Minireview

Role of PPARγ, a Nuclear Hormone Receptor in Neuroprotection

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Peroxisome proliferator-activated receptors (PPARs) belong to the nuclear receptor superfamily. PPAR-alpha is involved in wound healing, stimulation of lipid and folic acid catabolism, inflammation control, inhibition of ureagenesis and peroxisome proliferation. The PPARβ/δ is involved wound healing, cell proliferation, embryo implantation, adipocyte differentiation, myelination alteration and apoptosis. The PPARγ is involved in fat, lipid and calorie utilization, sugar control, inflammation control and macrophage (MQ) matutation. Homocysteine (Hcy) binds to nuclear peroxisome proliferator activated receptor. Increase in PPAR expression decreases the level of nitrotyrosine and increases endothelial nitric oxide concentration, decreases metalloproteinase activity and expression as well as elastinolysis and reverses Hcy-mediated vascular dysfunction. The PPARγ initially recognized as a regulator of adipocyte development has become a potential therapeutic target for the treatment of diverse disorders. In addition, the activation of PPARγ receptor ameliorates neurodegenerative disease. This review focuses on the recent knowledge of PPARγ in neuroprotection and deals with the mechanism of neuroprotection of central nervous system disorder by PPARγ.

Keywords: PPAR, Neuronal death, Ischemia, Neurodegenerative disorder, Alzheimer's disease, Parkinson's disease, Multiple Sclerosis

Introduction

Peroxisome proliferator activated receptors (PPARs): Structure, subtypes and functions

PPARs are ligand-inducible transcription factors that are members of the superfamily of proteins known as nuclear hormone receptors (NHRs)[1]. They play essential roles in the regulation of cellular differentiation, development, and metabolism of higher organisms. The function of PPARs is modified by the precise shape of their ligand-binding domain, and by a number of coactivator and corepressor proteins. These coactivators and/or repressors in conjunction with retinoid X receptors (RXRs) can stimulate or inhibit PPAR function. PPARs are characterized by five functional domains, namely: A/B, the N-terminal domains; C, the DNA-binding domain; D, the flexible Hinge region; E, the ligand binding domain; and F, the C-terminal domain. The amino terminal (A/B) domain contains a ligand-independent activation function 1 (AF-1) that contains a mitogen-activated protein kinase phosphorylation site[2]. The DNA binding domain (C) is highly conserved and its zinc finger domain is a common attribute amongst all members of the NHR family. The DNA binding domain is linked to the C-terminal ligand-binding domain (E/F) by a 'hinge' region. The E/F domains function to dimerize PPARs with RXRs and provide the ligand-dependent transactivation function of the receptor. The D domain is a docking domain for cofactors[3].

PPARs act principally as lipid sensors and regulate body metabolism in response to dietary intake of

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Abbreviations: AB, amyloid beta peptide; AD, Alzheimer's disease; CNS, central nervous system; COX, cyclooxygenase; EAE, experimental allergic encephalitis; FA, folic acid; Hcy, homocysteine; ICAM, inter cellular adhesive molecule; IL-1, interleukin; MCP, monocytic chemoattractant protein; MMP, matrix metalloproteinase; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MS, multiple sclerosis; NHR, nuclear hormone receptors; NSAIDS, non-steroidal anti-inflammatory drugs; NO, nitric oxide; NFkB, nuclear factor kappa B; NOS, nitric oxide synthase; NMDA, N-methyl D-asparatate; PPAR, peroxisome proliferator activated receptor; PPRE, peroxisome proliferator responsive element; ROS, reactive oxygen species; RXR, retinoid X receptor; STAT, signal transducers and activators of transcription; TDZ, thiazolidinedione; TIMP, tissue inhibitor of metalloproteinase; TNF, tumor nerosis factor; VLDL, vascular low density lipoprotein.

lipids. They also direct the subsequent lipid metabolism and storage. The natural ligands of these receptors are dietary lipids and their metabolites. All PPARs heterodimerize with the RXR and bind to specific regions on the DNA of target genes. PPARs stimulate gene expression by binding to conserved sequences of DNA known as peroxisome-proliferator response elements (PPREs), which are present in the promoter of their target genes. Ligand activation and binding of the PPARγ/RXR heterodimer are accompanied by the recruitment of co-activators. Without ligands, the heterodimers are physically bound with co-repressor complexes that suppress gene transcription[4]. Upon binding of the ligand to its receptor, the nuclear receptor co-repressor (N-CoR)-containing co-repressor complexes are replaced with co-activator complexes. These co-activator complexes are then linked to the basal transcription apparatus, initiating transcription of the gene[5].

Three isoforms of PPAR have been identified: α, β/δ, and γ, also known as *NR1C1*, *NR1C2* and *NR1C3*, respectively[6]. The three PPARs though structurally homologous have different tissue distribution. They have distinct but overlapping biological functions, depending on their target genes and tissue distribution. PPARα acts primarily to regulate energy homeostasis via its ability to stimulate the breakdown of fatty acids and cholesterol, driving gluconeogenesis and reduction in serum triglyceride levels. It acts as a lipid sensor and binds fatty acids, initiating their subsequent metabolism[7]. PPAR β/δ, the most widely expressed member of the family binds and responds to VLDL-derived fatty acids and eicosanoids, and appears to be mainly involved in β-oxidation of fatty acids[8]. PPARγ binds a variety of natural ligands including fatty acids, eicosanoids, and other natural lipid ligands. It predominantly stimulates adipocyte differentiation and regulates lipid metabolism in mature adipocytes[3] (Fig. 1).
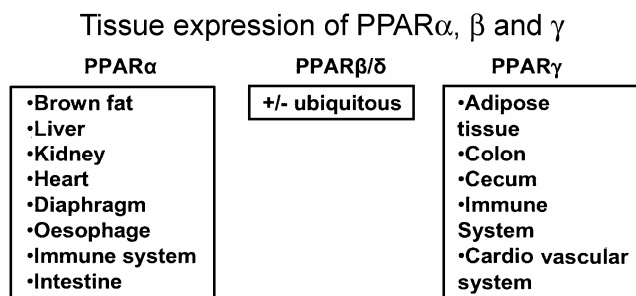
The PPARs are involved in several aspects of tissue differentiation and development, specifically in adipose tissue, brain, placenta and skin[4]. The developmental expression of PPAR isoforms differs in respect to tissue and time of expression, indicating different functions for each (Fig. 2). The developmental expression of PPARs is not known in humans. The PPARβ/δ shows a fairly ubiquitous expression from the early embryonic up to adult ages as compared to γ and α subtypes, which downregulates post-natal. Such distinct regulation of the PPARs suggests a prominent role for the receptor in brain development and differentiation. PPARβ/δ is expressed in neurons in different numerous parts of the brain, whereas other two subtypes are more restricted[5].

Another important aspect of PPAR action is repression of inflammatory pathways by trans-repression of transcription factors (like NF-κB, AP-1, NFAT and STATs) or it may also regulate the oxidative pathway[9]. PPARα activation induces expression and activation of anti-oxidant enzymes. The physical interaction of PPARs with TFs inhibits expression of the majority of pro-inflammatory cytokines, chemokines and enzymes. PPARs also exert the anti-inflammatory effect by sequestration of the common co-activators or co-repressors for transcription factors. Such regulation mediated by PPARγ includes repression of inducible nitric oxide synthase or cyclo-oxygenase 2, and reduced production of anti-inflammatory cytokines. Synthetic ligand mediated activation of PPAR resulting in suppression of inflammation has been demonstrated in different animal models of inflammatory diseases. However, it has been difficult to identify a unified mechanism of repression by activated PPARs[9]. Hcy binds to the nuclear peroxisome proliferator activated receptor. Increase in PPAR expression decreases the

Tissue expression of PPARα, β and γ

PPARα	PPARβ/δ	PPARγ
•Brown fat •Liver •Kidney •Heart •Diaphragm •Oesophage •Immune system •Intestine	+/- ubiquitous	•Adipose tissue •Colon •Cecum •Immune System •Cardio vascular system

Fig. 1—PPAR expression in various tissues

Physiological roles of PPARα, β and γ

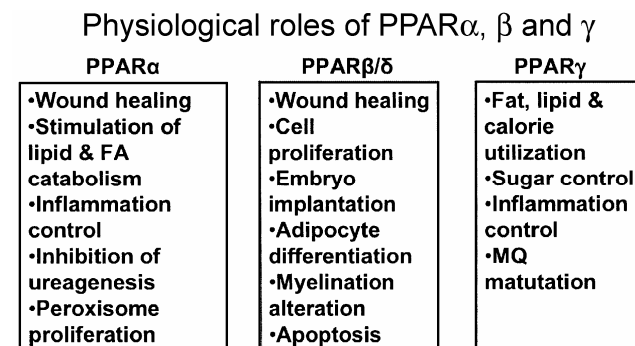| PPARα	PPARβ/δ	PPARγ
•Wound healing •Stimulation of lipid & FA catabolism •Inflammation control •Inhibition of ureagenesis •Peroxisome proliferation	•Wound healing •Cell proliferation •Embryo implantation •Adipocyte differentiation •Myelination alteration •Apoptosis	•Fat, lipid & calorie utilization •Sugar control •Inflammation control •MQ matutation

Fig. 2—Differential expression of PPAR and their function

level of nitrotyrosine and increases endothelial NO concentration, decreases metalloproteinase activity and expression as well as elastinolysis and reverses Hcy-mediated vascular dysfunction (Fig. 3).

PPARγ

The gene encoding PPARγ is located on chromosome 3 at position 3p25. Alternate splicing of the transcript produces two isoforms: PPARγ1 and PPARγ2, PPARγ1 protein is expressed in most tissues; PPARγ2, which produces the PPARγ2 protein, is found only in adipocytes[10,11]. PPARγ2 shows a stronger transcriptional activation as compared to PPARγ1. PPARγ activation is linked to a reduction in serum glucose levels, probably as a secondary effect of its ability to regulate endocrine factors.

The PPARγ protein increases insulin sensitivity and decreases insulin resistance in adipose tissue, skeletal muscle, and liver. In the vascular system, PPARγ confers anti-atherosclerotic effects[12]. It antagonizes the metabolic syndrome by down regulating peripheral inflammatory processes. This includes the suppression of proinflammatory cytokines and adhesion molecules[13]. Recent data have shown that PPARγ acts as a regulator of inflammation of the central nervous system (CNS) and is a pharmacological target for countering neurodegeneration[14,15].

Pathological processes involving inflammatory activation are responded to via microglia, macrophages, astrocytes and the peripheral immune system, where PPARγ is implicated as a potential molecule to suppress the inflammation. PPARγ is most extensively studied subtype implicated in

Fig. 3—PPAR competes with homocysteine [Clinical trails indicate that PPAR agonists improve CV function in HHcy, but levels of Hcy do not decrease, in fact increase slightly. The increased levels of Hcy compete and suppress the PPAR activity and cause oxidative stress by generating nitrotyrosine, activating MMP and decreasing the eNO concentration]

inflammation and neurodegeneration. Many substances have been suggested to be natural ligands for PPARγ, including fatty acids, eicosanoids (components of LDLs), and oxidized alkyl phospholipids[16].

PPARγ and neuronal death

It has previously been thought that PPAR activation could also be effective in regulating neuronal death in ischemic, inflammatory, or neurodegenerative cerebral diseases. All PPARs have been described in both the developing and adult brain, as well as the spinal cord. It has also been suggested that PPAR activation in neurons may directly influence neuron viability and differentiation[17]. PPARβ/δ is expressed in immature oligodendrocytes, where its activation promotes differentiation and myelin growth and turnover[18]. PPARα has been suggested to be involved in acetylcholine metabolism and is related to excitatory neurotransmission and oxidative stress defense[19]. PPARγ is the dominant isotype in microglia. Astrocytes contain all three isotypes in varying degrees, depending on brain area and age[20]. The role of PPARs in the CNS has primarily been implicated in lipid metabolism. However, these receptors have also been implicated in neural cell differentiation and death, as well as inflammatory and neurodegenerative conditions[21].

Neuronal death is induced by the combined process of inflammation as well as oxidative stress[22]. Inflammatory and oxidative processes induce both apoptotic and necrotic neuronal death. The transcription factor NF-kB plays a key role in regulation of inflammatory and oxidative stress leading to neuronal death. PPARs are able to regulate this pathway by transrepression of NF-kB, so PPARs have been considered as possible targets for neuroprotection[23]. Studies have demonstrated that PPARγ agonists modulate inflammatory responses to bacterial endotoxin in the brain, and also prevent neuronal death induced by endotoxins[24]. PPARγ agonists can prevent neuronal death from NMDA excitotoxicity induced in the brain[25]. Pioglitazone, a PPARγ agonist has been tested as a neuroprotective in mouse model of amyotrophic lateral sclerosis[26,27]. PPARα and PPARγ can inhibit microglial and macrophage activation that contribute to many degenerative, ischemic, or inflammatory processes leading to neuronal cell death. PPARs are also able to inhibit the access of inflammatory cells into the CNS
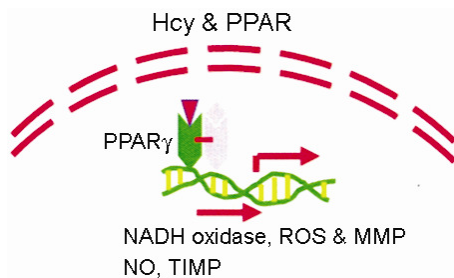
from the periphery by the inhibition of metalloproteinases, adhesion molecules, and cytokines[28].

PPARγ and cerebral ischemia

Cerebral ischemia results from a transient or permanent reduction of blood flow to the brain. Stroke is one of the leading causes of death and adult disability in industrialized countries with a mortality rate of approximately 30%. This poor prognosis results from a lack of effective therapies. Neurons that are localized in the core ischemic area die rapidly because of ischemia-induced energy failure and anoxic depolarization. Cerebral ischemia immediately elicits the recruitment of neutrophils within minutes, followed by the infiltration of ischemic tissue by monocytes/macrophages over the course of a few hours[29]. In the early phase of ischemia, neuronal death is due to excitotoxicity, characterized by large-scale activation of glutamate receptors, calcium overload, and a breakdown of ion homeostasis[30, 31]. In addition, ischemia results in the activation of endogenous microglia in the first two hours after the ischemia occurs. The microglia along with peripheral leukocytes mount a vigorous inflammatory response with the induction of cytokine and chemokine expression, as well as increased expression of iNOS and COX2 which act to amplify the tissue damage[32]. These inflammatory reactions are responsible for delayed neuronal death. Many studies have shown that suppression of the inflammatory response ameliorates stroke damage and improves clinical prognoses[33,34].

Recent data from animal experiments strongly indicate that ligands of PPARγ confer neuroprotection and neurological improvement following cerebral ischemia. PPARγ agonists demonstrably protect against cerebral ischemia in rodents, and this protection includes reducing rates of apoptosis[14]. Treatment with a PPARγ antagonist has been shown to increase infarct size[35].

Ischemic injury increases the expression of PPARγ mRNA and protein in neurons and microglia[25,36]. Increased PPARγ protein levels can be detected up to 14 days after ischemia occurs. Increased PPARγ expression might not be functionally significant, however, because cerebral ischemia reduces the DNA binding of PPARγ. It has been shown that DNA binding is fully restored by systemic treatment with rosiglitazone or by intercerebral application of the PPARγ agonist 15-deoxy-PGJ2[35,37].

It has been shown that systemic and intracerebroventricular application of thiazolidinedione (TDZ) PPARγ agonists reduces the expression of COX2 in areas around an infarct following occlusion of the middle cerebral or common carotid arteries[38]. By suppressing COX2, the TDZ reduces the presence of reactive oxygen species (ROS). In addition to downregulating COX2 expression, PPARγ agonists affect the production of ROS in other ways. Pioglitazone, for example, promotes the expression of the anti-oxidant enzyme Cu,Zn-superoxide dismutase, which reduces free oxygen radicals in ischemic tissue[39]. The treatment of rats with pioglitazone or rosiglitazone before occlusion of the common carotid artery was shown to decrease the production of ROS and nitrites, and decrease lipid peroxidation[40]. In addition, TZD and other PPARγ agonists cause a diminution of the expression of iNOS in inflammatory cells[41]. This is significant because iNOS is considered to be an important source of the deleterious radical peroxynitrite.

PPARγ and its agonists reduce immune reactions outside the CNS, but have also recently been shown to have a strong anti-inflammatory potential in ischemic brains. Activation of PPARγ reduces the expression of ICAM1, MMP9, and various inflammatory cytokines that are present in ischemic brain tissue[34, 42]. Systemic treatment of rodents with rosiglitazone has been shown to reduce the infiltration of microglia and macrophages into peri-infarct regions of the brain and downregulate the production of IL1-B[37]. Rosiglitazone and pioglitazone also inhibit NF-kB signaling and the activation of p38 kinase[40]. Ciglitazone, a PPARγ agonist ameliorated matrix protein changes in diabetes[43]. PPARγ agonists improve the level of recovery from ischemic stroke regardless of whether it is applied systemically or intracerebroventricularly. It is not clear, however, the extent to which the stimulation of peripheral, neuronal, cerebrovascular, or microglial PPARγ contributes to neuroprotection[44].

PPARγ and neurodegenerative disorders
Alzheimer's disease

Alzheimer's disease (AD) is the number one cause of dementia, and the number of people affected by the disease is dramatically increasing in the developed world. Drugs that are used to treat the disease principally target at improving the symptoms of the patient.

PPARγ and PPARα agonists have been tested in AD models[45]. The histopathological hallmarks of AD include extra-cellular amyloid β-peptide (AB) deposition in neuritic plaques and intracellular deposits of hyperphosphorylated Tau protein causing neurofibrillary 'tangles' and cell death. This is responsible for progressive memory loss and decline of cognitive functions[44]. PPARγ agonists have been promoted as a new disease altering approach to AD. There are a number of epidemiological studies that demonstrate that treatment with non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofin, indomethacin reduces the risk of AD by as much as 80%, and it is suggested that these effects might stem from the ability of these drugs to activate PPARγ and inhibit inflammatory responses in the diseased brain[28,45].

A recent study has shown that ibuprofen, if used for relatively short periods and although well-tolerated to gastroprotection, does not seem to be effective in tertiary prevention of mild-moderate AD[46]. Further, as indomethacin does not appear to be effective in altering the progression of symptoms in AD, thus, treatment of AD patients with indomethacin needs to be thoroughly reconsidered[47]. Neuronal expression of inflammatory enzymes, including iNOS has been described in AD[48] Neuronal expression of iNOS in neurons results in time-dependent neuronal cell death, which is prevented by activation of PPARγ[21]. PPARγ activation in microglial cells suppresses inflammatory expression of cytokines and iNOS, NO production, and inhibition of COX2[49]. These effects are due to the ability of PPARγ to suppress the promoters of proinflammatory genes by antagonizing the actions of the transcription factor NF-kB, and to a lesser extent AP-1 and STATs (signal transducers and activators of transcription)[15]. PPARγ agonists have been demonstrated to suppress the amyloid-β mediated activation of microglia and reduce the number of cortical or hippocampal AB-positive plaques[24,49,50].

Parkinson's disease

Parkinson's disease is characterized by a variety of disturbances to motor function, primarily by tremor, rigidity, and problems with gait and balance. These neurological deficits result from the progressive loss of dopaminergic neurons of the substantia nigra (of the midbrain). The death of these neurons is accompanied by astrogliosis (an abnormal increase in the number of astrocytes). It has been shown that

there is an accompanying activation of microglia and production of inflammatory molecules[51]. This microglial inflammatory response is thought to exacerbate the neuronal loss observed in the disease.

In the 1-methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine (MPTP) mouse model of Parkinson's disease, the oral administration of the PPARγ agonist pioglitazone has been reported to prevent the death of dopaminergic neurons in the substantia nigra pars compact a (SNNpc)[52]. In addition, treatment with the drug is associated with a reduction in the numbers of reactive astrocytes and microglia in the substantia nigra. It was subsequently reported that Pioglitazone is also reported to suppresse the microglial activation and production of proinflammatory mediators through elevation of inhibitory protein-kBa expression and inhibition of translocation of the NF-kB subunit 65p to the nucleus in dopaminergic neurons, glial cells, and astrocytes[53]. Another promising PPARγ agonist rosiglitazone provides effective neuroprotection to chronic MPTP mouse models[54].

Recent evidence has suggested that a non-steroidal anti-inflammatory drug (NSAID) indomethacin functions as a micromolar ligand for the adipogenic transcription factor PPARγ. The PPARγ is abundantly expressed in adipose tissue, where it functions as a key modulator of the adipocyte proliferation via a NSAID mechanism. Interestingly, the particular ibuprofen treatment may delay or prevent the development of Parkinson's[55] via a mechanism similar to NSAID protection in AD. Because ibuprofen passes the blood-brain barrier and acts as a PPARγ agonist[56], it is possible that PPARγ activation contributes to its beneficial effect on the Parkinson's epidemiology. These data suggest that treatment with PPARγ agonists may be a new therapeutic approach to the treatment of Parkinson's disease

Multiple sclerosis

Multiple sclerosis (MS) is a chronic autoimmune disorder of the central nervous system that affects primarily young adults. The disease is characterized by multiple areas of white matter inflammation, demyelination, and glial scarring (sclerosis). It is known that proinflammatory cytokines play a key role in the pathogenesis of MS, and this holds true for the experimental animal model of MS, called the experimental allergic encephalitis (EAE) model[57]. Several cytokines including TNF-alpha), interferon g, and interleukin-6 (IL-6) are regularly found in spinal

cord infiltrates and MS brain lesions of EAE mice[58]. Because PPARγ agonists have long-lasting anti-inflammatory effects in peripheral immune cells[59,60] and in autoimmune disorder models, they have been used experimentally in models of MS. It has also been shown that expression of PPARγ increases in astrocytes and microglia during EAE. This supports a role of this receptor in modulating MS inflammatory responses[61].

In a recent study, it has been demonstrated that IL-23 rather than IL-12 is crucial for modulating the character of the developing immune response towards a proinflammatory response and leading to EAE. IL-17 is a crucial effector cytokine, whose production is specifically triggered by IL-23, and it has been shown to be an essential inflammatory mediator in other autoimmune diseases and inflammatory conditions. Therapeutic neutralization of IL-17 with IL-17-receptor-Fc-protein in acute EAE ameliorates clinical symptoms. Neutralization of IL-17 with a monoclonal antibody also ameliorates the disease course. Thus, IL-17 is crucially involved in the cytokine network as an effector cytokine in EAE[62].

In both EAE and MS, inflammatory activation of endothelial and glial cells (as well as infiltrating leukocytes) contributes to neuronal demyelination and destruction. The entry of cells from the periphery into the CNS is modulated and stimulated by the release of chemokines (chemotactic cytokines)[63]. The PPARγ agonists have been shown to reduce the expression of several chemoattractant molecules, including the monocytic chemoattractant MCP1[64]. It has been shown in the EAE model that treatment with synthetic PPARγ ligands troglitazone and pioglitazone causes a decrease in key chemokines, supporting the hypothesis that a suppressed generation of chemotactic molecules contributes to the reduced infiltration of brain parenchyma by peripheral leukocytes (Fig. 4).

Therapeutic interventions of PPARγ in CNS disorders

The PPAR pathway plays an important role in recovery from CNS disorders. Several studies suggest that endogenous ligands that are present in the damaged CNS can activate the PPARγ pathway and contribute to preservation of the CNS anatomy. Studies have demonstrated that PPARγ antagonists increase tissue pathology after cerebral ischemia[35,65]. Endogenous PPARγ activation may be an essential

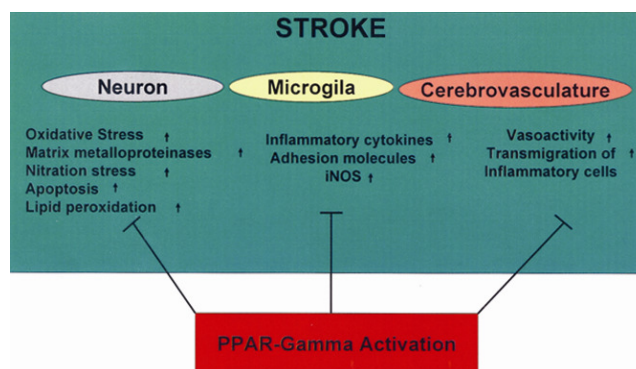Fig. 4—Effect of PPAR-γ activation in brain [The multiple actions of PPAR-γ agonists in brain injury such as anti-apoptosis in neuron, anti-inflammation in Gila, and stabilized vascular function]

component of promoting reparative mechanisms that are initiated in the injured CNS[66]. This endogenous response is submaximal, however, numerous studies have suggested that pharmacological activation of the PPARγ pathway subsequent to damage may significantly improve recovery[25,26]. Neuroprotection against acute ischemic injury using TZD derivatives as PPARγ agonists are clinically relevant, however a major issue is the penetration of peripherally applied drugs across the blood-brain barrier.

Because FDA approved PPARγ agonists are now available, clinical studies have been started to test these drugs in age-related dementia. Moreover, the PPARγ agonists are the only neuroprotective strategy with a glucose lowering component. This is clinically important, as hyperglycemia worsens the neurological outcomes of stroke. Another promising drug rosiglitazone, has been approved for treatment of type II diabetes. It has recently been shown to provide effective neuroprotection to chronic MPTP mouse models, in which it is known to cross the blood-brain barrier.

Conclusion

An increase in the understanding of the various effectors of PPARγ in the CNS and the development of novel agonists for the receptor subtype hold great promise to prevent neurodegeneration.

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