, CD40, CD28, and ICAM enhance the disease pathogenesis and CTLA4 inhibits EAE/MS [75]. Negative regulation of adhesion molecules may also account for reduced brain infiltration observed in PPARγ agonists treated EAE mice.

The immunomodulatory effects of PPARγ agonists were tested in human peripheral blood mononuclear cells (PBMCs). In vitro treatment of cells with pioglitazone, ciglitazone, and GW347845 abolished proliferation and cytokine secretion accompanied by DNA condensation and down-regulation of bcl-2, suggesting the induction of apoptosis in activated T lymphocytes. MS patients showed a decrease in the expression of PPARγ in immune cells and a reduction in the anti-inflammatory effects of pioglitazone when compared to healthy controls [35, 36, 76]. However, treatment of immune cells derived from diabetic patients with pioglitazone in vitro or by oral treatment in vivo increased the expression and DNA-binding activity of PPARγ [77]. In MS patients, pioglitazone increased the DNA binding activity of PPARγ and decreased the NF-κB activity by increasing IκBα. Activated microglial cells were significantly reduced at sites of neurodegeneration in pioglitazone-treated SOD1-G93A mice, as were the protein levels of COX-2 and iNOS. The mRNA levels of the suppressor of cytokine signaling 1 and 3 genes were also increased by pioglitazone [48], but their functional significance is not well known.

In vivo treatment with PPARγ agonists suppresses Aβ-evoked microglial activation and inflammatory cytokine expression, iNOS expression and NO production, and inhibition of COX-2 in Aβ-evoked animal models of AD and APP [42]. PPARγ agonists also suppress Aβ-mediated activation of microglia in vitro [40–43]. The expression of iNOS in neurons resulted in neuronal cell death which was prevented by activation of PPARγ in vitro and in vivo [42, 43]. Neuroinflammatory changes accompanied by activation of microglia and astrocytes and expression of TNFα, IL -1β, and iNOS play a pivotal role in PD [46]. An increase in infiltrating CD8+ T lymphocytes and IFNγ+ cells were also reported in the CNS with PD. Pioglitazone decreased microglia and astrocyte activation and reduced the number of iNOS-positive cells in the CNS [47]. In trauma, macrophages, and neutrophils are involved in the early stages of inflammation followed by leukocyte recruitment via VCAM-1, ICAM-1, IL-6, IL-8, and COX-2 [75]. The leukocytes and microglia mount inflammatory responses with elevated expression of cytokines, chemokines, adhesion molecules, iNOS, COX-2, and other inflammatory mediators that exacerbate the tissue damage [61]. Treatment with pioglitazone significantly reduced the induction of inflammatory genes, IL-1β, IL-6, monocyte chemoatractant protein-1, and intracellular adhesionmolecule-1. The PPARγ antagonist, 2-chloro-5-nitro-*N*-phenyl-benzamide (GW9662), prevented

the neuroprotective effect of pioglitazone [48], suggesting the involvement of PPARγ-dependent mechanisms in the regulation of inflammation and new therapeutic avenue for the treatment of MS.

The expression and activation of PPARα in T lymphocytes decreases IL-2 production and proliferation. PPARα-null mice show an augmented LPS-induced inflammatory response and oral treatment with gemfibrozil reduced CD4+ lymphocyte and macrophage infiltration into the CNS of mice with EAE. Several agonists of PPARα, including gemfibrozil and ciprofibrate, decreased murine lymphocyte proliferation in a concentration-dependent manner, in vitro [60]. The gemfibrozil and ciprofibrate-induced IL-4 production in murine and human lymphocytes, whereas IFNγ production was decreased. WY14,643, a synthetic PPARα agonist, reduced the IgG response in mice with EAE and impaired generation of IFNγ, TNFα, and IL-6 in response to MOG peptide in vitro. PPARα and PPARβ/δ are expressed in astrocytes, while the latter are present more in oligodendrocytes, thus playing a role in the process of remyelination [66]. In AD, the neuroinflammatory components include resident microglia, astrocyte, the complement system, cytokines, and chemokines. Microglia and astrocytes generate beta-amyloid protein that stimulate proinflammatory cytokines in AD brain. PPARα agonists inhibitAβ-stimulated expression of TNFα and IL-6 in a dose dependent manner [40, 42]. In trauma and spinal cord injury-induced edema, neutrophil infiltration and immunoreactivity to TNFα were augmented with a worsened recovery of limb function in PPARα knockout than wild type mice. CNS injury leads to rapid recruitment of microglia, macrophage, and astrocytes that secrete IL-1, TNFα, iNOS, PGs, and COX-2 [63]. Fenofibrate promotes neurological recovery by decreasing iNOS, COX2, MMP9 expression, and antioxidant effect in TBI. Although PPAR agonists inhibit neuroinflammation in many CNS diseases, their modes of action are not well characterized.

6. PPAR AGONISTS REGULATE IL-12 FAMILY CYTOKINES IN CNS DISEASES

IL-12, IL-23, and IL-27 are three IL-12 family cytokines produced by macrophage, microglia, and dendritic cells in the CNS. IL-12 is a 70 kD heterodimeric cytokine composed of p40 and p35 subunits encoded by two different genes that play a critical role in the differentiation of neural antigen-specific Th1 cells in EAE [78, 79]. We and others have shown earlier that in vivo treatment with neutralizing anti-IL-12p40 antibody prevents EAE [79]. Furthermore, therapeutic intervention of IL-12-signaling was effective in preventing EAE. We have shown that PPARγ agonists inhibit IL-12 production, IL-12 signaling, and differentiation of Th1 cells in EAE [30]. We have also shown that PPARγ-deficient heterozygous mice develop an exacerbated EAE in association with an augmented Th1 response [37], suggesting a physiological role for PPARγ in the regulation of IL-12/IFNγ axis in CNS demyelination. IL-23 is a heterodimeric cytokine composed of a common IL-12p40 subunit and an IL-23p19 subunit specific to IL-23 encoded by two different genes [70]. Signaling through its receptor, composed of IL-12Rβ1 and IL-23R, IL-23 induces the activation of Jak-Stat pathways and differentiation of IL-17 producing (Th17) cells from memory Th1 cells, leading to the pathogenesis of EAE [80]. Targeted disruption of IL-23p19 in mice was effective in preventing the pathogenesis of EAE [70, 81] and suggested that the IL-23/IL-17 axis plays a critical role in the pathogenesis of CNS inflammation and demyelination. Although IL-6 and TGFβ [82] are important mediators of Th17 differentiation in culture, their physiological role in activating Th17 cells in CNS disease is not known (Figure 2).

IL-27 is another heterodimeric cytokine consisting of EBI3 and p28 encoded by two different genes. IL-27 receptor is composed of WSX-1 and gp130 molecules that mediate IL-27-induced activation of the Jak-Stat pathway in naive CD4+ T cells [83]. In vivo treatment with anti-IL-27 antibody ameliorates EAE, suggesting its role in the pathogenesis of Th1 cell-mediated autoimmune diseases. Recent studies have also shown that IL-27 and IFNγ are potent inducers of T-bet, a T-box protein transcription factor, in T cells. Targeted disruption of T-bet or siRNA inhibition of T-bet was sufficient to prevent the pathogenesis of EAE, suggesting the critical role of IL-27/IFNγ/T-bet axis in the pathogenesis of demyelination [84]. PPARγ agonists regulate IL-27/IFNγ/T-bet axis in EAE. Interestingly, recent studies have shown that EBI3 can also heterodimerize with IL-12p35 to form IL-35 in CD4+-Foxp3+ regulatory T cells and functions as a potent anti-inflammatory cytokine [85]. Although PPARγ has been shown to upregulate Treg cells in vitro [86], the role of PPAR in the development of Treg cells or production of IL-35 in EAE/MS or other CNS diseases is not known.

7. PPAR AGONISTS REGULATE NF-κB SIGNALING PATHWAYS IN CNS DISEASES

The IL-12 family cytokines are produced by macrophage, microglia, and dendritic cells in response to autoantigens, TLR ligands, and CD40 ligands [87]. In earlier studies, we and others have shown that autoimmune cells secrete IL-12 in response to antigens and that this response was inhibited by treatment with PPARγ agonists [30]. PPARγ agonists also inhibit LPS and CD40L-induced secretion of IL-12 from macrophage, microglia, and dendritic cells. The induction of IL-12/IL-23 gene expression involves activation of the NF-κB signaling pathway in antigen-presenting cells [88]. NF-κB is a heterodimeric transcription factor composed of p50 and p65 subunits from the Rel family of proteins. It is sequestered in the cytoplasm as an inactive complex when associated with its inhibitor, IκB.Upon stimulation with specific inducers, IκB is phosphorylated and degraded through proteosome-mediated pathways. The activated NF-κB then translocates into the nucleus and binds to specific 10 bp response elements of the IL-12, IL-23, and IL-27 genes [88, 89] Activation of NF-κB is a complex process involving the successive action of proximal NF-κB-inducing kinase (NIK) and the IκB kinases, IKKα, IKKβ, and IKKγ [90]. The expression of the IL-12 p40 subunit is controlled by proximal cis-acting elements (NF-κB half site) interacting with NF-κB family members [91]. Inhibitors of IL-12 gene expression, including retinoids, acetyl salicylic acid, and

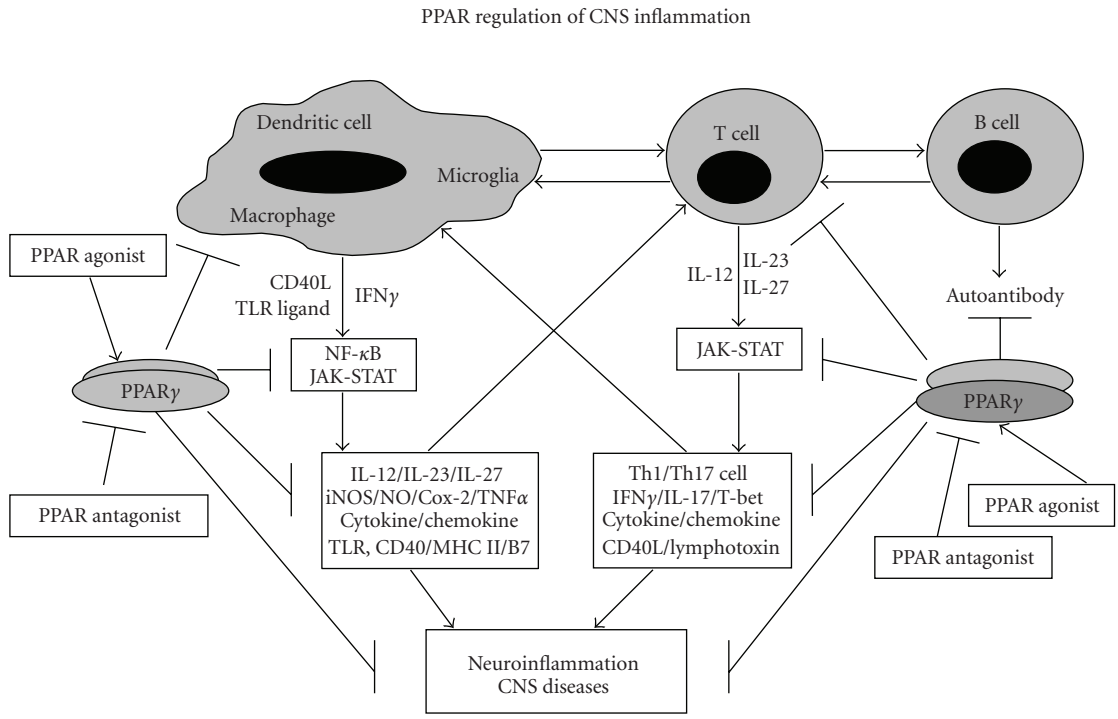

Figure 2: Regulation of neuroinflammation by PPAR agonists in CNS diseases. CD40/TLR induce the activation of NF-κB pathway leading to expression of IL-12 family cytokines from APCs which in turn signal through Jak-Stat pathway in T cells leading to Th1/Th17 differentiation and development of CNS diseases. PPAR agonists modulate signaling and transcription in APC and T cells thereby preventing CNS diseases.

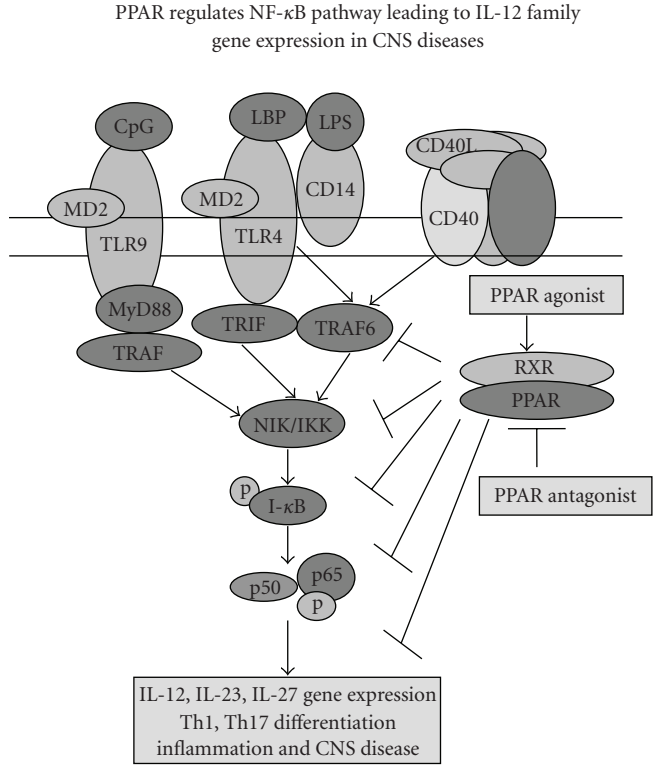

Figure 3: Regulation of NF-κB pathway by PPAR agonists in CNS diseases. The activation of microglia, macrophage and dendritic cells through toll-like receptor, CD40 or cytokine associated NF-κB pathway leads to secretion of inflammatory cytokines leading to pathogenesis of CNS diseases. PPAR agonists inhibit NF-κB pathway resulting in inhibition of CNS diseases.

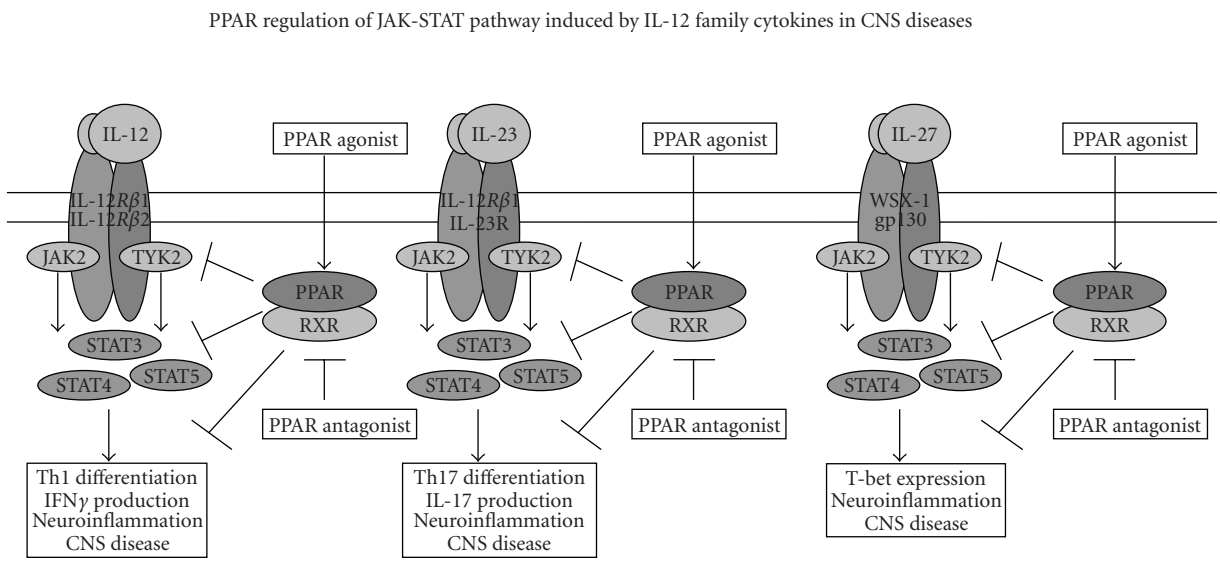

Figure 4: IL-12, IL-23 and IL-27 are heterodimeric cytokines signals through Jak-Stat pathway and induce Th1/Th17 differentiation and T-bet expression in T cells. Treatment with PPAR agonists regulate these responses in T cells resulting in inhibition of CNS inflammation.

1,25 dihydroxyvitamin D3, block NF-κB activation and bind within the IL-12p40 promoter [92, 93]. The inhibition of NF-κB pathway leading to the expression of IL-12 family cytokines by PPAR agonists suggests this be a mechanism by which PPAR agonists regulate CNS diseases (Figure 3).

The NF-κB family of proteins (RelA/p65, RelB, c-Rel, p50, p52) are widely expressed in the CNS [94] and activated in a number of CNS inflammatory diseases. Microglia plays a pivotal role in immune surveillance and host defense against infectious agents in the CNS. NF-κB, JNK, and p38 pathways are responsible for F-actin architecture during microglial activation. In AD, NF-κB activation is increased when compared to control brain. The brain samples from PD patients showed an increased nuclear p65 (RelA) in dopaminergic neurons when compared to age matched controls [95]. The spinal cord samples from ALS patients with degenerating motor neurons showed increased NF-κB activation in astrocytes that are controlled by c-jun, and JNK/SAPK kinases [96]. In MS patients, NF-κB and c-jun activities are increased in chronic lesions. PPARs are expressed in microglial cells and PPARγ agonists act as negative regulators for elements that contain Stat binding sites. While the inflammatory cascade is mediated via both NF-κB and JNK pathways, PPARγ agonists increase the levels of IκB-α and IκB-β and reduce the nuclear translocation of NF-κB [97]. While the induction of NF-κB promotes postischemic inflammation, PPAR agonists prevent postischemic inflammation and neuronal damage by inhibiting NF-κB pathway. Further analyses indicate that L-796,449 inhibits NF-κB signaling through both PPARγ-dependent and independent pathways. In addition, spinal cord injury (SCI) associated neuronal damage was less severe in NF-κB knockout mice. PPARγ induces transrepression of NF-κB-induced inflammatory genes through their association with corepressor complexes [96].

8. PPAR AGONISTS REGULATE JAK-STAT SIGNALING PATHWAY IN CNS DISEASES

The orchestrated interaction of APCs and T cells in the CNS leads to activation of Jak-Stat signaling pathway, secretion of inflammatory cytokines, and pathogenesis of neuroinflammatory diseases. The antigen-induced proliferation of T cells is a two-step process in which signaling through T cell receptor (signal 1) drives T cells from resting G0 to activated G1 phase of the cell cycle, whereas signaling through IL-2 or IL-12 receptor (second signal) is required for T cells to transit from G1 to S/G2/M phase of the cell cycle (proliferation). IL-12 is a potent inducer of G1 to S/G2/M phase transition and differentiation of Th1 cells that are critical in the pathogenesis of EAE and other CNS diseases. IL-12 signals through IL-12 receptor β1 and β2, members of the gp130 cytokine receptor super-family, expressed primarily on activated NK cells and T cells. Coexpression of IL-12Rβ1 and β2 leads to the formation of high affinity IL-12 receptors [87]. Signaling through its receptor, IL-12 induces tyrosine phosphorylation and activation of Jak2, Tyk2, Stat3, and Stat4 in T and NK cells [98, 99]. Activation of the Jak-Stat pathway leads to transcription of IL-12 response genes associated with proliferation, Th1 differentiation, and IFNγ production. IL-23 receptor is composed of common IL-12Rβ1 and a specific IL-23 receptor subunit [100]. Signaling through its receptor, IL-23 induces the activation of Jak2, Tyk2, Stat1, Stat3, Stat4, and Stat5 in T cells [98]. Activation of the Jak-Stat pathway leads to transcription of IL-23 response genes, including IL-17, which are associated with proliferation of memory T cells [101], whereas IL-27 and IFNγ activate a specific Jak-Stat pathway in T cells, resulting in the induction of T-bet in naive T cells [102]. Modulation of cytokine signaling by targeting protein tyrosine kinases or transcription factors has been considered a novel strategy

for the treatment of autoimmune diseases [103, 104]. We have shown earlier that the blockade of IL-12 signaling through Jak-Stat pathway by treatment with a Jak-2 inhibitor, tyrphostin AG490, quercetin, vitamin D, and curcumin inhibits Th1 differentiation and pathogenesis of EAE [105–108]. We have also shown recently that PPARγ agonists inhibit IL-12-induced tyrosine phosphorylation of Jak2, Tyk2, Stat3, and Stat4 in T cells, differentiation of Th1 cells and pathogenesis of EAE [30]. These findings suggest that IL-12 signaling through the Jak-Stat pathway is a molecular target in the regulation of autoimmune diseases. Recent studies have shown that the transcription factors such as Stat4 and T-bet are involved in the pathogenesis of EAE/MS, whereas Stat6 mediates recovery. While the induction of Stat1 and Stat3 promotes postischemic inflammation, and Stat-1 knockout mice develop less severe stroke lesions in the CNS [32], activation of PPARs prevents postischemic inflammation and neuronal damage (Figure 4).

The exact mechanism by which PPAR agonists negatively regulate neuroinflammation, and in particular, the Jak-Stat signaling pathway is not known. Suppressor of cytokine signaling (SOCS) proteins are negative regulators of Jak-Stat pathway. While PPARγ agonists inhibit Jak-Stat pathway in astrocytes and microglial cells, they rapidly induce the expression of SOCS 1 and 3, which in turn inhibit Jak activity in glial cells [109]. In addition, PPAR agonist can modulate Jak-Stat pathway through activation of Src homology 2 domain-containing protein phosphatase 2 (SHP2) in immune cells, thereby inhibiting neuroinflammatory diseases.

9. CONCLUSION

The neuroinflammatory diseases such as multiple sclerosis, Alzhimer's disease, stroke, and trauma are common health problems affecting more than five percent of the population worldwide. While the exact mechanisms are not known, the immune cell activation and secretion of inflammatory cytokines, involving NF-κB and Jak-Stat signaling pathways, play critical roles in the pathogenesis of many CNS diseases. Thus, interfering with the signaling network could be an effective approach in the treatment of MS and other neuroinflammatory diseases. PPAR is a family of nuclear receptor transcription factors that regulate CNS diseases by modulating neuroinflammatory signaling network. Since PPAR agonists are already in human use, they are likely to prove useful in the treatment of MS and other neuroinflammatory diseases in the near future.

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