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Mechanisms of anti-inflammatory and neuroprotective actions of PPAR-gamma agonists

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1. ABSTRACT

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors of the nuclear hormone receptor superfamily. The 3 PPAR isoforms (alpha, delta/beta and gamma) are known to control many physiological functions including glucose absorption, lipid balance, and cell growth and differentiation. Of interest, PPAR-gamma activation was recently shown to mitigate the inflammation associated with chronic and acute neurological insults. Particular attention was paid to test the therapeutic potential of PPAR agonists in acute conditions like stroke, spinal cord injury (SCI) and traumatic brain injury (TBI), in which massive inflammation plays a detrimental role. While 15d-prostaglandin J2 (15d PGJ_2) is the natural ligand of PPAR-gamma, the thiazolidinediones (TZDs) are potent exogenous agonists. Due to their insulin-sensitizing properties, 2 TZDs rosiglitazone and pioglitazone are currently FDA-approved for type-2 diabetes treatment. Recent studies from our laboratory and other groups have shown that TZDs induce significant neuroprotection in animal models of focal ischemia and SCI by multiple mechanisms. The beneficial actions of TZDs were observed to be both PPAR-gamma-dependent as well as -independent. The major mechanism of TZD-induced neuroprotection seems to be prevention of microglial activation and inflammatory cytokine and chemokine expression. TZDs were also shown to prevent the activation of pro-inflammatory transcription factors at the same time promoting the anti-oxidant mechanisms in the injured CNS. This review article discusses the multiple mechanisms of TZD-induced neuroprotection in various animal models of CNS injury with an emphasis on stroke.

2. INTRODUCTION

Stroke is the leading cause of long-term disability in the adult population worldwide. A variety of pathophysiological processes contribute to the irreversible neuronal injury that eventually results in neurological dysfunction after stroke. The complex nature of these processes involves specific cell types that effect several downstream signalling pathways. In a majority of stroke patients, only a small area of the brain tissue, the ischemic core, is irreversibly damaged. A much larger volume of the brain tissue surrounding the ischemic core, called the penumbra, can potentially recover if treatment is provided in a timely manner (3). Tissue protection and regeneration are tightly regulated by cell growth, survival and cell death signals provided by the cellular microenvironment. Hence, understanding the molecular mechanisms that govern this microenvironment is essential for the development of targeted therapies that will curtail post-ischemic brain damage (2).

2.1. Inflammation in stroke

In peripheral organs as well as in the central nervous system (CNS), inflammation is an essential component of tissue plasticity and regeneration, and is efficiently orchestrated when pro- and anti-inflammatory components are appropriately modulated (1). Inflammation following focal cerebral ischemia develops by the activation, expression and the secretion of numerous pro-inflammatory genes/proteins from both the brain parenchyma as well as from infiltrating vascular cells (4). The timing and the level of activation of these inflammatory mediators define the beneficial versus the

damaging effects of inflammation since some inflammation is essential for clearing the dead cells and induce plasticity, whereas uncontrolled inflammation precipitates neuronal death (4, 7).

The endothelium which serves as the blood-brain barrier (BBB), is an important regulatory component of cerebral inflammation. The increased expression of adhesion molecules on blood vasculature mediates leukocyte-endothelial cell interactions followed by BBB breakdown and leukocyte infiltration into the brain parenchyma (diapedesis) (1). It has been well established that the extravasation of blood-borne neutrophils and macrophages into the brain tissue is associated with the activation of resident microglia and astrocytes (5). Following injury to the CNS, infiltrating blood-borne cells as well as neurons, astrocytes, microglia and oligodendrocytes generate pro-inflammatory mediators including cytokines, chemokines, prostaglandins and free radicals which exacerbate post-ischemic neuronal death (6).

Cytokines are important molecular signals in the inflammatory response to cerebral ischemia. Several cytokine receptors are known to be expressed constitutively throughout the CNS, albeit at low levels (6, 25). Transient focal ischemia has been shown to induce the expression of several pro-inflammatory cytokines such as tumor necrosis factor (TNF)-alpha, interleukin (IL)-1beta, IL-6 and IL-12 (1, 25, 34, 98). Cytokines upregulate the expression of adhesion molecules such as intracellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1, E-selectin, P-selectin and integrins, thereby mediating the initial attachment and rolling of leukocytes along the vessel walls and finally, their infiltration into brain tissue. Chemokines such as monocyte chemoattractant protein (MCP)-1, macrophage inflammatory protein (MIP)-1alpha and IL-8 are also released by activated microglia and macrophages. They are thought to play a role in inducing and/or sustaining strong interactions between adhesion molecules and leukocytes. Furthermore, chemokines have been suggested to play a role in initiating the transmigration of adhered leukocytes across the BBB into the brain parenchyma (35).

Reactive oxygen species (ROS) have been indicated as one of the earliest components of focal ischemia-induced reperfusion injury (8, 9). Occlusion of a blood vessel impairs oxygen supply to the surrounding tissue, thereby impairing aerobic metabolism leading to depletion of intracellular ATP levels and disturbing the cellular homeostasis. Concurrently, oxidative phosphorylation in the mitochondria is compromised, along with the accumulation of various metabolites which either directly or indirectly cause cellular injury. The continuous actions of these sequential events ultimately lead to necrotic cell death. Reperfusion during ischemia replenishes oxygen supply to the brain tissue, restoring energy and ionic homeostasis to a certain extent but this process actually exacerbates ischemic injury due to elevated production of oxygen- and nitrogen-derived free radicals (9, 27). Free radicals confer considerable oxidative stress on the brain during reperfusion due to the high rate of oxidative metabolic activity, high levels of polyunstaturated fatty acids leading to lipid peroxidation and DNA damage (9, 10).

2.2. Role of transcription factors in post-ischemic inflammation

Cerebral ischemia induces massive changes in gene transcription within minutes of onset (126). Transcription factors are being studied as molecular targets for therapeutic repair, since they intricately regulate a variety of genes that modulate cellular functions. Recent studies from our laboratory and other groups have shown the induction of several transcription factors such as Egr-1, STAT-3, HIF-1, IRF-1, NF-kappaB, ATF-3, CREB and CREM that play a very important role in modulating the expression of inflammatory genes after focal ischemia (68, 69, 127, 128). Transcriptional activation can be viewed as a double-edged sword since individual transcription factors can induce either neuroprotective or neurotoxic genes. Recent studies have shown that transcription factors like interferon regulatory factor (IRF)-1, signal transducer and activator of transcription (STAT)-3, nuclear factor (NF)-kappaB, CCAAT/enhancer binding protein (C/EBP)-beta and early growth response (EGR)-1 promote inflammatory gene expression and thus precipitates severe neuronal damage (60, 69, 123, 128, 129). On the other hand, the activation of transcription factors like nuclear factor-E2 related factor (Nrf)-2, peroxisome proliferator-activated receptor (PPAR)-alpha and PPAR-gamma, cAMP response element- binding protein (CREB) and hypoxia-inducible factor (HIF)-1 have been suggested to be neuroprotective since they curtail oxidative stress and inflammatory gene expression (33, 52, 107, 114, 122). As the transcription of inflammatory genes is the first step of any inflammatory cascade, therapies that target the pro-inflammatory transcriptional events will potentially curtail inflammation at the very beginning of the signalling process.

2.3. Peroxisome proliferator-activated receptor-gamma

PPARs are ligand-activated transcription factors that belong to the nuclear hormone receptor superfamily. Three types of PPARs have been identified – alpha, delta/beta and gamma. They play an important role in glucose and lipid metabolism and cell proliferation and differentiation (11, 12). More recently, much of the research has focused on the anti-inflammatory effects of PPAR activation by its endogenous and exogenous ligands on peripheral organs and the CNS after acute and chronic insults. The PPAR-gamma isoform behaves as a “molecular sensor”, binding a wide range of molecules involved in metabolism, and has been studied extensively in diabetes and obesity due to its role in regulating glucose metabolism (45, 81). PPAR-gamma shows a highly restricted pattern of expression and is mainly observed in adipose tissue where it regulates adipocyte differentiation and lipid metabolism (13). Its expression is also observed in cells of the immune system such as monocytes and macrophages, B and T cells (16). In the normal adult brain, PPAR-gamma shows a relatively low level of expression primarily limited to the granule cells of the hippocampal dentate gyrus (16). Some PPAR-gamma expression has also been observed in the caudate putamen and globus pallidus of the basal ganglia,

Table 1. PPAR distribution and functions in various tissues

PPAR isoform	Organ	Functions
PPAR-alpha	Liver, kidney, skeletal & cardiac muscle	Lipid metabolism, β-oxidation, anti-inflammatory
PPAR-beta/delta	Ubiquitously expressed	Cell differentiation, lipid metabolism, regulation of organogenesis
PPAR-gamma	Adipocytes, immune response cells (monocytes, T & B cells, dendritic cells), epithelial cells	Cell differentiation, lipid metabolism, lipid storage, glucose metabolism and insulin sensitization, anti-inflammatory, anti-angiogenic

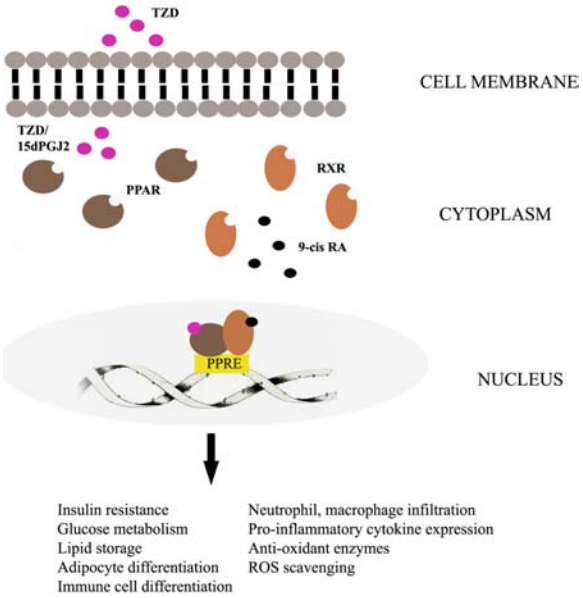

Figure 1. Upon ligand binding, PPAR and RXR dimerize. The heterodimeric complex translocates into the nucleus, where it binds to the PPRE to activate or trans-repress the downstream genes. This leads to the modulation of several physiological and pathological events.

thalamus and the piriform cortex (17). Recent studies indicate that in brain, PPAR-gamma expression is mostly localized in the microglia and astrocytes, the cell types that play a significant role in the inflammatory responses of the CNS (53) (Table 1).

2.3.1. PPAR-gamma ligand-binding and target gene transcription

PPAR-gamma is a ligand-activated transcription factor that forms heterodimers with the retinoid X receptors (RXRs) and binds to specific peroxisome proliferator response elements (PPREs) at the enhancer sites of downstream genes, regulating their transcription (11, 13). PPARγ has the ability to bind a variety of small lipophilic compounds derived from both metabolism and nutrition, which in turn determines the specific co-factors that the transcription factor recruits, and ultimately, the complex pathways by which it regulates gene transcription (24). 15dPGJ2, a non-enzymatic breakdown product of prostaglandin D2, is postulated to be an endogenous PPAR-gamma agonist while a class of synthetic, insulin-sensitizing compounds called thiazolidinediones (TZDs) have emerged as potent, exogenous agonists of PPAR-gamma (11, 14). However TZDs are also known to exert several PPAR-gamma-independent effects (15, 31). Upon ligand binding to PPAR-gamma, the PPAR-gamma:RXR heterodimeric complex recruits co-factor complexes and transactivates (or transrepresses) target genes that are under PPAR control. On the other hand, in the absence of a ligand, the PPAR-gamma:RXR complex can recruit co-repressor complexes and bind to PPRE, suppressing the transcription of target genes (Figure 1).

2.3.2. Metabolic and anti-inflammatory effects of PPAR-gamma

PPAR-gamma activation by its ligands has been thought to regulate glucose and lipid metabolism as well as promote lipid storage and adipocyte differentiation throughout the body (81, 82). In addition, PPAR-gamma has an anti-proliferative function, stimulating the differentiation of fibroblasts into adipocytes (81, 82). Obese Zucker rats show increased number of adipocytes upon treatment with PPAR-gamma agonists, which can be attributed to accelerated adipocyte differentiation (83). Similarly, PPAR-gamma has been implicated in lipid accumulation in activated macrophages (81). PPAR-gamma indirectly improves insulin sensitivity and enhances glucose disposal in adipose tissue and skeletal muscles (24). PPAR-gamma activation by TZDs increases insulin sensitization in patients with type II diabetes mellitus but interestingly, they have no effect in healthy humans and animals (62, 84). Currently, two TZDs, rosiglitazone and pioglitazone, are approved by the Food and Drug Administration (FDA) for human use (47, 66). Besides decreasing insulin resistance, TZDs positively affect the vasculature by decreasing the intimal medial thickness and inhibiting the transendothelial migration of monocytes (66). Thus, TZDs lower hypertension and its associated risks, such as atherosclerosis and stroke (91, 104).

2.3.3. Anti-inflammatory effects of PPAR-gamma activation by TZDs

More recently, the anti-inflammatory functions of PPAR-gamma have received much attention since its agonists have been shown to exert a broad spectrum of protective effects in several animal models of neurologic and cardiovascular diseases (43, 44, 49, 56). A majority of studies have focused on the effects on monocyte/macrophages and endothelial cells since PPAR-gamma may modulate the production of inflammatory cytokines by these cells and might control immune cell differentiation and function (13, 20). Monocytes and macrophages release pro-inflammatory cytokines such as TNF-alpha and IL-6 and free radicals such as NO and superoxide. PPAR-gamma expression is augmented in activated peritoneal murine macrophages and T cells and its activation by specific ligands inhibits the expression of inducible nitric oxide synthase (iNOS), gelatinase B and scavenger receptor A genes (19). PPAR-gamma agonists reduced the production of ROS in human coronary artery endothelial cells and in cardiac fibroblasts (50, 51). Pre-treatment of rats with 3 mg/kg of pioglitazone for 7 days

Table 2. PPAR-gamma ligands

Ligands	Derived from	Binding affinity	Function
Natural			
Linoleic acid	PUFA [1]	μM	
Arachidonic acid	PUFA	μM	
EPA [2]	PUFA	μM	
DHA [3]	PUFA	μM	Lipid-lowering, insulin-sensitizing
9-HODE [4]	Linoleic acid	μM	
13-HODE [5]	Linoleic acid	μM	
15dPGJ2 [6]	Prostaglandin derivative	μM	Anti-inflammatory, insulin-sensitizing
azPC [7]	Oxidized alkyl phospholipid	nM	Induces COX-2 [8] expression, increases PGE2 [9] secretion
Synthetic			
Troglitazone	TZD [10]	~2 - 3 μM	
Ciglitazone	TZD	~8 - 12 μM	Anti-inflammatory
Rosiglitazone	TZD	~ 100 nM	insulin-sensitizing, lipid lowering
Pioglitazone	TZD	> 100 μM	

Polyunsaturated fatty acid,[1] eicosapentaenoic acid [2], docosahexaenoic acid [3], 9-hydroxy-10,12-octadecadienoic acid [4], 13-hydroxy-9,11-octadecadienoic acid [5], 15-deoxy-Δ-12,14- prostaglandin J2 [6], hexadecyl azelaoyl phosphatidylcholine [7], cyclooxygenase-2 [8], prostaglandin E2 [9], thiazolidinedione [10].

Table 3. Genes regulated by PPAR-gamma agonists

Gene	Function
Adipophilin	Fatty acid transport and storage
L-FABP [1]	Fatty acid transport and storage
Regeneration gene IA	Proliferation of pancreatic β and acinar cells
Gob-4 (hAG-2) [2]	Maturation of intestinal goblet cells
NGAL [3]	Anti-inflammatory, lipid metabolism
NF-kappaB [4]	Pro-inflammatory, development
TNF-alpha [5]	Pro-inflammatory, development
IL-2 [6]	Pro-inflammatory cytokine
Catalase	Anti-oxidatant enzyme
Cu/Zn SOD [7]	Anti-oxidatant enzyme
CD36	Macrophage scavenger receptor
SOCS3	Cytokine negative modulator

Liver fatty acid binding protein,[1] human homologue of anterior gradient-2 [2], neutrophil gelatinase-associated lipocalin [3], nuclear factor-kappaB [4], tumor necrosis factor-α [5], interleukin-2 [6], copper/zinc superoxide dismutase [7]

prior to coronary ligation significantly decreased the expression levels of ICAM1 and MCP-1 and also the number of infiltrating macrophages in the ischemic region (90). Thus, pretreatment with pioglitazone was able to limit the extent of myocardial damage in the early inflammatory stage (90). Treatement with 15d-PGJ2 or troglitazone was shown to inhibit the overexpression of IL-1beta, IL-6 and TNF-alpha in phorbol 12-myristate 13-acetate-stimulated human peripheral monocytes (20) (Table 2).

The systemic inflammation related to rheumatoid arthritis possibly accelerates atherogenesis, causing arthritic patients to be at a higher risk for developing coronary heart disease (97). PPAR-gamma agonists decrease the inflammation in joints associated with rheumatoid arthritis and also in the intestine and pancreas, in diabetic patients (45, 92, 94, 97). Cerulein-induced pancreatitis in mice resulted in a robust inflammatory response involving neutrophil infiltration into lung and pancreatic tissue. The enhanced lipid peroxidation and increased immunoreactivity for nitrotyrosine and ICAM1 in the pancreas was decreased by rosiglitazone treatment (93). COX-2 expression, which is an immediate early response to microcirculatory disturbance, resulting in capillary leakage in pancreatitis, was reported to be reduced following PPAR-gamma activation by 15d-PGJ2 (92, 93) (Table 3).

2.3.4. Anti-inflammatory effects of PPAR-gamma activation: contrasting evidence

There have however been some contrasting opinions regarding the role of PPAR-gamma in inflammatory processes. For instance, PPAR-gamma inhibits endothelial cell migration, and plays a key role in influencing the vascular response to atherosclerosis, possibly by reducing the expression of metalloproteinases which are involved in plaque destabilization (51, 61). Rosiglitazone treatment decreased the blood serum levels of matrix metalloproteinase (MMP)-9, TNF-alpha and serum amyloid A in diabetic patients with coronary artery disease, and also decreased T-cell activation, thereby curtailing the inflammatory response (87). In contrast, PPAR-gamma activation was thought to play a pro-atherogenic role, by stimulating the expression of scavenger receptor CD36 and the uptake of oxidized LDL by macrophages (61, 81). Also, the finding that TZD and non-TZD PPAR-gamma agonists, with the exception of 15dPGJ2, do not inhibit LPS-induced production of cytokines led to the hypothesis that PPAR-gamma activation is not the major mechanism by which monocyte activation is inhibited, and that PPAR-gamma agonists prevent cytokine production by macrophages by a PPAR-gamma-independent mechanism (63). Patients with type-II diabetes mellitus are known to be at a higher risk for cardiovascular disorders and as mentioned earlier, TZDs

have been effectively used to improve insulin sensitivity and regulate glucose metabolism in diabetics (24, 62, 66, 84). A recent study showed that diabetic patients who were chronically treated with rosiglitazone, were at a higher risk to suffer from myocardial infarction and cardiovascular disorders in general, compared to those who received placebo. This raises concerns regarding the use of rosiglitazone as an anti-diabetic drug, since most diabetic patients are being treated effectively with rosiglitazone (120). Further studies need to be carried to determine exactly how rosiglitazone administration increases the risk for cardiovascular disorders.

Rosiglitazone and pioglitazone have been beneficial in treating various kidney injuries including nephropathy resulting from diabetes, hypertension and cyclosporine-induced renal injury (95). The observed protection has been attributed to improved insulin sensitivity and glucose metabolism and reduced inflammation and apoptosis in the kidneys. 15d-PGJ2 was also shown to protect the kidneys from ischemic injury by inhibiting NF-kappaB activation and other pro-inflammatory proteins like AP-1, ICAM1 and iNOS, thereby decreasing oxidative stress (23, 95, 96)(Table 3).

3. PPAR-GAMMA EFFECTS IN THE CNS

Interest in PPAR-gamma activation in regulating several CNS metabolic functions under both normal as well as pathological conditions stemmed from studies of non-steroidal anti-inflammatory drugs (NSAIDS) in Alzheimer's disease (AD). NSAIDs were shown to decrease neuronal vulnerability by inhibiting COX-2, a key component of the inflammatory cascades following AD (86). PPAR-gamma activation in macrophages was shown to reduce the expression of TNF-alpha and iNOS, thus limiting the inflammatory damage and improving cognition AD patients (42, 56). TZDs have been shown to be beneficial in several cellular and animal models of CNS diseases where inflammation is a major component of the progressive neurological deficit (54, 55, 56, 65, 119). Their efficacy in improving insulin sensitivity correlates with the reduction of diabetes-induced acute brain damage, since chronic hyperglycemia is a major risk factor for neuropathy and vasculopathy (81). Treatment with TZDs significantly reduced the symptoms associated with Parkinson's disease and showed improved protection of dopaminergic neurons (21).

Multiple sclerosis (MS) is a chronic degenerative disease in which the oligodendrocytes and myelin sheath are destroyed, resulting in focal sclerotic lesions in the CNS and progressive axonal damage (64). In MS, myelin-reactive T-cells are activated, accompanied by cytokine secretion and the differentiation of encephalogenic Th1 cells. In experimental autoimmune encephalomyelitis, which is an animal model of MS, PPAR-gamma agonists suppressed T-cell activation (54). Furthermore, PPAR-gamma induction in microglia and macrophages correlated with decreased microglial and macrophage activation, decreased release of pro-inflammatory mediators and improved neurological outcome (64, 65). Amyotrophic lateral sclerosis (ALS) is characterized by a loss of motor neurons associated with a robust glial response including microglial and astrocytic activation and the upregulation of COX-2 and iNOS in the spinal cord (89). Similar pathological features can be observed in the ALS animal model, transgenic mice overexpressing SOD1-G93A (117). Oral treatment of these mice with pioglitazone decreased motor neuronal loss and muscular atrophy and prevented microglial activation at the degenerative sites (88). In addition, pioglitazone treated-SOD1-G93A mice showed decreased pro-inflammatory gene expression, and a simultaneous upregulation of anti-inflammatory gene expression, which ultimately delayed the overall progression of ALS (88).

4. PPAR-GAMMA LIGANDS INDUCE NEUROPROTECTION AFTER SPINAL CORD INJURY

Spinal cord injury (SCI) results in a necrotic area of cavitation that progressively increases in area due to secondary neuronal death promoted by acute inflammation, edema, apoptosis and glial scarring (39, 57, 59). The acute loss of motor neurons and degeneration of white matter tracts results most often in irreversible motor dysfunction (57). As in the case of focal cerebral ischemia, PPAR-gamma is upregulated after SCI (39, 59). Our group recently showed that treatment with rosiglitazone and pioglitazone effectively reduces inflammation, the development of motor dysfunction and neuropathic pain after SCI in adult rats (59). Acute administration of these TZDs significantly decreased the lesion size, by curtailing microglial activation and astrogliosis (59). In particular, pioglitazone administration prevented the induction of pro-inflammatory IL-1beta, IL-6 and MCP-1, compared to vehicle-treated controls or animals pre-treated with PPAR-gamma antagonist GW9662 (59). Knockout mice lacking pro-inflammatory genes such as ICAM1 and NF-kappaB show decreased neuronal loss after SCI (58). Similarly, in adult rats treated with TZDs, post-SCI induction of ICAM1 and NF-kappaB was significantly curtailed (59). Rats treated with pioglitazone for 7 days after a mid-thoracic contusion showed significantly improved Basso, Beattie and Bresnahan (BBB) scores during the following 5 weeks, and greater preservation of grey and white matter sparing around the epicenter, compared to vehicle-treated animals (39). Thus, the ability of PPAR-gamma agonists to suppress the expression of pro-inflammatory mediators following acute and chronic CNS insults provided a link between their activation and the observed protection in neuroinflammatory conditions.

5. PPAR-GAMMA AND FOCAL CEREBRAL ISCHEMIA

Neuronal injury following focal cerebral ischemia is associated with massive inflammation, resulting in brain damage (1, 79, 118). Several groups have studied the effects of PPAR-gamma activation by its endogenous and synthetic ligands in ameliorating inflammatory cascades in animal models of focal ischemia. As mentioned

earlier, the synthetic ligands of PPAR-gamma, rosiglitazone and pioglitazone, which belong to the TZD class of agonists, have been approved by the FDA to treat type-II diabetes mellitus. Diabetic patients face an increased propensity to suffer a stroke, and stroke inflicts significantly more damage in diabetic and hypertensive patients than in normoglycemic and/or normotensive individuals (32, 33, 101). It was first observed that the PPAR-alpha and the PPAR-gamma agonists protect against stroke and that this beneficial outcome is associated with improved endothelial relaxation, reduced oxidative stress and decreased VCAM1 and ICAM1 expression (26, 101, 104). Several animal studies have demonstrated the beneficial effects of TZDs in improving post-ischemic functional outcome. After focal ischemia, PPAR-gamma expression was observed to be increased in the brain, especially in the peri-infarct area, but surprisingly, its DNA-binding activity was reported to be reduced (15, 37). Also, PPAR-gamma agonists trans-repress the transcription of downstream pro-inflammatory genes after ischemia (37)(Table 3). Furthermore, the administration of rosiglitazone or pioglitazone increases the translocation of PPAR-gamma to the nucleus in neurons and this is further enhanced in the presence of retinoic acid (37, 38). Freshly prepared peripheral blood monocytes treated with TZDs showed decreased cytokine release after activation and 15d-PGJ2 modified target gene expression changes when administered to peritoneal macrophages (20, 85). Based on these findings, a recent study demonstrated that PPAR-gamma inhibits scavenger receptor-A, iNOS and MMP-9 expression by antagonizing the AP-1, STAT and NF-kappaB transcriptional pathways, possibly by decreasing DNA binding (19, 29, 30).

5.1. Pretreatment with PPAR-gamma agonists induces neuroprotection after cerebral ischemia

Several pre-conditioning experiments, where animals were either injected with TZDs or fed TZD-fortified diets, have shown significant neuroprotection when these animals were subjected to focal cerebral ischemia (15, 40, 41). In adult rodents, pre-treatment with rosiglitazone or pioglitazone one day prior to ischemia resulted in decreased microglial activation and macrophage infiltration, as well as decreased expression of pro-inflammatory COX2, iNOS and IL-1beta mRNA in the ischemic hemisphere (33, 41). Rosiglitazone pre-treatment in both rats and mice also significantly decreased the infarct volume following focal ischemia and this effect was completely reversed when a specific PPAR-gamma-antagonist, GW9662 was administered prior to TZD treatment (33, 37). Direct intracerebroventricular administration of pioglitazone for 5 days prior to and 2 days following ischemia also resulted in increased sensory neurologic scores compared to untreated controls accompanied by reduced infarct volume and edema (40). In another study, rats tube-fed with rosiglitazone for 7 days prior to and 3 days following transient focal ischemia showed increased endothelial nitric oxide synthase (eNOS) levels that correlated with increased angiogenesis and ischemic tolerance (46). PPAR-gamma agonist-induced neuroprotection seems to be specific for injuries in which the main propagator of cell death is either inflammation or free radical generation. For instance, rats fed on a pioglitazone-enriched diet for three days developed significantly smaller infarcts and showed better neurological outcomes following transient focal ischemia. The observed neuroprotection was thought to be mediated in part by the upregulation of antioxidant enzymes, catalase and copper/zinc superoxide dismutase (Cu/Zn-SOD), which minimizes oxidative stress by decreasing oxygen and nitrogen free radical generation (95, 111). The beneficial effect of pioglitazone pre-treatment was not observed in rats that were subjected to permanent focal ischemia, as against rats subjected to transient focal ischemia, indicating that the beneficial effects of TZDs are limited to reperfusion-induced damage (36). *In vitro*, pre-treatment with PPAR-gamma agonists protected an immortalized mouse hippocampal cell line against oxidative stress induced by glutamate or hydrogen peroxide (H_2O_2) (49).

5.2. TZDs prevent ischemic cell death by decreasing oxidative stress and ROS production

Tureyen *et al.* (33) showed a dose-dependent increase in rosiglitazone-induced neuroprotection in normotensive as well as in spontaneously hypertensive adult rats. The reduction in infarct volume was accompanied by a decrease in pro-inflammatory gene expression concomitant with an increase in anti-oxidant and anti-inflammatory gene expression (33). Rosiglitazone treatment induced neuroprotection even with a single dose administered as late as 2h of reperfusion (33). The anti-oxidant enzyme catalase, is ubiquitous to all cell types including glia and neurons (115, 116). It is mainly present in the peroxisomes, where it protects cells from the toxic effects of H_2O_2 by degrading it. In the cytosol, Cu/Zn-SOD plays a major role in degrading free oxygen radicals and endothelial Cu/Zn-SOD prevents free oxygen-mediated reduction of eNOS (111). Under conditions of natural stress, catalase and Cu/Zn-SOD proteins are significantly upregulated, suggesting increased cell viability through decreased oxidative stress. The catalase and SOD gene promoters contain the PPRE, indicating that they are directly regulated by PPAR-gamma (18, 111). It is known that transient cerebral ischemia causes a marked increase in the production of ROS, while at the same time, reducing hippocampal levels of glutathione (GSH), an important ROS scavenger (8). In normotensive and hypertensive animals treated with rosiglitazone, ischemic hemispheres showed increased catalase and Cu/Zn-SOD activity in the peri-infarct region, indicating activation of anti-oxidant mechanisms in response to excessive ROS production. This increase in catalase and Cu/Zn-SOD corresponded to decreased COX-2 and iNOS immunostaining in peri-infarct neurons (33). Furthermore, the depletion of GSH was prevented by both pioglitazone and rosiglitazone treatment in adult rats subjected to cerebral ischemia (8). Similarly, in a mouse model of transient focal ischemia, intraperitoneal injections of rosiglitazone at various concentrations induced increased translational activity of PPAR-gamma, associated with reduced infarct volume and improved neurological scores and this effect was completely blocked by the PPAR-gamma antagonist GW9662-(41).

Cyclooxygenase-1 (COX-1) plays an important role in maintaining physiological homeostasis in almost all mammalian cells and in protecting brain tissue from ischemia-reperfusion injury through the production of prostaglandins (74). COX-1 overexpression induces neuroprotection by inducing vasodilator prostaglandins PGI_2, PGD_2 and PGE_2 after focal ischemia, while this protective effect was abolished in COX-$1^{-/-}$ mice, which showed increased levels of pro-inflammatory leukotriene B4 production (75). Another isoform of COX, COX-2, has similar enzymatic properties as COX-1, but different biological functions. It is virtually undetectable in brain cells under physiological conditions but is rapidly and robustly induced in response to pro-inflammatory stimuli, growth factors and mitogens (76). In rats with adenovirally amplified production of COX-1, the endogenous ligand of PPAR-gamma, 15d-PGJ2 was increased by nearly 3 fold in the cortex, compared to controls (76). Increased expression of 15d-PGJ2 or the infusion of rosiglitazone was accompanied by decreased infarct volume, reduced necrotic and apoptotic cell death as evidenced from reduced caspase-3 levels and decreased concentrations of H_2O_2 after focal ischemia (77). This beneficial effect was eliminated by the administration of GW9662, showing that both rosiglitazone as well as 15d-PGJ2 induced neuroprotection in a PPAR-gamma-dependent manner (77).

The generation of ROS is known to be associated with the induction of apoptosis and TZDs have been postulated to reduce apoptotic cell death in the ischemic hemisphere (112, 113). For instance, pioglitazone prevented ischemia-induced increases in pro-apoptotic Bax, while increasing anti-apoptotic Bcl-2 expression in the peri-infarct area following focal ischemia (47, 48). Cytochrome-C release from mitrochondria (a marker for apoptosis) occurs due to the switch from a 4-electron reduction of oxygen to a 1-electron reduction (80). Overexpression of Bcl-2 prevents apoptosis by blocking cytochrome-C release (80). Following acute and chronic CNS insults, NMDA receptor-mediated neurotoxicity mediates the production of oxygen free radicals and nitric oxide (NO) (78, 79). In cortical cultures, pre-treatment with catalase or SOD results in a partial reduction in apoptosis triggered by low concentrations of NMDA (78). However this reduction depends on the intensity of the initial insult and necrotic cell death induced by high concentrations of NMDA are not prevented by catalase or SOD (78). Thus after an acute insult like ischemia, administration of TZDs significantly increases the production of anti-oxidant enzymes such as catalase and SOD, increasing free radical scavenging in the peri-infarct area (33).

5.3. Ligand efficacy of PPAR agonists, rosiglitazone and pioglitazone in CNS injury

The relative efficacies of the different TZDs have not been clearly understood. For instance, of the TZDs, rosiglitazone binds to the receptor with ten times more affinity (Kd of ~40nM) than pioglitazone (Kd of ~400nM) (11, 121). However, pioglitazone crosses the blood brain barrier much more easily than rosiglitazone, which may indicate that higher doses of rosiglitazone might be needed to achieve the same degree of neuroprotection as that induced by pioglitazone (11). In addition, it appears that pioglitazone also functions as a partial PPAR-alpha agonist, whereas rosiglitazone functions as a pure PPAR-gamma agonist (47). PPAR-alpha activation is also known to induce neuroprotection after focal ischemia (26, 122). The fact that pioglitazone, which has a lower affinity for PPAR-gamma activation, is effective at much lower concentrations than a pure PPAR-gamma agonist such as rosiglitazone, indicates that other factors must be involved in determining the efficacy individual TZDs. Studies from our lab showed that comparable doses of rosiglitazone and pioglitazone are needed to induce the same degree of neuroprotection following focal ischemia as well as SCI despite the 10 times higher affinity of rosiglitazone for PPAR-gamma (33, 59)(Table 2).

6. PPAR-GAMMA-INDEPENDENT-MECHANISMS

The endogenous ligand of PPAR-gamma, 15d-PGJ2, has been shown to directly (without involving PPAR-gamma) prevent microglial and astroglial activation by bacterial endotoxins (53). A recent study also showed that 15d-PGJ2 was unable to activate a PPAR reporter gene transfected into a glial cell line, suggesting that it might act independently of PPAR-gamma activation (22). Subsequent studies by several groups have shown that 15dPGJ2 mediates its anti-inflammatory effects by directly binding to and inactivating I-kappaB kinase (23). This enzyme is responsible for phosphorylating and degrading the I-kappaB protein, which is a necessary step for NF-kappB activation. In addition, a recent study showed that 15d-PGJ2 probably reduces NF-kappaB binding by alkylating the p50/p65 dimers (29). Huang *et al.* (28) demonstrated that IL-4 induces the generation of endogenous ligands for PPAR-gamma by activating the 12/15-lipoxygenase pathway in macrophages, suggesting an IL-4-mediated down-regulation of iNOS expression. These studies suggested that PPAR-gamma agonists might mediate anti-inflammatory effects through PPAR-gamma-independent mechanisms as well.

A novel mechanism for the PPAR-gamma-independent anti-inflammatory actions of TZDs, is the involvement of the Janus kinase (JAK) and the STAT signaling pathways (33, 67, 68). Transphosphorylation of the cytokine receptor-associated JAK leads to its dimerization and phosphorylation of the downstream STATs. Phosphorylated STATs dimerize, translocate into the nucleus and bind to the response element on DNA, leading to the production of the suppressor of cytokine signaling (SOCS) proteins. SOCS acts as a negative feedback regulator and inhibits further JAK and STAT phosphorylation, thus preventing the upregulation and binding of cytokines to their receptors after an acute CNS insult (33, 67). Our recent studies showed that focal ischemia induces a massive upregulation of IL-6, which increases the phosphorylation of the JAK2 and STAT3 isoforms in the ischemic hemisphere (68, 69, 123). Although physiological levels of STAT3 activation are essential for normal cellular functions, its excessive phosphorylation as seen after focal cerebral ischemia is neurotoxic. Thus, inhibiting STAT3 phosphorylation using

an siRNA specific for STAT3 induced significant neuroprotection (68). Similarly, knocking down SOCS3 protein induction with an antisense oligonucleotide exacerbates ischemic neuronal damage (69). Our laboratory showed that rosiglitazone treatment as late as 2h of reperfusion after focal ischemia, induced SOCS3 expression and prevented both JAK2 as well as STAT3 phosphorylation, conferring neuroprotection (33).

15d-PGJ2 and rosiglitazone are potent inducers of SOCS proteins and the overexpression of either SOCS1 or SOCS3 diminished STAT phosphorylation in primary astrocytes (67). CD40, a member of the tumor necrosis factor receptor superfamily, is expressed on a wide variety of immune response cells such as B cells, microglia, macrophages, endothelial cells, fibroblasts and tumor cells (124). Its signaling activity results in the upregulation of pro-inflammatory adhesion molecules (ICAM1, VCAM1, E-selectin and P-selectin) and cytokines and chemokines (IL-1, IL-6, IL-8, IL-12, TNF-alpha and MIP-1alpha) and has been implicated in the pathogenesis of several CNS disorders (71, 72). Wesemann *et al.* (70) showed that overexpression of SOCS1 inhibits CD40 expression by preventing STAT1 phosphorylation, suppressing TNF-alpha secretion and the subsequent NF-kappaB activity in macrophages stimulated by IFN-gamma (70).

In addition to the neuroprotective actions of SOCS1 and SOCS3 by 15d-PGJ2 and rosiglitazone, two other family of proteins, the SH2-containing phospatases (SHPs) and the protein inhibitors of activated STATs (PIAS) act cooperatively with the SOCS proteins to inhibit cytokine overproduction (67, 73). Park *et al.* (67) proposed that SHP activation in microglia might be directly related to attenuated brain inflammation. Thus, the induction of SOCS proteins after treatment with TZDs provides a novel mechanism for the observed neuroprotection, which is independent of PPAR-gamma activation, since SOCS proteins can negatively modulate cytokine production by inhibiting the JAK-STAT signaling pathway or by cooperatively acting via the SHPs and PIAS, or, they can suppress NF-kappaB activity by decreasing TNF-alpha secretion by macrophages in response to inflammatory stimuli.

7. PPAR-ALPHA AND PPAR-DELTA/BETA AGONIST-INDUCED NEUROPROTECTION

The mechanisms of action of the other isoforms of PPAR, PPAR-alpha and PPAR-delta/beta have also been studied in the context of cellular metabolism, inflammation and immune reponse in the CNS and peripheral organs after injury. The binding of fibrates and endogenous eicosanoids and fatty acids to PPAR-alpha regulates lipid homeostasis (99). Permanent PPAR-alpha stimulation has been observed in obese patients, caused by the elevation of fatty acids in the blood (62). PPAR-alpha has been implicated in the inflammatory response to injury since it is expressed when human monocytes differentiate into macrophages (125). Similar to the action of PPAR-gamma, PPAR-alpha agonists also inhibit the NF-kappaB pathway by increasing I-kappaB-alpha, which correlates with the diminished activity of NF-kappaB in aged animals following PPAR-alpha agonist administration (100). PPAR-alpha plays a very important regulatory role in response to injury or stress. In atherosclerotic studies, PPAR-alpha activation decreases the level of pro-atherosclerotic fibrinogen and C-reactive protein (62). Treatment with fenofibrate, a potent exogenous PPAR-alpha agonist, inhibited left ventricular hypertrophy by stimulating free fatty acid uptake and beta-oxidation (101). In contrast, obesity is attributed to the permanent stimulation of PPAR-alpha, which leads to excessive beta-oxidation and free fatty acid uptake, which ultimately results in lipotoxicity and cardiomyopathy (102). PPAR-alpha agonist-induced neuroprotection after cerebral ischemia involves both cerebral and vascular mechanisms. Used as a lipid-lowering agent, fenofibrate prevents post-ischemic dysfunction of vascular endothelium and improves endothelium-dependent vasodilation in patients with hypertriglyceridemia (103). Thus, PPAR-alpha agonists are thought to induce neuroprotection by lowering oxidative stress and inflammation (26). A 14 day pre-treatment with fenofibrate significantly reduces the susceptibility of mice deficient in apolipoprotein E and decreases the infarct volume in wild type mice subjected to focal cerebral ischemia (26). It has been shown that bezafibrate, a PPARalpha/gamma dual agonist, decreases mortality associated with global cerebral ischemia in gerbils by decreasing anerobic metabolism in the injured tissue (106). In both SCI as well as cerebral ischemia models, PPAR-alpha agonists exert neuroprotection primarily when administered prior to the injury, mainly by increasing endothelial-dependent vasodilation, which is independent of eNOS, since fibrates have limited capability to cross the BBB (26, 42). Fibrates prevent secondary neuronal death by oxidative stress by enhancing the expression of anti-oxidant enzyme, Cu/Zn-SOD and by decreasing VCAM-1 expression in CNS blood vessels, possibly by inhibiting the NF-kappaB pathway (42, 108).

PPAR-delta/beta is ubiquitously expressed in all tissues and recent studies have shown that PPAR-delta/beta plays a key role in lipid metabolism by regulating serum lipid profiles and fatty acid beta-oxidation in muscle and adipose tissue (11, 12, 81, 104). In cultured cardiomyocytes, PPAR-delta/beta agonist GW0742 inhibited LPS-induced TNF-alpha secretion, while the absence of PPAR-delta/beta further increased TNF-alpha secretion (109). Intracerebroventricular administration of high affinity PPAR-delta/beta agonists such as L-165041 and GW501516 significantly decreased the infarct volume at 24h of reperfusion after cerebral ischemia in rats (110). Furthermore, PPAR-delta/beta agonists prevented the loss of striatal dopamine after MPTP administration, suggesting that PPAR-delta/beta could serve as a potential therapeutic target in several CNS diseases (110).

8. CONCLUSIONS

The treatment of acute CNS insults, especially, cerebral ischemia, has been limited to either the prevention of the risk factors associated with the induction of the insult, or to the careful regulation of the coagulation

processes that occur during the acute phase. Uncontrolled inflammation has been identified as one of the key events in exacerbating the neuronal damage after ischemic and traumatic insults to the CNS, since inflammatory cascades progressively induce cells even in the peri-infarct areas to undergo apoptosis. This results in an expansion of the secondary injury, worsening the neurological outcomes. Transcriptional regulation of metabolism under physiological conditions involves the transduction of specific signals to the nucleus to target specific genes, which affects long-term expression levels of key proteins. This regulation is disturbed under pathophysiological conditions (81). Hence, transcription factors have emerged as novel targets for drug therapy research, since they regulate several pro- and anti-inflammatory genes in a time-dependent fashion after a CNS insult. Therapies that promote anti-inflammatory gene expression and/or control the extent of inflammation will prove to be effective at curtailing secondary neuronal death. PPAR-gamma activation by TZDs has been shown to exert multi-factorial anti-inflammatory effects in several peripheral organ models of inflammation. In the CNS, PPAR-gamma mRNA is increased after an insult and the administration of its exogenous ligands like TZDs prior to or immediately after an insult increases PPAR-gamma DNA-binding and the transcription of several anti-inflammatory target genes. TZD administration has been shown to exert neuroprotection by decreasing uncontrolled microglial activation and neutrophil/macrophage infiltration, decreasing pro-inflammatory gene expression, and also, by increasing anti-oxidant enzymatic activity and heat-shock gene expression. PPAR-gamma-independent mechanisms of neuroprotection have been described for both TZDs as well as its naturally occurring ligand, 15d-PGJ2. In this case, PPAR-gamma agonists directly inhibit pro-inflammatory cytokine signaling pathways while increasing the production of anti-inflammatory-SOCS-proteins.

Thus, the hypothesis that PPAR-gamma agonists could decrease neuronal death after acute CNS insults and chronic neurodegenerative diseases is supported by much experimental evidence from models of focal cerebral ischemia, SCI, MS, AD and PD. A lot of work has been carried out elucidating possible PPAR-gamma-independent mechanisms of its agonists. However, more studies are necessary to identify the pathways underlying the direct regulation of the inflammatory response by PPAR-gamma agonists.

Agonists for the three PPAR isoforms have distinct as well as overlapping effects on the inflammatory response. Furthermore, different concentrations of these ligands also exert different effects on cytokine expression. For instance, PPAR-gamma-specific agonist, ciglitazone, efficiently inhibited IL-2 production by activated T cells, while low concentrations of WY14,643, a PPAR-alpha agonist, strongly inhibited IFN-gamma expression and only modestly inhibited IL-2 production, while augmenting IL-4 production (13). In contrast, a highly potent PPAR-alpha agonist, GW7647 did not increase IL-4 levels (13). PPAR-alpha agonist fenofibrate has been shown to be effective in rendering the brain resistant to the incidence of stroke, since it induces cytoprotective proteins such as anti-oxidant enzymes and heat shock proteins, while inhibiting inflammatory, oxidative and apoptotic genes (105). The development of more potent PPAR-gamma agonists and/or the use of a combination of agonists for the different PPAR isoforms might provide further improvements in the treatment of acute CNS insults and increase functional recovery. Furthermore, genetic manipulations by which PPAR activity is increased only in the tissue of interest will potentially prevent any toxic side-effects that have been observed with the use of high concentrations of these drugs.

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