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Peroxisome proliferator-activated receptor γ (PPARγ): A master gatekeeper in CNS injury and repair

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Abstract

Peroxisome proliferator-activated receptor γ (PPARγ) is a widely expressed ligand-modulated transcription factor that governs the expression of genes involved in inflammation, redox equilibrium, trophic factor production, insulin sensitivity, and the metabolism of lipids and glucose. Synthetic PPARγ agonists (*e.g.* thiazolidinediones) are used to treat Type II diabetes and have the potential to limit the risk of developing brain injuries, such as stroke, by mitigating the influence of comorbidities. If brain injury develops, PPARγ serves as a master gatekeeper of cytoprotective stress responses, improving the chances of cellular survival and recovery of homeostatic equilibrium. In the acute injury phase, PPARγ directly restricts tissue damage by inhibiting the NFκB pathway to mitigate inflammation and stimulating the Nrf2/ARE axis to neutralize oxidative stress. During the chronic phase of acute brain injuries, PPARγ activation in injured cells culminates in the repair of gray and white matter, preservation of the blood-brain barrier, reconstruction of the neurovascular unit, resolution of inflammation, and long-term functional recovery. Thus, PPARγ lies at the apex of cell fate decisions and exerts profound effects on the chronic progression of acute injury conditions. Here, we review the therapeutic potential of

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PPARγ in stroke and brain trauma and highlight the novel role of PPARγ in long-term tissue repair. We describe its structure and function and identify the genes that it targets. PPARγ regulation of inflammation, metabolism, cell fate (proliferation/differentiation/maturation/survival), and many other processes also has relevance to other neurological diseases. Therefore, PPARγ is an attractive target for therapies against a number of progressive neurological disorders.

Keywords

Thiazolidinedione; Nrf2; stroke; traumatic brain injury; inflammation; remyelination

1. Introduction

Peroxisome proliferator-activated receptor γ (PPARγ) is a member of the pleiotropic nuclear receptor 1C (NR1C) family (also known as the PPAR family) (Janani and Ranjitha Kumari, 2015). This nuclear receptor family encompasses a group of ligand-modulated transcription factors with broad tissue distributions and a wide array of target genes and functions (Grygiel-Gorniak, 2014). PPARγ is a master gatekeeper of the expression of numerous genes, including G-protein coupled receptors, growth factors, antioxidant enzymes, stem cell genes, kinases, cytokines/chemokines, pro-inflammatory factors, ion channels, and transporters. PPARγ plays a well-established role in the regulation of adipocyte differentiation and the metabolism of lipid and glucose (Janani and Ranjitha Kumari, 2015). Thus, synthetic PPARγ ligands such as thiazolidinediones (TZDs or glitazones) are currently prescibed worldwide to treat hyperglycemia and diabetes and can be readily side-tracked for use in other conditions. Aside from its role in metabolic regulation, anti-inflammatory and protective effects of PPARγ have also been widely studied. For example, PPARγ activation is known to mitigate neuroinflammation and exert direct neuronal protection after central nervous system (CNS) injuries (Gillespie *et al.*, 2011).

Acute CNS injuries are among the leading causes of disability, mortality, and morbidity worldwide (Murray and Lopez, 1997). Tissue damage in these conditions is elicited by both primary and secondary mechanisms, and impacts almost every component of the CNS, including grey matter, white matter, and the vascular network. A growing body of evidence indicates that PPARγ is critically involved in the long-term promotion of tissue repair and rescue of brain cells. In addition, PPARγ directly or indirectly controls the manifestation of comorbid diseases such as diabetes and hypertension, which can profoundly influence the onset and outcome of CNS injuries. Given its dominant position as a master gatekeeper of gene expression, PPARγ is an attractive therapeutic target for injury conditions such as ischemic stroke, hemorrhagic stroke, traumatic brain injury (TBI), and spinal cord injury (SCI).

In this article, we briefly review the numerous functions of PPARγ and their effects on CNS injury. We begin by describing the pathophysiological mechanisms underlying CNS injury in both the acute injury phase and the chronic repair phase. We discuss the contributions of comorbidities to increased disease incidence and negative clinical outcomes and their

modulation by PPARγ. The key role of PPARγ in tissue repair and regeneration is highlighted throughout this review. Finally, we will end with our perspectives on PPARγ-related translational therapies.

2. PPARγ overview

2.1 PPARγ structure and CNS distribution

PPARs, or NR1Cs, were first cloned in rodent hepatocytes in the 1990s, and found to be activated by a group of peroxisome proliferators (Issemann and Green, 1990). PPARs are ligand-activated transcription factors that influence the expression of a number of genes, among which metabolism-related genes are the best documented (Michalik and Wahli, 2006). Three isotypes of PPARs have been identified in mammals—PPARα (NR1C1), δ/β (NR1C2), and γ (NR1C3). As with all other nuclear receptors, PPARs share similar structural features and contain the following functional domains: a N-terminal ligand-independent functional domain, a DNA-binding domain that specifically recognizes peroxisome proliferator response elements (PPREs), a flexible hinge region, and a C-terminal ligand binding domain (LBD) (Zoete *et al.*, 2007). The three PPAR isotypes are encoded by genes located on different chromosomes (Greene *et al.*, 1995) and exhibit distinct tissue distribution patterns and biological functions. PPARα is mainly expressed in tissues with high fatty acid metabolism, including liver, kidney, and white and brown adipose tissue (Delerive *et al.*, 2000; Lo Verme *et al.*, 2005; Neschen *et al.*, 2007). PPARδ/β is ubiquitously and abundantly expressed in a broad range of tissues and regulates fatty acid oxidation (Wang *et al.*, 2003b; Stephen *et al.*, 2004). PPARγ consists of two isoforms in human and rodents—PPARγ1, a ~54.5 kDa shorter form, and PPARγ2, a ~57.6 kDa longer form (Chen *et al.*, 2012) (Figure 1A). PPARγ2 is restricted to adipose tissue and plays an important role in adipocyte differentiation. In contrast, PPARγ1 is expressed in various cell types, including brain cells such as neurons and glia, and bone marrow derived immune cells (Zhu *et al.*, 1995; Elbrecht *et al.*, 1996)

Post-translational modulations (PTMs) of specific amino acids influence PPARγ activity and its functional states (Kim *et al.*, 2013). The major types of PTMs that regulate PPARγ function are phosphorylation, SUMOylation, and ubiquitination (Figure 1B). Ser112 phosphorylation decreases PPARγ activity if induced by mitogen-activated protein kinases (Hu *et al.*, 1996; Shao *et al.*, 1998), but increases PPARγ activity if induced by cyclin-dependent kinase (CDK) 7 and CDK9 (Compe *et al.*, 2005; Iankova *et al.*, 2006). CDK5-mediated Ser273 phosphorylation of PPARγ leads to reduced insulin sensitivity (Choi *et al.*, 2010; Choi *et al.*, 2011). SUMOylation at Lys107 results in decreased activity, whereas Lys395 SUMOylation is strongly associated with PPARγ transrepression of nuclear factor (NF)-κB (Yamashita *et al.*, 2004; Pascual *et al.*, 2005; Jennewein *et al.*, 2008; Pourcet *et al.*, 2010). The latter function is particularly important in anti-inflammatory effects and will be descibed in Section 2.3. Ubiquitination of PPARγ tags it for proteasomal degradation, a process that is enhanced by interferon (IFN)-γ (Waite *et al.*, 2001) and tumor necrosis factor (TNF)-α (He *et al.*, 2008), and repressed by sirtuin 1 (Picard *et al.*, 2004; Floyd *et al.*, 2008).

All three subtypes of PPARs are expressed in the CNS, albeit at different levels (Elbrecht *et al.*, 1996; Braissant and Wahli, 1998; Cullingford *et al.*, 1998; Moreno *et al.*, 2004). Whereas PPAR δ/β is broadly and robustly expressed in the CNS, PPARα and PPARγ exhibit a more restricted pattern of distribution (Braissant and Wahli, 1998; Cullingford *et al.*, 1998; Moreno *et al.*, 2004). Under physiological conditions, PPARγ is readily detectable in select areas, such as the basal ganglia, thalamus, piriform cortex, and hippocampus (Braissant and Wahli, 1998 ; Moreno *et al.*, 2004) and this expression is mainly in neuronal cells (Ferguson *et al.*, 2014). A fraction of astrocytes (20-40%) also express PPARγ, predominantly in processes rather than somata (Warden *et al.*, 2016). Although PPARγ expression has been observed in microglial cultures (Bernardo *et al.*, 2000), it is barely detectable in this cell type *in vivo* under physiological conditions. However, lipopolysaccharide (LPS) stiumlation significantly increases microglial PPARγ expression in the brain, indicating that microglial PPARγ expression may be dependent on inflammation status (Warden *et al.*, 2016).

2.2 PPARγ ligands

PPARγ ligands can be classified into three major categories. Category A includes natural (endogenous) agonists, such as unsaturated fatty acids, eicosnanoids, oxidized phospholipids, and nitroalkenes. Among these agonists, an eicosanoid termed prostaglandin metabolite 15-deoxy-D12, 14 prostaglandin J2 (15d-PGJ2) was the first specific endogenous ligand of PPARγ to be identified and has been widely used in studies of PPARγ in various disease models (Forman *et al.*, 1995). Category B includes synthetic agonists: 1) TZDs such as pioglitazone (PGZ), ciglitazone (CGZ), triglitazone (TGZ), and rosiglitazone (RGZ), 2) non-TZD agonists, 3) dual-α/γ agonists, 4) pan-α/β/γ agonists, and 5) selective PPARγ modulators. Among these, TZDs were the first to be synthesized and are widely used in diabetic patients (Lehmann *et al.*, 1995), as well as in experimental models to assess the effects of PPARγ activation. Category C includes synthetic antagonists, such as bisphenol A diglyceryl ether, GW9662, LG100641, PD068235, T0070907, and SR-202. Among these, GW9662 is an irreversible PPARγ antagonist that has been widely applied in research on PPARγ (Leesnitzer *et al.*, 2002; Chen *et al.*, 2012).

It is important to note that almost all of the aforementioned PPARγ agonists not only activate PPARγ, but also activate other PPARs, as well as PPAR-independent pathways (Park *et al.*, 2003; Bernardo *et al.*, 2009). As a result, the effects of PPARγ agonists, including TZDs, work through both PPARγ-dependent and independent mechanisms that are not easily differentiated and can confound the interpretations of studies. Furthermore, regardless of the route of delivery (iv, ip, oral, or intracerebral), TZDs can affect PPARγ in the CNS (Culman *et al.*, 2007), although it is not known whether all TZDs cross the blood-brain barrier (BBB). PGZ has been reported to cross the BBB (Grommes *et al.*, 2013), but unpublished observations by GlaxoSmithKline have been used to claim that RGZ cannot cross the BBB (Pedersen *et al.*, 2006), although this awaits verification.

2.3 PPARγ functioning patterns

As with all other nuclear receptors, PPARγ functioning patterns involve ligand-independent repression, ligand-dependent transactivation, and ligand-dependent transrepression (Glass

and Ogawa, 2006) (Figure 2). As there are no known endogeous PPARγ-inhibiting ligands, all "ligands" in this review refer to PPARγ-activating ligands.

The classic view of PPARγ function is that it forms a heterodimer with the retinoid X receptor (RXR) (Berger and Moller, 2002). Under basal conditions, in the absence of ligands of RXR or PPARγ, the heterodimer is associated with corepressors, such as nuclear receptor corepressor (NCoR), transducin β-like protein, and histone deacetylases (HDACs). This complex binds to PPREs in the promoter region of target genes and retains the genes in a suppressed state defined as ligand-independent repression. Following ligand binding, however, the PPARγ/RXR heterodimer undergoes conformational changes, dissociates from co-repressors, and recruits co-activators such as thyroid hormone-associated protein 220, thereby upregulating PPRE target gene transcription (Dekkers *et al.*, 2012). This effect is known as ligand-dependent transactivation (Figure 2A). Ligands of either PPARγ or RXR can both initiate ligand-dependent transactivation, whereas binding of both receptors simultaneously can lead to additive effects on gene expression (Fajas *et al.*, 1997). Both ligand-independent repression and ligand-dependent transactivation involve the regulation of promoters located at PPREs, and PPARγ is known to maintain lipid metabolic homeostasis by these mechanisms.

Ligand-dependent transrepression is more complex and denotes PPARγ-dependent repression of genes other than PPREs, typically NF-κB and activator protein-1, in the absence of direct binding of PPARγ to DNA. The HDAC3/NCoR complex binds to NF-κB to maintain a repressed state, which is terminated upon NCoR degradation. Ligand-dependent transrepression of PPARγ occurs when ligands induce PPARγ SUMOylation, which guides PPARγ to the HDAC3/NCoR complex, inhibits NCoR degradation, and causes NF-κB target gene repression (Pascual *et al.*, 2005; Dekkers *et al.*, 2012) (Figure 2B). As NF-κB is part of a prototypical pro-inflammatory signaling cascade, SUMOylation-dependent transrepression is the predominant means by which PPARγ promotes anti-inflammatory effects. Other mechanisms involved in PPARγ-induced NF-κB inhibition include ubiquitin-dependent degradation of NF-κB, exportation of NF-κB out of the nucleus, cofactor competition with NF-κB, and steric inhibition of NF-κB binding to DNA (Sauer, 2015) (Figure 2C). The sophisticated, multidimensional nature of PPARγ PTMs and functioning patterns confers this protein with the flexibility demanded of a master gatekeeper.

2.4 PPARγ target genes

The observation that PPARγ knockout is embryonically lethal indicates a vital and indispensible role for this protein (Semple *et al.*, 2006). PPARγ response networks are complex and different genes are regulated in cell-specific manners. PPARγ regulates a variety of target genes relevant to adipogenesis *(e.g. adipoq, lpl, nr1h3, uc*p1), fatty acid metabolism (*e.g. acadl, acadm, acox*1), lipid transport (*e.g. angptl4, apoe, olr1*), cell proliferation (*e.g. clu, eln, hspd1*), insulin signaling (*e.g. cpt1a, dgat1, pck1*), and inflammation *(e.g. nfkb, mmp9)*. The activation of PPARγ increases metabolic activities such as lipid metabolism and storage, adipogenesis, insulin sensitization, glucose homeostasis, and sodium and fluid retension (Ahmadian *et al.*, 2013). Nevertheless, not all

of these functions involve direct transcriptional regulation. The regulated genes can be grouped into three major categories (Chen *et al.*, 2012): 1) fatty acid/glucose metabolism, 2) inflammation/oxidative stress/apoptosis, and 3) cancer. A large variety of genes are found in the area of overlap of these three categories and positive regulation is more common than negative regulation. Most of PPARγ signal transduction cascades in CNS pathologies are directly or indirectly associated with NF-κB, and this serves as a major mechanism whereby PPARγ regulates the stress response to injuries in the brain.

In addition to NF-κB, PPARγ also regulates the prototypical redox-sensing nuclear factor erythroid 2- related factor 2 (Nrf2) pathway, acting in synergy with this pathway to mute the destructive effects of oxidative stress (Figure 3) (Ikeda *et al.*, 2000; Shih *et al.*, 2005; Cho *et al.*, 2010; Polvani *et al.*, 2012; Zhao and Aronowski, 2014). Nrf2 is a master transcription factor that binds the antioxidant response element (ARE) and activates numerous genes critical for the maintenance of redox homeostasis, such as those related to the glutathione and superoxide dismutase antioxidant systems (Zhang *et al.*, 2013). The interactions between PPARγ-Nrf2 signaling pathways can be classified into four categories. First, in addition to PPARγ-mediation modulation of the Nrf2/ARE axis, Nrf2 also regulates PPARγ, suggestive of a bidirectional loop (Cho *et al.*, 2010). For example, Nrf2-mediated PPARγ induction protects mice against acute oxidant damage to the lung *in vivo* (Cho *et al.*, 2010). Second, some antioxidant genes, such as catalase (Guan *et al.*, 2000; Girnun *et al.*, 2002), glutathione S-transferase (Rushmore and Pickett, 1990; Rushmore *et al.*, 1991; Park *et al.*, 2004a) and superoxide dismutase (SOD) (Yoo *et al.*, 1999; Zelko *et al.*, 2002; Jurkunas *et al.*, 2010) contain both a PPRE and an ARE and are regulated by both PPARγ and Nrf2 to elicit anti-oxidative effects. Third, microglial/macrophagic CD36 is under the regulation of both PPARγ (Tontonoz *et al.*, 1998; Yamanaka *et al.*, 2012) and Nrf2 (Ishii *et al.*, 2004; Wang *et al.*, 2014; Zhao *et al.*, 2015a). CD36 is important in microglial/macrophage phagocytosis and subsequent debris clearance, which facilitates resolution of neuroinflammation (Li *et al.*, 2015). Fourth, PPARγ and Nrf2 synergistically elicit anti-inflammatory effects by inhibition of the NF-κB pathway (Wardyn *et al.*, 2015; Zhao *et al.*, 2015b).

PPREs have been found in target genes with potential roles in tissue preservation and repair and functional recovery after acute brain injury. Examples include tight junction protein *zona occludens-3* (BBB integrity), *synaptogyrin 4* (synaptic function), *ubiquitin conjugating enzyme E2 S* (protein quality control), *G1/S-specific cyclin, p21-activated kinase 4, homeodomain-interacting protein kinase 4* (cell cycle), *mitogen activated protein kinase organizer 1, transciption factor jun-D* (cell survival), *TOMM40, TIMM13, TIMM44*, and *electron transfer flavoprotein subunit beta* (mitochondrial function) (Heinaniemi *et al.*, 2007). Furthermore, a genome-wide identification of PPREs revealed functional clusters of PPAR-regulated genes related to chromatin remodeling, DNA damage response, cell differentiation, and cell growth/maintenance (Lemay and Hwang, 2006). Aside from the tissue reparative nature of these target genes, PPREs with well-established roles in lipid metabolism and inflammation might be critical for the repair of myelin and clearance of debris in the CNS. Indeed, a critical role for PPARγ in peripheral wound repair has been well established (Yessoufou and Wahli, 2010); PPARγ is activated by lipid mediators produced by necrotic tissue, and upregulates genes involved in anti-fibrotic, anti-oxidative,

and anti-apoptotic effects (Michalik and Wahli, 2006). As discussed further below, the genomic studies identifying potential PPREs are consistent with the view that PPARγ lies at the nexus between perturbations of the internal milieu and a concerted effort to transcribe an abundance of genes that preserve homeostasis and repair tissue.

3. Evidence favoring a beneficial role of PPARγ in the injured CNS

CNS injuries encompass a variety of pathogenic mechanisms, including neurovasculopathy, trauma, neurodegeneration, tumor formation, and CNS autoimmunity, and may arise due to systemic diseases. In the present review, we will restrict our focus to those conditions with CNS abnormalities as the primary underlying pathology. This group of CNS injuries—ischemic stroke, hemorrhagic stroke, TBI, and SCI—share a number of pathophysiologic/repair processes in common. In the next section, we briefly describe alterations in PPARγ expression in CNS injuries and present evidence favoring its beneficial effects. We will then introduce the mechanisms underlying PPARγ-mediated protection against CNS injury, promotion of CNS repair, and regulation of comorbidities (Figure 4).

3.1 PPARγ expression and activity following CNS injuries

Ischemic stroke is caused by transient or permanent local reduction of cerebral blood flow, and is characterized by a number of cellular disturbances, including BBB dysfunction, vasogenic brain edema, and neuronal death (Yin *et al.*, 2014; Krueger *et al.*, 2015). In response to middle cerebral artery occlusion (MCAO), PPARγ mRNA levels are upregulated by 3.3-fold and 7.5-fold in the ipsilateral cerebral cortex of the rat at 6h and 24h post-MCAO, respectively (Ou *et al.*, 2006). *In situ* hybridization studies further reveal that PPARγ mRNA expression is restricted to neurons within the ischemic territory (Ou *et al.*, 2006). Similarly, Victor *et al.* observed PPARγ upregulation at both the mRNA and protein levels in ischemic neurons following MCAO in rats (Victor *et al.*, 2006). Elevated expression of PPARγ protein was detected by immunohistochemistry as early as 4h after stroke, with a peak at 24h, and lasted for at least 14d after stroke (Victor *et al.*, 2006). Despite increased PPARγ expression in neurons after ischemic insults, there is decreased PPARγ DNA binding activity in the ischemic hemisphere. In the ischemic brain, PPARγ-PPRE binding activity 8 h after the insult is only ~44% of the values in the contralesional brain, as evaluated by electrophoretic mobility shift assays and densitometry (Victor *et al.*, 2006). The reason for the reduction in the PPRE binding activity of PPARγ after ischemic injury is still unknown. It is possible, however, that PPARγ protein levels may be elevated in the ischemic brain to compensate for the decrease in PPARγ DNA binding activity.

Hemorrhagic stroke is elicited by the rupture of a weakened blood vessel or a brain aneurysm followed by bleeding into surrounding brain regions. There are two subtypes of hemorrhagic stroke—intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH) (Qureshi *et al.*, 2001; Tholance *et al.*, 2015). Xu *et al.* injected autologous whole blood into the right striatum of male Sprague-Dawley rats to induce an ICH model (Xu *et al.*, 2016). Significantly elevated expression of PPARγ and 15(S)-hydroxyeicosatetraenoic acid (15(S)-HETE) was found in the ipsilateral brain in ICH rats compaired to sham-treated controls (Xu *et al.*, 2016). Furthermore, PPAR-γ protein levels and PPARγ-targeted gene expression were

significantly increased in rats treated with the PPARγ agonist, exogenous 15(S)-HETE, in comparison to vehicle-treated ICH rats (Xu *et al.*, 2016). Intrastriatal injections of 15d-PGJ_2 significantly increased PPARγ-DNA binding activity and the expression of catalase in the perihemorrhagic area 3h after ICH (Zhao *et al.*, 2006). However, in an experimental SAH model, PPARγ mRNA and protein levels were significantly reduced in the cortex compared to sham controls (Chang *et al.*, 2015a).

Following TBI, cerebral inflammation is one of the major triggers of progressive neuronal cell death (Morganti-Kossmann *et al.*, 2001). In a TBI model induced by controlled cortical impact (CCI), PPARγ mRNA expression was not altered either following TBI or treatment with the PPARγ agonists PGZ and RGZ (Thal *et al.*, 2008; Thal *et al.*, 2011). However, inflammatory genes such as inducible nitric oxide synthase (iNOS), TNF-α, interleukin (IL)-1β and IL-6 were upregulated following TBI, and this response was inhibited by PGZ treatment (Thal *et al.*, 2011). In contrast, Yi *et al.* reported a two-fold increase in PPARγ mRNA expression 24h after experimental TBI and this was increased four-fold by RGZ treatment (Yi *et al.*, 2008). The methodological differences in experimental trauma models might explain these discrepancies.

It is well accepted that apoptosis, inflammation, and excitotoxicity contribute to secondary neuronal damage after SCI. One day following experimental SCI, the expression of PPARγ is significantly increased in the spinal cortex surrounding the lesion area (Zhang *et al.*, 2010). In contrast, another study demonstrated that PPARγ protein levels were significantly reduced in spinal cord homogenates one day after SCI (Paterniti *et al.*, 2013).

3.2 Protective effects of PPARγ in CNS injuries

A large body of seminal work in healthy control, diabetic, or obese animals revealed that PPARγ agonists decrease myocardial infarct size and increase glucose uptake and insulin sensitivity (Yue Tl *et al.*, 2001; Khandoudi *et al.*, 2002; Shiomi *et al.*, 2002; Sidell *et al.*, 2002; Wayman *et al.*, 2002; Lee and Chou, 2003; Liu *et al.*, 2004). Consistent with these studies, mounting evidence also demonstrates that PPARγ activation is beneficial to the injured brain (Zhao and Aronowski, 2014). For example, Zhao and colleagues demonstrated that neuron-specific PPARγ knockout mice experience greater brain damage and oxidative stress after MCAO (Zhao *et al.*, 2009b). Furthermore, systemic or intracerebroventricular administration of PPARγ agonists, either prior to and/or after stroke, elicit potent neuroprotective effects in various animal models of ischemic stroke, as shown by reductions in infarct size and superior neurological function (Sundararajan and Landreth, 2004; Luo *et al.*, 2006; Wang *et al.*, 2009; Kaundal and Sharma, 2010). Even delayed intraperitoneal administration of the PPARγ agonist RGZ—beginning 24 h after cerebral ischemia—is able to confer protection in a middle cerebral artery embolization stroke model in rats (Allahtavakoli *et al.*, 2009). These findings may be important because they suggest a wide therapeutic window for PPARγ agonists. However, the dose must be chosen with care, as PPARγ agonists may promote cell survival at low concentrations but increase cell loss at high concentrations (Wang *et al.*, 2002b; Lin *et al.*, 2006; Wu *et al.*, 2009).

Aside from ischemic stroke, PPARγ agonists also exhibit neuroprotective effects in hemorrhagic stroke models (Zhao *et al.*, 2006; Zhao *et al.*, 2007; Zhao *et al.*, 2009a; Wu *et*

al., 2015). For example, in a rat model of striatal ICH, intrastriatal 15d-PGJ_2 treatment increased PPARγ DNA binding activity and subsequent catalase expression, resulting in significant decreases in neurologic deficits compared to rats receiving saline (Zhao *et al.*, 2006). Similarly, intraperitoneal administration of RGZ at 5 min, 6 h, and 24 h after TBI increased PPARγ mRNA levels in cortical tissue surrounding the contusion area within 24 h after brain injury and significantly reduced the cortical lesion volume compared to vehicle-treated mice (Yi *et al.*, 2008). Similarly, the survival of hippocampal CA3 neurons was increased after intraperitoneal injection of 6 mg/kg RGZ in a controlled cortical impact model of TBI (Liu *et al.*, 2016). Nevertheless, a number of studies have shown contradictory results, particularly in TBI models. It has therefore been argued that the neuroprotective effects of PGZ in TBI—as shown by reduced contusion volume, decreased cerebral inflammation, and reduced microglial activation—are the result of PPARγ-independent mechanisms (Thal *et al.*, 2011; Liu *et al.*, 2016). Other possible reasons for these discrepancies include: 1) differing rodent species and strains; 2) varying degrees of injury severity, reflecting differences in the diameter of the impactor tip, impact velocity, impact duration, and displacement; 3) differences in lesion location within the brain; 4) different administration methods and timing of PPARγ agonists; and 5) different times of evaluation. In short, the interpretation of this body of work awaits further confirmation and greater reproducibility across studies.

Application of PPARγ agonists is protective in various animal models of SCI. In a study by McTigue and colleagues, rats received a moderate mid-thoracic contusion and were intraperitoneally injected with either low or high doses of PGZ or vehicle at 15 min after SCI and then every 12h for 7 days (McTigue *et al.*, 2007). In this study, PGZ significantly protected white matter, gray matter, and motor neurons from SCI. In a compression model of SCI, vascular clips were applied to the mouse dura with a force of 24g via four-level T_5-T_8 laminectomy (Genovese *et al.*, 2008). In this model, intraperitoneal injections of the PPARγ agonist 15d-PGJ_2 ameliorated spinal cord inflammation, tissue injury, neutrophil infiltration, NF-κB activation, and cell apoptosis after SCI. In addition, the PPARγ agonist PGZ was found to ameliorate sensory dysfunction after SCI (Iwai *et al.*, 2008) and reduce neuropathic pain after SCI and peripheral nerve injury (Jia *et al.*, 2013; Griggs *et al.*, 2015). Although there remain some debates, the abovementioned findings suggest that PPARγ agonists elicit structural and functional protection of the brain in diverse injury models.

4. PPARγ protects against CNS injury

A series of pathological processes are initiated during the acute phase following CNS injuries. Following the acute period, a wave of secondary injury expansion also emerges. Necrosis of neural tissue triggers a powerful inflammatory cascade, resulting in further neuronal apoptosis and excitotoxicity, oxidative stress, and other feed-forward mechanisms. Neuroinflammation contributes to the amplification and spread of local injury, predisposing surrounding cells to secondary injuries (Kawabori and Yenari, 2015). Vulnerable brain vessels and the BBB release pro-inflammatory factors and facilitate immune cell infiltration into the injured brain (de Wit *et al.*, 2017). In this section, we will summarize pathophysiological processes after CNS injury and the beneficial effects of PPARγ in these processes.

4.1 PPARγ protects against neuroinflammation following CNS injuries

The immune system serves as the sentinel and guardian of the organism. For many decades, the CNS was falsely believed to be immunoprivileged. The CNS is now viewed as immune competent, actively engaging in interactions with the peripheral immune system (Carson *et al.*, 2006). Furthermore, a lymphatic vascular system has been discovered in the brain (Molina-Holgado and Molina-Holgado, 2010; Aspelund *et al.*, 2015) and neural inflammation is thought to drive disease processes into a secondary phase of injury expansion.

4.1.1 An introduction on neuroinflammation following CNS injuries—

Inflammatory responses following CNS injury are initiated by damage-associated molecular patterns (DAMPs) that are released from injured tissue (Sharma and Naidu, 2016). High mobility group box 1 is rapidly released by cells undergoing necrotic or pyroptotic cell death (Sharma and Naidu, 2016). High mobility group box 1 is detected in the serum half an hour after 90 min stroke in rodents, and is observed within the first hour after symptom onset in ischemic stroke patients (Liesz *et al.*, 2015). In addition, heat shock protein (HSP) 72 can be detected in the serum of CNS trauma patients (Pittet *et al.*, 2002). Release of S-100 protein from the injured CNS occurs within the first 24h in patients with TBI, ischemic stroke, and transient ischemic attacks (Elting *et al.*, 2000). Furthermore, the early release of nuclear DNA, the IL-1 family, histones, and other intrinsic cell components from the injured CNS serves to ignite the inflammatory response after acute CNS injuries (Sharma and Naidu, 2016).

Both local and systemic inflammatory cells participate in acute CNS injury. Microglia are the resident immune cells of the brain and are among the first cells to respond to CNS injury. Injury signals are transported through the CNS lymphatic vessels and the blood vessels, possibly delivered by the drainage of damage-associated molecular patterns directly to peripheral immune organs (Louveau *et al.*, 2015). Injury signals might also be carried by dendritic cells (DCs) (Clarkson *et al.*, 2012). Macrophages take up residence in the CNS vessel bed and are also poised to sense and transmit information about disruptions in homeostasis (Goverman, 2009; Kivisakk *et al.*, 2009). Activation of the peripheral immune response results in a surge of infiltrating immune cells that home in on the CNS lesion zone (Pennypacker and Offner, 2015).

In ischemic stroke, the pro-inflammatory profiles of microglia may be inactivated at early stages after ischemic stroke. However, as the immune reactions progress, pro-inflammatory microglia participate in the promotion of neural inflammation (Hu *et al.*, 2012; Patel *et al.*, 2013; Wang *et al.*, 2013; Jin *et al.*, 2017). In a transient MCAO model, brain infiltration of macrophages appeared as early as 12h after ischemia and peaked after 24h, followed by a gradual decrease by day 7 (Gelderblom *et al.*, 2009). Similarly, infiltrating neutrophils were detected at 12 h, peaking on day 2-3 and gradually disappearing by day 7 (Gelderblom *et al.*, 2009). Although a deleterious role has been reported for natural killer cells in ischemic stroke (Gan *et al.*, 2014), the infiltration of this cell population is not always evident. However, T and B lymphocytes from the adaptive immune systems appear in the ischemic lesion site at 3-7 days after stroke (Gelderblom *et al.*, 2009), even though they represent only

a small portion of infiltrated immune cells. In animal models of hemorrhagic stroke, microglial activation is observed 1-4 h after hemorrhage, peaking at 3-7 days, and returning to baseline by 21-28 days (Hickenbottom *et al.*, 1999; Gong *et al.*, 2000; Xue and Del Bigio, 2000; Wang *et al.*, 2003a; Wang and Tsirka, 2005). Neutrophil infiltration occurs as early as 4h after the formation of the hematoma, peaking at 2-3 days, and subsiding by 7 days.

In traumatic CNS injuries such as TBI and SCI, the BBB is directly disrupted by the primary damage, followed by the entry of blood components into the CNS (McKee and Lukens, 2016). As in peripheral injured tissue, neutrophils are the first to be mobilized to the brain after TBI. In a rat model of CCI, neutrophil infiltration was detected within hours post-trauma, and this further exacerbated the loss of BBB integrity. Microglia and macrophages are increased between 12 and 72 h in damaged cortical regions after TBI (Clark *et al.*, 1994; Soares *et al.*, 1995). A large number of chemokines are released into the injured CNS, inducing the migration of activated neutrophils, lymphocytes, monocytes, and macrophages (Ghirnikar *et al.*, 1998).

Together with the resident microglia in the CNS, infiltrated peripheral immune cells promote ongoing neural inflammation with direct cytotoxicity or secretion of inflammatory factors. Microglia produce proinflammatory cytokines such as IL-1, IL-6, IL-12, IL-23, nitric oxide (NO), and TNFα, and contribute to local oxidative stress by inducing iNOS and generating reactive oxygen species (ROS) (Hu *et al.*, 2012; Wang *et al.*, 2013). $CD8^+$ cell cytotoxic T lymphocytes (CTLs) and natural killer cells produce cytolytic granzyme-b (Chaitanya *et al.*, 2011) and perforin (Mracsko *et al.*, 2014) to induce direct neuronal death after ischemic stroke. Immune cell-derived cytokines, including IFN-γ, TNF-α, various interleukins, macrophage inflammatory protein 1α and 1β, and monocyte chemotactic protein (MCP)-1β not only convey immune signals but also induce apoptosis of cells in the stroke penumbra (Jin *et al.*, 2010b; Gan *et al.*, 2014). In addition, chemokines are produced in the inflamed zone of injury, both by infiltrating leukocytes and the injured brain tissue itself, in order to attract even more peripheral immune cells in a self-amplifying cascade (Losy *et al.*, 2005; Jin *et al.*, 2010b; Wang *et al.*, 2012b; Wolinski and Glabinski, 2013). Matrix metalloproteinases (MMPs) are released mainly from neutrophils and cause damage to the BBB, facilitating the entry of additional peripheral leukocytes. In addition, activated endothelial cells in microvessels express adhesion molecules that promote the rolling and firm adhesion of leukocytes and platelets (Yilmaz and Granger, 2008). It is worth noting that the deleterious effects of the aforementioned inflammatory factors are relatively non-specific, resulting in broad injury to cells in the lesion zone and surrounding tissues, including neurons, white matter-forming oligodendrocytes, and all components of the BBB.

4.1.2 PPARγ protects against post-injury neuroinflammation—Widespread expression of PPARγ has been detected in various immune cells, including CNS glial cells (Bernardo *et al.*, 2000) and peripheral leukocytes (Ricote *et al.*, 1998; Clark *et al.*, 2000; Faveeuw *et al.*, 2000; Padilla *et al.*, 2000; Zhang *et al.*, 2004a). A strong suppressor of the pro-inflammatory transcriptional factor NF-κB, PPARγ fine-tunes neural inflammation by limiting the activation of immune cells, reducing the generation of pro-inflammatory cytokines, chemokines, and adhesion molecules, and mitigating oxidative stress (Kapadia *et al.*, 2008).

Treatment with PGZ reduces microglial proliferation in stroke-prone renovascular hypertensive rats (Lan *et al.*, 2015). In addition, RGZ decreases parenchymal accumulation of neutrophils in a mouse MCAO model (Luo *et al.*, 2006) and 15d-PGJ2 inhibits neutrophil infiltration following ICH injury (Zhao *et al.*, 2006). In rodent TBI models, RGZ reduces activated microglia/macrophages, and this can be reversed by GW9662 (Yi *et al.*, 2008). *In vitro* experiments reveal that RGZ impedes the maturation of human monocyte-derived DCs (Gosset *et al.*, 2001). Although it is not known if lymphocyte activation is affected by PPARγ, the tempering of DC activation suggests this to be the case.

A large body of evidence indicates that activation of PPARγ attenuates neural inflammation by reducing inflammatory mediators in ischemic stroke (Culman *et al.*, 2007), ICH (Zhao *et al.*, 2007; Aronowski and Zhao, 2011), TBI (Qi *et al.*, 2010), and SCI (Zhang *et al.*, 2010; Li *et al.*, 2013). PPARγ stimulation inhibits the expression of a wide array of pro-inflammatory mediators in microglia and macrophages, including TNF-α, IL-1β, IL-6, iNOS, inducible cyclooxygenase (COX) 2, and the IL-12 family (Bernardo *et al.*, 2000; Luna-Medina *et al.*, 2005; Storer *et al.*, 2005). Appel *et al.* reported that 15d-PGJ2 or TGZ treatment of magnet-sorted human DCs (stimulated with toll-like receptor ligands) significantly down-regulated the production of cytokines (IL-12, IL-6, TNF-α, *etc.*) and chemokines (CCL2, CCL3, CCL5) that are involved in T cell recruitment and activation (Appel *et al.*, 2005). Furthermore, PPARγ agonists have been shown to reduce the expression of IFNγ (da Rocha Junior *et al.*, 2013), IL-17, and IL-23 in T cells (Klotz *et al.*, 2009). In human endothelial cells, adenovirus-mediated expression of a constitutively active, mutant version of PPARγ suppressed the expression of vascular adhesion molecules intracellular adhesion molecule-1, vascular cell adhesion molecule-1 and E-selectin (Wang *et al.*, 2002a).

Severe neural inflammation following acute CNS injury causes apoptosis of neurons (Aktas *et al.*, 2007), degeneration of white matter (Rosenberg, 2009), and breakdown of the BBB (Hawkins *et al.*, 1991). PPARγ activation ameliorates these consequences of neural inflammation and oxidative stress in various acute CNS diseases (Culman *et al.*, 2007; Qi *et al.*, 2010; Zhang *et al.*, 2010; Aronowski and Zhao, 2011). However, PPARγ may also be essential for microglial survival (Liu *et al.*, 2010; Kane *et al.*, 2011; Pan *et al.*, 2013). Furthermore, a PPARγ agonist has been shown to restore compromised pro-inflammatory responses in diabetic mice soon after stroke, whereas inflammatory responses were suppressed at later time points in both control and diabetic mice (Kumari *et al.*, 2010). These data demonstrate a sophisticated, bidirectional regulation of microglia by PPARγ.

4.2 Neuronal death

4.2.1 Mechanisms of neuronal death following CNS injury—CNS injury-associated neuronal death can be classified as primary or secondary. Primary neuronal death arises from energy failure in ischemic stroke, mechanical damage associated with mass effects in intracerebral hemorrhage (Qureshi *et al.*, 2009), and mechanical damage from blunt force traumas in TBI and SCI (McTigue, 2008). The loss of neurons typically occurs immediately following injury and continues for hours to days. An important feature of primary neuronal death is that it is generally believed to be non-regulatable and non-

intervenable. On the contrary, secondary neuronal death may be regulated with interventions and is therefore the focus of the following discussion.

Glutamate receptors belong to two major classes—G-protein coupled metabotropic receptors and ligand-gated ionotropic receptors, such as the N-methyl-D-aspartic acid (NMDA) receptor, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor, and kainate receptor. Excitotoxicity is induced by excessive activation of glutamate receptors by extracellular glutamate and is a major contributor to neuronal death following CNS injury (Puyal *et al.*, 2013). Energy failure after ischemia leads to decreased ATP production, thereby disrupting Na^+/K^+-ATPase, Ca^{2+}/H^+-ATPase and Na^+/Ca^{2+}-transporters and leading to depolarization of the cellular membrane. Diffusely depolarized presynaptic neurons release excessive glutamate into the synaptic cleft (Terasaki *et al.*, 2014; Hamming *et al.*, 2016). Another mechanism of excessive glutamate release is via connexin hemichannels in activated astrocytes and microglia (Takeuchi *et al.*, 2006; Ouyang *et al.*, 2014). Ultimately, over-activation of the NMDA receptor leads to the sustained excitement of neurons and an excessive influx of calcium, which causes loss of neuronal viability (Randall and Thayer, 1992; Tymianski *et al.*, 1993; Owens *et al.*, 1997; Lai *et al.*, 2014).

Aside from excitotoxicity-induced neuronal cell death, oxidative stress may also elicit cell loss in CNS injury conditions. The predominant ROS are the superoxide anion ($O_2^{\bullet}$), hydrogen peroxide (H_2O_2), hydroxyl radical ($^{\bullet}OH$), peroxyl ($RO_2^{\bullet}$), peroxynitrite anion ($ONOO^{\bullet}$), and nitrogen dioxide ($^{\bullet}NO2$) (Dhawan, 2014; Yang *et al.*, 2016). Excessive intracellular Ca^{2+} accumulation results in overactivation of calcium-dependent enzymes such as nicotinamide adenine dinucleotide phosphate oxidase (NOX) and xanthine oxidase, both of which are capable of producing ROS. Disruptions in the electron transport chain also elicit the leakage of ROS from mitochondria (Piantadosi and Zhang, 1996; Galeffi *et al.*, 2016). Other mechanisms of ROS production include lipid peroxidation and increased mitochondrial ROS production stimulated by the release of Ca^{2+}, Na^+, and adenosine diphosphate (ADP) from damaged cells (Schulz *et al.*, 2000; Viola and Hool, 2013). Furthermore, blood components, particularly hemoglobin, can undergo auto-oxidation upon erythrocyte lysis, which may serve as a major source of ROS in ICH, SAH, TBI, and SCI (Simoni *et al.*, 1990; Asano, 1999). ROS are typically released within 1h post-injury in diverse models (Gaetani *et al.*, 1990; Marklund *et al.*, 2001). The cellular source of this oxidative stress might be neurons, other parenchymal cells, and vascular cells (Chen *et al.*, 2014). ROS can directly damage neuronal components by promoting lipid peroxidation, protein breakdown, and DNA damage, and also act as executioners of cell death by activating pro-apoptotic pathways (Zhang *et al.*, 2004b). Finally, ROS can promote neuroinflammation, BBB disruption, and the release of vasospastic mediators that indirectly harm neurons by induction of leukocyte infiltration and enhancement of inflammation, thereby exacerbating ischemic injury (Clark *et al.*, 1993).

4.2.2 PPARγ protects against neuronal death following CNS injury—PPARγ has been shown to decrease excitotoxicity in various pathologic settings. For example, 15d-PGJ2 protects neurons against NMDA-induced toxicity both *in vivo* and *in vitro* (Zhao *et al.*, 2006). Similarly, the PPARγ agonist RGZ promotes neuronal survival and neurite outgrowh *in vitro* following exposure to glutamate (Zuhayra *et al.*, 2011). In a rodent ischemic stroke

model, the PPARγ antagonist T0070907 abolished neuroprotection mediated by ischemic preconditioning, and increased glutamate release and reduced glutamate uptake in neuron-astrocyte co-cultures (Romera *et al.*, 2007). Similar effects have also been reported in other disease models. TGZ diminishes glutamate-induced excitotoxicity to the same degree as NMDA receptor antagonists in retinal ganglion cells (Aoun *et al.*, 2003). Furthermore, RGZ decreases glutamate release in glioblastoma multiforme, and this can be reversed by the PPARγ antagonist GW9662 (Ching *et al.*, 2015). The underlying mechanism by which PPARγ reduces excitotoxicity may involve upregulation of the glutamate transporter (GLT)-1 (Romera *et al.*, 2007; Ching *et al.*, 2015). GLT-1 is found in astrocytes and is responsible for up to ~90% of glutamate uptake (Robinson, 1998; Schousboe and Waagepetersen, 2005; Arbo *et al.*, 2016). On the other hand, Yao *et al* observed no changes in GLT-1 expression in response to RGZ injection in a model of TBI (Yao *et al.*, 2015). In addition, no evidence supporting the effects of PPARγ on excitotoxicity has been reported in SCI and hemorrhagic stroke models. Nevertheless, increased astrocytic glutamate uptake following PPARγ activation would be expected to reduce overall tissue damage (Romera *et al.*, 2007; Ching *et al.*, 2015), as excitotoxicity is a major cause of death not only for neurons, but also for oligodendrocytes and other types of CNS cells (Huria *et al.*, 2015).

The anti-oxidative effects of PPARγ are better established than its effects on excitotoxicity. First, PPARγ can directly inhibit ROS generation, partly by inhibiting ROS-generating enzymes. RGZ has been shown to promote neuronal survival and neurite outgrowh *in vitro* following exposure to the Parkinson's oxidative toxicant 6-hydroxydopamine (Zuhayra *et al.*, 2011). Systemic administration of RGZ or PGZ after ischemia/reperfusion reduces ROS and the expression of COX-2, an important enzyme involved in ROS generation, and attenuates neuronal loss (Collino *et al.*, 2006). Similarly, 15d-PGJ2 inhibits iNOS expression and subsequent apoptosis in cerebellar granule cells (Heneka *et al.*, 1999). NOX activation is another major driving force in ROS generation, and its relationship with PPARγ has been examined in primary cortical neurons subjected to oxygen-glucose deprivation (OGD) (Wu *et al.*, 2016). NOX expression was enhanced by both GW9662 treatment and PPARγ-siRNA transfection, and was inhibited by PPARγ transfection or exposure to 15d-PGJ2. Second, PPARγ prevents oxidative stress by induction of anti-oxidant molecules. For example, both RGZ and PGZ can restore glutathione, the most ubiquitous biological antioxidant, in a mouse MCAO model (Collino *et al.*, 2006). Furthermore, in a rodent TBI model, RGZ induces the expression of the antioxidant enzymes catalase and SOD-1 (also known as Cu/Zn SOD), as well as heme oxygenase-1 and the chaperones heat shock protein (HSP) 27 and HSP70, and these responses are abolished by GW9662 administration (Yi *et al.*, 2008). As mentioned above, PPARγ also interacts with the Nrf2/ARE axis to mute the toxic sequelae of oxidative stress (Ikeda *et al.*, 2000; Shih *et al.*, 2005; Cho *et al.*, 2010; Polvani *et al.*, 2012; Zhao and Aronowski, 2014). Collectively, these findings reveal the molecular mechanisms underlying powerful anti-oxidative actions of PPARγ. As oxidative stress contributes to almost all CNS pathologies and impairs tissue repair, the upregulation of multiple antioxidant pathways by PPARγ is expected to accelerate the recovery process.

Another mechanism underlying PPARγ-afforded neuroprotection may be through the energetic and neurotrophic support provided by glial cells. Production of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) in CNS trauma models is enhanced

after administration of PPARγ agonists, although the cellular source of the neurotrophins has not been identified (Meng *et al.*, 2011; Mandrekar-Colucci *et al.*, 2013). Astrocytes have long been known to provide nutritional and metabolic support to neurons (Wang *et al.*, 2016), and activated astrocytes produce BDNF following injury (Zhao *et al.*, 2004). Consistent with its established role in bioenergetics, PPARγ modulates glucose metabolism in astrocytes. For example, PPARγ agonists increase glucose uptake and glycolysis in primary astrocytes (Dello Russo *et al.*, 2003; Izawa *et al.*, 2009). The subsequent increase in cerebral glucose utilization and metabolism might attenuate neurodegeneration (Garcia-Bueno *et al.*, 2007). These effects might be especially important in diseases related to energy deprivation—such as ischemic stroke—and may broaden the temporal window during which drugs might be administered, in addition to increasing cell survival. Microglia also secrete trophic factors (*e.g.* insulin-like growth factor (IGF)-1 and BDNF) to support neuronal survival (Choi *et al.*, 2008; Trang *et al.*, 2011; Wang *et al.*, 2017). However, it is not known if PPARγ activation increases trophic factor expression in microglia.

4.3 Demyelination

4.3.1 Mechanisms of demyelination following CNS injury—White matter injury is characterized by demyelination and axonal degeneration. Demyelination is defined as loss of the axonal myelin sheath that is formed by the processes of oligodendrocytes. Myelination is essential for efficient signal transduction across different brain regions, and serves to protect the ensheathed axon by providing metabolic support and acting as a physical barrier against biochemical insults (Irvine and Blakemore, 2008; Funfschilling *et al.*, 2012; Lee *et al.*, 2012). Axonal degeneration can ensue as a consequence of demyelination, and these secondary effects are largely responsible for the debilitating effects of white matter injury. Thus, the consequences of demyelination include sensorimotor dysfunction and profound neurobehavioral and cognitive impairments (Desmond, 2002).

Oligodendrocytes in white matter are highly vulnerable to ischemic injury for a number of reasons. First, white matter has much lower blood flow and lack of collateral circulation in comparison with gray matter (Rosenberg, 2016). Second, cells of the oligodendrocyte lineage, such as oligodendrocyte precursor cells (OPCs), are particularly vulnerable to ischemia-induced oxidative stress and inflammation (Husain and Juurlink, 1995). In the rat MCAO model, 30 min of vascular occlusion leads to conspicuous swelling of oligodendrocytes and 3 h of occlusion results in lethal injury in large numbers of oligodendrocytes (Pantoni *et al.*, 1996). Demyelination persists for at least 4 weeks after 60 min of transient MCAO in mice, as evidenced by decreased expression of myelin basic protein (MBP) in white matter (Jiang *et al.*, 2016). Consistent with these *in vivo* observations, *in vitro* studies show that 30 min of OGD results in the death of 90% of oligodendrocytes within 9h after reperfusion (Tekkok and Goldberg, 2001). The pattern of demyelination in other CNS injuries, such as intracerebral hemorrhage, SCI, and TBI is similar to that observed in ischemic stroke. In other words, demyelination commences within hours to days after injuries and is sustained for a prolonged period, often up to months or even years (Wasserman and Schlichter, 2008).

The molecular mechanisms underlying CNS injury-induced demyelination and oligodendrocyte death can be summarized as follows. First, oligodendrocytes express all three types of glutamate receptors—AMPA, kainate, and NMDA (Salter and Fern, 2005; Butt, 2006), and are therefore subject to excitotoxicity. As in neurons, excess extracellular glutamate leads to over-activation of glutamate receptors on oligodendrocytes and elicits the accumulation of cytosolic calcium, which triggers oligodendrocyte toxicity (Benarroch, 2009). Second, oxidative stress is another major contributor to demyelination. Oligodendrocytes have high energy demands, abundant iron stores, and low levels of molecular antioxidants, rendering them particularly sensitive to increased ROS (Juurlink, 1997; Oyinbo, 2011; Shereen *et al.*, 2011; Yang *et al.*, 2017). Third, inflammatory reactions also contribute to demyelination after ischemia. Activation of resident microglia and astrocytes, as well as the infiltration of peripheral immunocytes lead to excess production of proinflammatory cytokines, key mediators of pathology in demyelination disorders. For example, high levels of IFN-γ lead to oligodendrocyte apoptosis and demyelination (Lin *et al.*, 2005). Furthermore, TNF-α inhibits the proliferation and differentiation of OPCs, and induces oligodendrocyte apoptosis (Hovelmeyer *et al.*, 2005; Pang *et al.*, 2005; Shi *et al.*, 2015).

Interactions between oligodendrocyte lineage cells and other white matter components such as microglia, astrocytes, and axonal fibers also play a critical role in injury-induced demyelination. Activated microglia can exhibit pro-inflammatory and anti-inflammatory properties, respectively (Hu *et al.*, 2015) and may influence oligodendrocyte survival (Wang *et al.*, 2013). Similarly, activated astrocytes also exhibit dual roles. Glutamate is taken up by astrocytes and converted into lactate, which then serves as an energy substrate for axons and oligodendrocytes following intracellular entry through monocarboxylate transporters and connexins. Astrocytes thereby transiently provide energy for oligodendrocytes and axons under stressful conditions (Matute *et al.*, 2007). However, activated astrocytes may exacerbate oligodendrocyte cell death by increasing intracellular uptake of zinc and stimulation of Ca^{2+}-permeable AMPA receptors (Johnstone *et al.*, 2013).

Traumatic axonal injury (TAI) is localized to white matter and is initiated by mechanical force, such as impact to the head and rapid acceleration-deceleration of the head or the spinal cord (Armstrong *et al.*, 2016b). The proliferation, migration, survival, and differentiation of oligodendrocytes depend upon axon-derived signals (Shi *et al.*, 2015), such that loss or degeneration of axons can directly cause myelin pathologies. TAI causes axonal degeneration, which is accompanied by mitochondrial swelling, disruption of vesicular transport, cytoskeleton breakdown, and the formation of end bulbs at the sites of axotomy or disconnection. An important feature of TAI is that the injury is dispersed among the intact axons within white matter tracts; this expands the lesion and increases disease severity (Gennarelli, 1993). Mild TBI with low TAI density does not impair oligodendrocyte survival, as a single oligodendrocyte can maintain myelin sheaths around a cohort of axons, and damaged axons are a minor proportion of the total number of axons present. Nevertheless, damage to axons can dysregulate myelin maintenance signals to the oligodendrocyte, resulting in aberrant myelin synthesis and subsequent formation of redundant myelin, as evident in double-layered myelin sheaths around damaged axons (Rosenbluth, 1966; Armstrong *et al.*, 2016a). Mild TBI may be accompanied by some

degree of demyelination, as there also co-exist other pathogenic factors related to demyelination, including glutamate excitotoxicity, excessive ROS, neuroinflammation, and microglial activation (Clarner *et al.*, 2012; Sullivan *et al.*, 2013; Mierzwa *et al.*, 2015). Consistent with these observations, in a closed-skull impact mouse model mimicking mild TBI, demyelination of intact axons is observed as early as 3 days, and lasts up to 6 weeks post-injury, in the absence of frank oligodendrocyte death (Mierzwa *et al.*, 2015). In that model, chronic inflammation contributes to the long-lasting demyelination. Moderate or severe TBI with TAI is often accompanied by microhemorrhages or severe neuroinflammation (Armstrong *et al.*, 2016a), resulting in focal lesions, and a higher proportion of axons in the lesion site are damaged, leaving the myelinating oligodendrocytes without any viable axons to wrap (Armstrong *et al.*, 2016b). This lack of nearby axons causes myelin degradation and oligodendrocyte death. It is worth noting that TBI and SCI also cause mechanical damage in gray matter, leading directly to neuronal death (Bayly *et al.*, 2005). Thus, axons can become disconnected from damaged neurons and undergo orthograde degeneration, ultimately leading to myelin degradation and oligodendrocyte death, as outlined above. For these and other reasons, death of oligodendrocytes in white matter is evident within 12 h in a rat model of moderate fluid percussion injury, and this increases progressively through the following week and is maintained for 2 months post-injury (Conti *et al.*, 1998), perhaps mediated by the caspase-3 apoptotic pathway (Flygt *et al.*, 2013).

4.3.2 PPARγ protects against demyelination following CNS injury—Most studies on PPARγ in CNS injury focus on gray matter. In a recent study, however, Han *et al.* investigated the effect of PGZ on white matter integrity in a 60 min transient MCAO mouse model, and reported less loss of white matter integrity at 21d post injury, partly due to increased microglial M2 polarization (Han *et al.*, 2015). There are also protective effects of PPARγ on autoimmunity-induced demyelination, consistent with its beneficial role in stroke, TBI, and SCI. In rodent experimental autoimmune encephalomyelitis (EAE) models, TGZ decreases pathology by attenuating pro-inflammatory cytokine production (Niino *et al.*, 2001). Similarly, PGZ reduces injury symptoms in EAE models, and this is accompanied with decreased lymphocyte infiltration, demyelination, and chemokine and cytokine expression, and increased expression of the NF-κB inhibitor, IκB, in the brain (Feinstein *et al.*, 2002).

In vitro studies have demonstrated potential mechanisms underlying the protective effects of PPARγ against demyelination. For example, endogenous prostaglandin derivatives are natural PPARγ activators and inhibit production of nitrite and pro-inflammatory cytokines, including IL-6, IL-1β, TNF-α, and MCP-1 from LPS-stimulated microglia and astrocytes (Storer *et al.*, 2005). In a study exploring T-cell mediated demyelination in three-dimensional aggregating rat brain cell cultures, Duvanel *et al.* demonstrated that PGZ rescued anti-myelin oligodendrocyte glycoprotein autoantibody-induced demyelination by reducing heat shock responses and downregulating TNF-α (Duvanel *et al.*, 2003). Apart from its anti-inflammatory properties, PPARγ also mitigates oxidative stress in oligodendrocytes. Treatment of rat oligodendrocytes with PGZ or 15d-PGJ2 enhances their antioxidant defenses by increasing levels of catalase and Cu/Zn SOD, while maintaining the

equilibrium of the glutathione redox system (Bernardo *et al.*, 2009). Although there is little direct evidence regarding the influence of PPARγ on excitotoxicity-induced demyelination, PPARγ is known to decrease excitotoxicity in general, as discussed in section 4.2.2. However, whether PPARγ can help relieve demyelination caused by TAI-induced oligodendrocyte death is not yet known.

Collectively, the available evidence supports the therapeutic potential of PPARγ in CNS injury- induced demyelination, although evidence regarding direct effects of PPARγ on demyelination is still limited, especially in the context of acute CNS injuries. Furthermore, the underlying mechanisms are poorly understood and warrant further studies.

4.4 BBB disruption

4.4.1 Mechanisms of blood-brain barrier disruption in CNS injury—As a physical, transport, and metabolic barrier, the blood-brain barrier (BBB) controls the exchange of various molecules and nutrients between the blood and brain compartments, while keeping bacteria, viruses, and other xenobiotics outside the brain (Weiss *et al.*, 2009). The major structural bases of the BBB consist of brain capillary endothelial cells, the tight junctions that connect them, astrocyte end feet, and pericytes (Weiss *et al.*, 2009; Thal and Neuhaus, 2014; Attwell *et al.*, 2016). Rapid alterations of endothelial permeability occur in many neurological conditions, including ischemic stroke and TBI (Salehi *et al.*, 2017). The effects of CNS injuries may occur either directly on the endothelium or indirectly through other cells types in the neurovascular unit that affect the endothelium (Thal and Neuhaus, 2014). Reactive oxidants, inflammatory cytokines, and MMPs contribute to BBB permeability and cause the degradation of endothelial junctions, loss of vascular integrity, and BBB dysfunction after CNS injuries. Within 30-60 min following ischemic stroke, aberrant actin polymerization, stress fiber formation, and destruction of junctional proteins in brain endothelial cells result in an early breach of the BBB in response to activation of Rho-associated protein kinase/myosin light chain signaling and loss of inhibition by actin depolymerizing factor. This is followed by the infiltration of MMP-secreting neutrophils and macrophages into the brain, setting in motion a cascade of events that culminates in tissue damage and loss of neurological function (Shi *et al.*, 2016a; Shi *et al.*, 2016b). Increased BBB permeability may also facilitate edema formation and hemorrhagic transformation, thereby aggravating neurological outcomes (Dirnagl *et al.*, 1999). All of these changes lead to primary brain damage and post-ischemic secondary injury (Hacke *et al.*, 1996; Yin *et al.*, 2010).

4.4.2 PPARγ protects against blood-brain barrier disruption following CNS injury—The BBB is partly composed of cerebral vascular endothelial cells and the tight junctions holding them together. A growing number of studies reveal that PPARγ is expressed in the cerebral vascular endothelium and plays important roles in the regulation of cerebrovascular structure and function (Culman *et al.*, 2007; Beyer *et al.*, 2008; Halabi *et al.*, 2008; Hamblin *et al.*, 2009). For example, PPARγ activation by TZDs can regulate endothelial migration and angiogenesis (Duan *et al.*, 2008), consistent with a role for PPARγ in BBB repair. PPARγ promotes human umbilical vein cell migration by inducing the expression of a member of the class-3 semaphorins, Sema3g (Ming *et al.*, 2015).

Activated endothelial cells trigger immune responses through the secretion of pro-inflammatory cytokines/chemokines, such as IL-1 and TNF-α (Ross, 1993, 1999; Tesfamariam and DeFelice, 2007). Many studies have demonstrated that PPARγ agonists reduce the activation and inflammation of endothelial cells by inhibiting proinflammatory cytokines/chemokines (Jackson *et al.*, 1999; Marx *et al.*, 2000; Pasceri *et al.*, 2000; Imamoto *et al.*, 2004; Verrier *et al.*, 2004; Sasaki *et al.*, 2005; Chen *et al.*, 2015). PPARγ in endothelial cells protects against IL-1β-induced endothelial dysfunction (Mukohda *et al.*, 2016). Furthermore, Yin and colleagues found that the PPARγ agonist PGZ significantly reduces OGD-induced endothelial cell death (Yin *et al.*, 2013). In the same study, the effects of adenovirus-mediated gain or loss of PPARγ function strongly support a cytoprotective role for PPARγ in endothelial cultures. Consistent with these *in vitro* findings, PPARγ agonists also significantly reduce ischemia-triggered increases in cerebrovascular/BBB permeability in mice (Yin *et al.*, 2013). Hind and colleagues established an *in vitro* BBB model using human brain microvascular endothelial cells and human astrocyte co-cultures (Hind *et al.*, 2015). They discovered that the PPARγ agonist cannabidiol decreased BBB permeability when administered either before or after OGD. Furthermore, vascular cell adhesion molecule-1 expression was decreased. Min *et al.* reported that activation of PPARγ by telmisartan attenuates BBB impairment in a type 2 diabetic mouse model (Min *et al.*, 2012). In that study, significant decreases in the expression of tight junction proteins (ZO-1, occludin, claudin3, and claudin5) and increases in MMP-2 and MMP-9, oxidative stress, and pro-inflammatory cytokines (MCP-1, IL-6, TNF-α) were observed in the mouse brain after treatment with the PPARα antagonist (Min *et al.*, 2012). Collectively, these studies indicate that PPARγ activation regulates BBB permeability and this may partly underlie its protective role against CNS injuries.

5. PPARγ promotes CNS repair

The chronic phase of CNS injury can progress for weeks to years, even after the CNS commences repair to restore homeostasis. Thus, the injury and reparatory phases are not completely separable and exhibit considerable overlap. During the chronic phase, neural inflammation is eventually controlled and resolved. Debris in and around the lesion zone is isolated and removed by local microglia and/or by infiltrating peripheral immune cells. Neurons may be replenished in limited numbers through neurogenesis. White matter is repaired by neurite outgrowth and remyelination. Angiogenesis and revascularization reseal the compromised BBB. In the next section, we will discuss repair processes, mainly in the chronic phase, and describe the involvement of PPARγ. As discussed in Section 2.4, the existence of PPREs on gene clusters that control cell survival, differentiation, chromatin remodeling, and the DNA damage response support an important role of PPARγ in tissue repair (Lemay and Hwang, 2006; Heinaniemi *et al.*, 2007).

5.1 Resolution of inflammation

5.1.1 An introduction on the resolution of inflammation following CNS injury—

Resolution of inflammation is initiated immediately after the onset of CNS challenges, at the same time as the inflammation commences. Clearance of debris is the first step toward the resolution of inflammation, and will be discussed in Section 5.2. Contraction of the immune

cell population in the CNS is also essential to restore homeostasis. Neurotrophic factors from the immune system help regenerate injured tissue and prevent cell loss. Anti-inflammatory cells and factors work in concert to complete the process of inflammation resolution.

Both innate and adaptive immune systems have components that regulate inflammation. Immediately after CNS injury, the pro-resolution M2 phenotype predominates in the microglial and macrophage populations for the first 3-5 days, and this is followed by M1 polarization (Hu *et al.*, 2012; Wang *et al.*, 2013). However, within weeks following CNS injury, the pro-inflammatory M1 microglial phenotype gradually subsides and is replaced by the pro-resolution M2 phenotype. The M2 phenotype promotes 1) phagocytosis to clear debris, 2) secretion of anti-inflammatory cytokines, such as IL-10 and transforming growth factor (TGF) β, and 3) release of a plethora of trophic factors, including IGF-1. Concomitantly, infiltrating neutrophils and macrophages undergo apoptosis to help resolve inflammation. The N2 neutrophil population expresses pro-resolution markers, such as CD206 and Ym1, and this is associated with increased neutrophil clearance in the MCAO mouse model (Cuartero *et al.*, 2013). In the adaptive immune system, the best-studied regulatory lymphocytes are known as CD4+CD25+FoxP3+ regulatory T cells (Tregs), which facilitate the resolution of inflammation after CNS injury (Shevach *et al.*, 2006; Zhou *et al.*, 2017). Treg cells can directly suppress effector T cells and myeloid cells by secreting suppressor cytokines such as IL-10, IL-35, and TGF-β, and compete for IL-2, which induces T cell apoptosis due to deprivation of activating cytokines and granzyme-dependent cytotoxicity. Furthermore, by suppressing the functions of antigen presenting cells, Treg cells indirectly modulate the responder T cells. Tregs prevent activation, maturation, and access to effector cells, impeding the immune stimulatory function of antigen presenting cells (Shevach, 2009). In addition, Tregs can express neurotrophic factors such as BDNF and the levels of circulating BDNF+ Tregs are correlated with positive disease outcomes in ischemic stroke patients (Feddersen and Van Ness, 1989).

5.1.2 PPARγ promotes resolution of inflammation—Although beneficial effects of PPARγ agonists have been widely reported in ischemic stroke, ICH, TBI, and SCI, the mechanisms whereby PPARγ promotes resolution of inflammation in acute CNS diseases are poorly understood. Our previous study reported that application of RGZ in a transient MCAO mouse model increased the expression of CD206 on microglia, a marker of the inflammation-resolving M2 phenotype (Han *et al.*, 2015). Furthermore, treatment with RGZ enhances the phagocytic activity of microglia in the mouse distal permanent MCAO model (Ballesteros *et al.*, 2014). Zhao and colleagues reported that RGZ administration promotes hematoma resolution by enhancing microglial phagocytosis after intrastriatal blood injection in both mice and rats (Zhao *et al.*, 2007). Administration of RGZ also promotes infiltration of neutrophils into the ischemic lesion zone, followed by direct neutrophil polarization to the N2 phenotype and microglia/macrophage clearance of neutrophils in the MCAO mouse model (Cuartero *et al.*, 2013). RGZ treatment in mice subjected to permanent MCAO accelerates neutrophil recruitment into the ischemic core, as shown by increased numbers of neutrophils in the ipsilesional hemisphere at 24h after ischemia. RGZ also increased the expression of Ym1 and CD206 by two-fold in these infiltrated neutrophils. Furthermore,

RGZ treatment facilitated neutrophil clearance in the infarct core by microglia/macrophages. Taken together, these findings indicate that PPARγ activation might enhance the beneficial functions of microglia and neutrophils. Furthermore, PPARγ agonists prevent excessive activation of neutrophils by promoting their clearance (Cuartero *et al.*, 2013). These collective actions of PPARγ are expected to accelerate tissue repair and functional recovery.

In contrast to the effects of PPARγ activation on microglia and neutrophils, the effects of PPARγ on Tregs in acute CNS diseases are poorly understood. PPARγ is known to be essential for the development of Tregs in highly enriched mouse adipose tissue (Cipolletta *et al.*, 2012; Park and Pan, 2015). Administration of CGZ enhances Treg development and its suppression of Th17 cells in a graft-versus-host disease mouse model (Wohlfert *et al.*, 2007; Park and Pan, 2015). Although the cellular source has not been established, intraperitoneal administration of RGZ after SCI increases the levels of NGF and BDNF (Meng *et al.*, 2011; Mandrekar-Colucci *et al.*, 2013). Furthermore, Tregs can be a source of BDNF and other trophic factors, as discussed in Section 5.1.1.

In conclusion, resolution of inflammation is not an isolated process; it is fully integrated into the chronic recovery phase. Timely clearance of necrotic debris or injured cells prevents oxidative stress and the release of pro-inflammatory factors, impeding the feed-forward cycles that characterize inflammation. Contraction of the immune cell populations after fulfillment of their beneficial functions decreases the risk of excessive immune reactions and the resulting deleterious auto-immune responses. Neurotrophic factors are also essential for the reconstruction of tissue in acute CNS diseases. Direct and indirect evidence outlined above suggests that activation of PPARγ fosters the resolution of inflammation and the recovery of function through some of these mechanisms.

5.2 Clearance of debris and infiltrating cells

5.2.1 An introduction on the clearance of debris and infiltrating cells—Severe CNS injuries cause cell death and the subsequent production of cellular debris. Necrotic or apoptotic neuron somata and axonal debris or detached myelin pieces are detrimental for several reasons. First, they activate immune responses and lead to subsequent chronic inflammation, which causes further cell death and tissue damage. Second, the debris-induced chronic inflammation impairs axonal regeneration and maturation of OPCs, which are vital for post-injury remyelination. Furthermore, infiltrating polymorphonuclear neutrophils (PMNs) and erythrocytes may also be detrimental after hemorrhage and trauma. Application of PMNs onto post-OGD organotypic hippocampal slice cultures causes a remarkable exacerbation of neuronal damage (Neumann *et al.*, 2008), perhaps due to the release of ROS, proteases, and proinflammatory cytokines such as TNF-α (Jordan *et al.*, 1999). In ICH, extravasated erythrocytes in the hematoma undergo lysis within hours to days after ICH, releasing cytotoxic hemoglobin, heme, and iron, thereby negatively influencing the viability of surrounding neurons and oligodendrocytes (Zhao *et al.*, 2009a). Thus, efficient clearance of damaged cellular components by phagocytosis relieves secondary tissue damage and favors tissue repair after CNS injury.

Phagocytosis after CNS injuries is mainly carried out by resident microglia and infiltrated hematogenous macrophages. Using green fluorescent protein (GFP) transgenic bone marrow

chimeric mice to distinguish microglia from peripheral macrophages, Schilling and colleagues reported that activated microglia exhibited phagocytic responses beginning on the first day after 30 min of transient MCAO (Schilling *et al.*, 2005). Furthermore, the number of activated microglia increased gradually and peaked on day 10. Peripheral macrophage infiltration was not evident until day 4 after MCAO, peaking in the following 3 days, and then decreasing until 2 weeks after the ischemic insult. Phagocytic microglia accounted for one quarter of total activated microglia and reached maximal levels as early as 24 h post-ischemia and were maintained at this level until the infiltration of hematogenous macrophages. These findings lead to the hypothesis that microglia play a predominant role in debris clearance in the early stages, while assistance from infiltrated macrophages occurs subsequently. Similarly, in a moderate contusion injury model of SCI, Greenhalgh *et al.* used lysozyme M enhanced GFP-knockin mice to tag hematogenous macrophages and discovered that 1) phagocytic microglia appeared as early as 24 h post-SCI, 2) microglia were the predominant phagocytic cell type until day 3, and 3) infiltrating macrophages become the predominant phagocytic cell on day 3 and persisted for up to 42 days (Greenhalgh and David, 2014). It is noteworthy that only a small percentage of microglia contained phagocytic material at 7d (~3%), while phagocytic material was still evident in a high percentage of infiltrating macrophages at 42 d (~30%) after SCI. Phagocytosis of red blood cells by microglia has also been observed in ICH and promotes hematoma resolution (Zhao *et al.*, 2007). In a closed skull injury-induced mouse TBI model, activated microglia were immunoreactive for galactose-specific lectin (Galectin)-3 (formerly called Mac-2), a receptor involved in the activation of myelin phagocytosis (Rotshenker, 2009). The microglia were most abundant one day following injury, followed by a decrease up to 28 days after TBI, but still were significantly elevated in TBI brains compared to sham control brains (Venkatesan *et al.*, 2010).

The benefits of phagocytosis after acute CNS injuries have been well documented. As mentioned above, external application of invading PMNs to OGD-treated organotypic brain slices dramatically enhances ischemic neurotoxicity (Neumann *et al.*, 2008). However, additional application of microglia counteracted this effect by rapid engulfment of PMNs, followed by neuroprotection that could be abrogated by interfering with microglial PMN engulfment (Neumann *et al.*, 2008). Phagocytosis of blood components by resident microglia and macrophages in ICH mitigates further damage (Zhao *et al.*, 2009a). Accordingly, phagocytosis and subsequent hematoma resolution are associated with improvements in neurological recovery (Chen *et al.*, 2017), whereas loss of phagocytosis exacerbates brain swelling and impedes clot resolution (Ni *et al.*, 2016). Enhanced microglial phagocytosis of myelin and cell debris is also beneficial for the survival of injured neurons and myelin regeneration in acute SCI and TBI, thereby facilitating functional recovery (Rotshenker, 2003; Boekhoff *et al.*, 2012; Redondo-Castro *et al.*, 2013). Molecular mechanisms involved in microglia/macrophage-afforded phagocytosis have been widely studied. In this context, priming is defined as any condition or event that facilitates the interaction between phagocytic receptors and their targets. Priming allows the phagocyte to engulf its targets by exposing ligand binding sites. This exposure endows phagocytic receptors with increased mobility in the plane of the membrane, thereby enhancing the probability of encountering target particles (Freeman and Grinstein, 2014). A large number

of inflammatory stimuli promote the transition of the integrins from a bent (closed) conformation to an extended (open) conformation, resulting in enhanced exposure of binding sites (Shattil *et al.*, 2010). Other priming factors include G protein-coupled receptor ligands (Freeman and Grinstein, 2014), Toll-like receptor (TLR) ligands (Patel and Harrison, 2008), and growth factors such as macrophage colony-stimulating factor (Kheir *et al.*, 2005). After priming, specific membrane receptors on phagocytes and downstream signaling pathways contribute to the recognition and engulfment of target microparticles. In general, there are two functionally distinct types of receptors—one with a high binding affinity to foreign microbial pathogens, such as TLRs, and one that recognizes apoptotic cellular substances, such as triggering receptor expressed on myeloid cells 2. During post-injury debris clearance, the latter receptor is more instrumental. Other receptors involved in phagocytosis include Fc receptors (Anderson *et al.*, 1990), complement receptors (Ross *et al.*, 1992), scavenger receptors (Patel *et al.*, 2004), pyrimidinergic receptor P2Y (Koizumi *et al.*, 2007), G-protein coupled receptors (Riyahi *et al.*, 2011; Dustin, 2016) macrophage antigen complex 2 (Rotshenker, 2009), and mannose receptors (Ezekowitz *et al.*, 1990). Furthermore, different surface receptors on phagocytes may be involved in tethering (recognition and binding of cell corpses) and tickling (internalization and activation of downstream signaling) processes. Phosphatidylserine is a dominant “eat me” signal when cells undergo apoptosis (Fadok *et al.*, 1998). The recognition of phosphatidylserine is mediated by at least one tethering and one internalization receptor (Henson and Hume, 2006). For example, integrins and CD36 are involved in tethering, while Gas and protein S are involved in tickling (Majai *et al.*, 2007). Tethering and tickling lead to activation of Rac pathway, which mediates the uptake of dead cells (Majai *et al.*, 2007).

In the context of acute CNS injuries, CD36 and Galectin-3 are the most important and widely studied phagocytosis receptors. CD36, a member of the scavenger receptors, is involved in the recognition and removal of modified lipoproteins, apoptotic cells, and pathogens (Canton *et al.*, 2013). Upregulation of CD36 during the acute (3d) and recovery (7d) periods has been documented in mouse models of ischemia and is correlated with higher phagocytic indices in brain immune cells (Woo *et al.*, 2016). Furthermore, CD36 deficiency compromises microglial phagocytosis of RBCs and slows hematoma absorption (Fang *et al.*, 2014). The importance of CD36 is confirmed by the observation that addition of anti-CD36 antibodies to human macrophages reduces phagocytosis of apoptotic neutrophils by 50% (Fadok *et al.*, 1998). In addition, CD36 is involved both in tethering and ligand internalization processes. Specifically, CD36 functions as an integrin-associated protein and cooperates with integrins to accomplish tethering (Majai *et al.*, 2007). During ligand internalization, CD36 forms a heteromeric complex with β1 and/or β2 integrins and the tetraspanins CD9 and/or CD81, thereby linking to the adaptor Fc receptor γ, which bears an immunoreceptor tyrosine activation motif. By coupling to Fc receptor γ, CD36 is able to engage the Src-family kinases and Syk, which in turn drives the internalization of CD36 and its bound ligands (Majai *et al.*, 2007). Finally, Galectin-3 may activate phagocytosis by upregulating and prolonging KRas-GTP-dependent phosphatidylinositol 3-kinase activity (Rotshenker, 2009).

During phagocytosis, high levels of pro-oxidative molecules and pro-inflammatory mediators are produced and may adversely affect the survival of phagocytes (Zhao *et al.*,

2007; Yi *et al.*, 2008). Thus, resolution of inflammation and oxidative burden facilitate phagocytosis by preventing injury to microglia/macrophages. For example, upregulation of the antioxidant enzyme catalase is known to promote phagocytosis (Donnan *et al.*, 2008).

5.2.2 PPARγ promotes clearance of debris and infiltrating cells—The functional role of PPARγ in microglia/macrophage-afforded phagocytosis has been widely studied. PPARγ is dramatically upregulated during the maturation of human macrophages from monocytes, a process that endows macrophages with more efficient phagocytic capacities (Majai *et al.*, 2007). PPARγ agonists can upregulate microglial phagocytosis of *Staphylococcus aureus* in bacterial brain abscesses (Kielian *et al.*, 2008). In the brains of Alzheimer's patients, PPARγ activation is associated with elimination of Aβ by microglia and a reduction in the oxidative burden in damaged tissue (Yamanaka *et al.*, 2012). Consistent with these findings, PPARγ deficiency in macrophages delays skin wound healing in mice by impairing apoptotic cell clearance (Chen *et al.*, 2015). Furthermore, the application of PPARγ antagonists during the differentiation process impairs macrophage-mediated phagocytosis of apoptotic cells, which may be partly attributed to downregulation of CD36 (Majai *et al.*, 2007).

PPARγ-afforded promotion of phagocytosis may be attributed to three factors. First, PPARγ may promote inflammation-resolving M2 polarization in microglia/macrophages. Although somewhat controversial, phagocytosis is more often considered an M2 characteristic (Tang and Le, 2016). Second, PPARγ favors the resolution of inflammation and may therefore reduce proinflammatory cytokines such as IFN-γ, IL-1β, and TNF-α, which could impair the phagocytic activity of microglia (Koenigsknecht-Talboo and Landreth, 2005). Third, PPARγ reduces oxidative stress, which also serves to promote phagocytosis (Donnan *et al.*, 2008).

A number of studies support the view that PPAR-γ activation in microglia and macrophages promotes phagocytosis after CNS injuries. In models of ICH, the activation of PPARγ increases the clearance of blood deposited in primary microglia cultures and in animals, thereby improving hematoma resolution (Heppner *et al.*, 2015). PPARγ activation is followed by upregulation of catalase and CD36 by phagocytes (Donnan *et al.*, 2008) and by inhibition of NF-κB in ICH, all of which serve to boost phagocytosis. Similarly, PPARγ activation with RGZ induces CD36 expression in resident microglia in a mouse model of permanent focal cerebral ischemia, increasing the ability of microglia to engulf dead neutrophils (Ballesteros *et al.*, 2014). The effects of PPARγ activation on phagocytosis in SCI or TBI are not known.

5.3 Neurogenesis

5.3.1 An introduction on neurogenesis in the adult brain after CNS injury—For many years, it was believed that the brain is extremely limited in its capacity for self-renewal (Streilein, 1995). However, we now know that the adult CNS undergoes active self-repair and neurogenesis after CNS injuries, a finding that holds immense translational potential. Two neurogenic niches containing neural stem/progenitor cells (NSCs/NPCs) have been identified in the adult brain—the subventricular zone (SVZ) of the lateral ventricles and the

subgranular zone (SGZ) of the hippocampal dentate gyrus (Lindvall and Kokaia, 2015). Neurogenesis in these two niches follows different patterns. Putative NSCs within the SVZ are known as type B cells and are intermixed with ependymal cells. They are characterized by the astrocytic marker glial fibrillary acidic protein (GFAP) and astrocyte-like processes. Once quiescent type B cells are activated, they proliferate and begin to express NPC markers such as nestin. At this stage, they are called transit amplifying precursors or type C cells. After three proliferative cycles, type C cells transform into neuroblasts (type A cells) that migrate towards the olfactory bulb along the rostral migratory stream and differentiate into mature neurons while integrating into olfactory circuits (Doetsch *et al.*, 1997; Quinones-Hinojosa *et al.*, 2006). Neurogenesis in the SGZ originates in another type of NSCs (type I cells) that share properties with radial glial cells and express GFAP and nestin. When activated, type I cells transform into NPCs (type IIa cells) that further develop into type IIb cells and express markers of neuroblasts such as doublecortin. Type IIb cells then generate type III neuroblasts and develop dendrites. Notably, approximately 80% of type III cells die of apoptosis within 2 weeks (Arvidsson *et al.*, 2002), and those that survive mature into NeuN-expressing neurons (Eriksson *et al.*, 1998; Seri *et al.*, 2001). These newly generated neurons form synaptic connections with pyramidal cells of the hippocampus, which play a critical role in cognitive recovery after CNS injury (Seri *et al.*, 2001; Ramirez-Amaya *et al.*, 2006; Clelland *et al.*, 2009; Sahay *et al.*, 2011).

During the past two decades, novel neurogenic niches other than in the SVZ and SGZ have been reported, including in the hypothalamus (Kokoeva *et al.*, 2005; Xu *et al.*, 2005; Migaud *et al.*, 2010; Pierce and Xu, 2010), striatum, neocortical areas, amygdala (Bernier *et al.*, 2002; Dayer *et al.*, 2005; Luzzati *et al.*, 2006), and brainstem (Bauer *et al.*, 2005). Neurogenesis in the spinal cord after SCI is more elusive. Spinal cord ependymal cells may act as NSCs (Duan *et al.*, 2016), but develop into oligodendrocytes and astrocytes and not into neurons, although their NSC potential is preserved *in vitro* (Johansson *et al.*, 1999; Meletis *et al.*, 2008; Barnabe-Heider *et al.*, 2010). One explanation is that the spinal cord provides a non-permissive microenvironment that specifically blocks neuronal lineage differentiation, unlike the brain (Lee-Liu *et al.*, 2013). However, these ideas await confirmation.

Stroke and TBI both trigger the proliferation, differentiation, and migration of neurons in the SVZ and SGZ (Arvidsson *et al.*, 2002; Masuda *et al.*, 2007; Shen *et al.*, 2008), suggesting a link between CNS injury and neurogenesis. However, whether neurogenesis is vital for CNS recovery after injury is not clear. When neurogenesis is abolished by ablation of doublecortin-expressing neuroblasts in mice subjected to MCAO, infarct sizes and behavioral deficits are increased at 24 h post-injury (Jin *et al.*, 2010a). Furthermore, these effects last up to 12 weeks after MCAO, suggesting a crucial role for neurogenesis in long-term recovery (Wang *et al.*, 2012a). A similar phenomenon is also evident in models of TBI with selective ablation of nestin-expressing NPCs (Blaiss *et al.*, 2011).

5.3.2 PPARγ in neurogenesis—Only a few studies have focused on the role of PPARγ in neurogenesis, and none of them involve CNS injuries. Nevertheless, PPARγ enables normal brain development and global knockout is embryonically lethal (Wada *et al.*, 2006). This has led to the speculation that PPARγ is indispensable in adult neurogenesis. In this

section, we will discuss PPARγ-dependent neurogenesis in physiological and disease conditions, and make some inferences about its neurogenic role in CNS injuries. A role for PPARγ in neurogenesis is consistent with genomic studies confirming the presence of PPREs in gene clusters that control cell survival and differentiation (Lemay and Hwang, 2006; Heinaniemi *et al.*, 2007).

PPARγ is essential in normal stem cell proliferation and neural differentiation *in vitro*. Wada *et al.* reported a decrease in cell growth rate in cultured PPARγ$^{+/-}$ and PPARγ$^{-/-}$ NSCs (Wada *et al.*, 2006). In PPARγ$^{+/+}$ NSCs, cell proliferation was enhanced by RGZ and reduced by GW9662. PPARγ agonists can also promote neural differentiation. For example, 15d-PGJ2 promotes the differentiation of embryonic midbrain cells into dopaminergic neurons (Park *et al.*, 2004b). Similarly, PGZ promotes neural differentiation and neurite outgrowth in SH-SY5Y neuroblastoma cells (Park *et al.*, 2004b). Taheri *et al.* reported an increase in PPARγ mRNA in both the NPC stage and neural cell stage during the differentiation of cultured human embryonic stem cells (hESCs) (Taheri *et al.*, 2015). Notably, NPC markers are decreased by GW9662, but not increased by 15d-PGJ2.

The effects of PPARγ on neurogenesis have been examined in some disease models. During an exploration of hyperglycemia-induced decreases in neurogenesis, advanced glycan end products (AGEs) were found to inhibit NSC proliferation and differentiation, and this was associated with decreased PPARγ expression (Wang *et al.*, 2009). Exogenous RGZ administration rescued AGE-induced repression of NSC proliferation by inhibition of caspase-dependent NSC apoptosis. However, RGZ failed to prevent AGE-mediated inhibition of NSC differentiation (Wang *et al.*, 2009). Intraperitoneal delivery of LPS (5 mg/kg) decreases hippocampal neurogenesis by 50% and this is associated with memory impairments that are reversed by oral intake of RGZ, indicating a protective role of PPARγ against inflammation-induced suppression of neurogenesis (Ormerod *et al.*, 2013). However, conflicting results were reported during congenital cytomegalovirus (CMV) infection of the CNS (Rolland *et al.*, 2016). In that study, CMV infection was associated with increased PPARγ expression and activity, as well as increases in 9-hydroxyoctadecadienoic acid, a known PPARγ agonist. PPARγ activation with 15d-PGJ2 led to impaired neurogenesis in uninfected NSCs, and treatment of NSCs with 9-hydroxyoctadecadienoic acid decreased NSC neural differentiation. Consistent with these findings, treatment of CMV-infected NSCs with the PPARγ inhibitor T0070907 restored normal differentiation rather dramatically. These results suggest complex effects of PPARγ on neurogenesis, and possibly distinct roles in various diseases and experimental models. Although PPARγ is significantly increased by CNS injuries such as cerebrovascular events and trauma, its effects on neurogenic processes remain unknown and need further exploration.

5.4 Remyelination

5.4.1 An introduction on remyelination during CNS repair—Remyelination refers to the progressive restoration of the entire myelin sheath around demyelinated axons, a process that reinstates saltatory conduction (Smith *et al.*, 1979) and resolves functional deficits (Jeffery and Blakemore, 1997; Liebetanz and Merkler, 2006). Remyelination is characterized by the formation of thinner myelin with shorter internodes compared to

sheaths that are not injured (Blakemore, 1974). The *g* ratio refers to the circumference of the axon divided by the circumference of the myelin sheath, and is used to assess the degree of remyelination (Franklin and Ffrench-Constant, 2008). Generally, remyelination consists of three phases: OPC proliferation, OPC recruitment, and OPC maturation. There is consensus that OPCs serve as the major origin of newly generated oligodendrocytes post-demyelination (Dawson *et al.*, 2003). First, retroviral and autoradiographic tracing studies indicate that remyelinating oligodendrocytes originate from dividing cells in normal adult white matter, which are likely to be adult OPCs, although this awaits confirmation (Gensert and Goldman, 1997; Carroll *et al.*, 1998). Second, transplanted OPCs remyelinate demyelinated axons quite effectively (Groves *et al.*, 1993). OPCs repopulate focal demyelination sites, where both oligodendrocytes and OPCs have died, prior to the appearance of new oligodendrocytes; these temporal and spatial patterns strongly suggest that OPCs are indeed the source of remyelinating cells (Sim *et al.*, 2002). Fourth, cells transiently express OPC as well as oligodendrocyte markers at the onset of remyelination (Fancy *et al.*, 2004). In response to injury, microglia, astrocytes, and other inflammatory cells become activated and produce mitogenic factors and pro-migratory factors, including platelet-derived growth factor and basic fibroblast growth factor, which switch OPCs from a quiescent state to a regenerative phenotype and recruit OPCs to the demyelination zones (Franklin and Ffrench-Constant, 2008). In the final phase of remyelination, the recruited OPCs differentiate into myelinating oligodendrocytes and ensheath the demyelinated axons.

The adult brain undergoes remyelination and white matter repair after CNS injuries, but only to a very limited extent. In the closed-skull impact mouse model of TBI, newly generated oligodendrocytes appear as early as 3 days post-injury (Mierzwa *et al.*, 2015). Remyelination is evident within 1 week post-TBI and prolonged for at least 6 weeks. Similar patterns of post-injury remyelination have been reported in animal models of ischemic stroke (Mandai *et al.*, 1997), SCI (Harrison *et al.*, 1975; Tripathi and McTigue, 2007; Hesp *et al.*, 2015), and ICH (Joseph *et al.*, 2016). Remyelination failure can result from failure of OPC recruitment or failure of differentiation. Experimental and clinical data suggest that differentiation is the most vulnerable phase of remyelination (Franklin and Ffrench-Constant, 2008).

5.4.2 PPARγ in remyelination (703)—As mature oligodendrocytic processes form the myelin sheath, promoting NSC differentiation toward the mature oligodendrocytic lineage might directly increase myelination. PPARγ agonists can augment NSC differentiation into mature oligodendrocytes (Kanakasabai *et al.*, 2012; Wan Ibrahim *et al.*, 2013), although the underlying mechanisms remain unknown (Figure 5A).

The effects of PPARγ in OPC maturation are better studied than its effects on NSCs (Figure 5B). Recent findings demonstrate that PPARγ activation positively contributes to differentiation of multiple lines of OPCs. Studies on B12 glioma-derived cells and primary rat spinal cord OPCs show that PPARγ activation promotes the commitment of OPCs toward differentiation into myelin basic protein-expressing (MBP^+) mature oligodendrocytes (Roth *et al.*, 2003). B12 cells express all three PPAR isoforms but only respond to PPARγ agonists. Activation of PPARγ in B12 cells arrests cell proliferation and increases process extension (Roth *et al.*, 2003). Furthermore, treatment with PGZ drives primary rat OPCs to

differentiate and mature into oligodendrocytes (Bernardo *et al.*, 2009; De Nuccio *et al.*, 2011). Our recent work demonstrates that RGZ enhances OPC proliferation and increases the number of newly-generated mature oligodendrocytes after MCAO (Han *et al.*, 2015). Nonspecific PPARγ activators such as statins have also been studied for their effects on OPCs. Statins are 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors and activate PPARγ through depletion of geranylgeranyl-pyrophosphate and subsequent RhoA-Rho kinase inactivation (Sim *et al.*, 2008; Paintlia *et al.*, 2010). Statins contribute to activation of PPARγ and directly promote survival and differentiation of rodent and human OPCs *in vitro* and increase myelin repair in the EAE model of multiple sclerosis *in vivo* (Paintlia *et al.*, 2005; Miron *et al.*, 2007; Paintlia *et al.*, 2008).

As the ability of PPARγ to promote OPC maturation has been established, the mechanisms underlying this process are also being examined. First, PPARγ is heavily involved in cellular lipid metabolism, and lipid metabolism is of vital importance to oligodendrocyte process formation. PPARγ agonists can promote rat B12 cell maturation by enhancing the formation of myelin-rich lipid plasmalogen, as shown by an increase in alkyl-dihydroxyacetone phosphate synthase (Roth *et al.*, 2003). Second, PPARγ activation blunts the oxidative stress arising from rapid lipid metabolism during OPC differentiation. As mentioned above, recent studies suggest that PPARγ activation upregulates expression of the antioxidant enzymes Cu/Zn SOD and catalase and maintains the equilibrium of the glutathione redox systems, which would mitigate the oxidative stress generated from OPC maturation-related metabolism (Bernardo *et al.*, 2009). Third, PPARγ activation enhances the function of mitochondria during OPC maturation. Repeated administration of PPARγ agonists accelerates primary rat OPC maturation and expression of myelin basic protein by increasing activity of the mitochondrial respiratory chain complex IV and upregulating ADP-induced Ca^{2+} waves (De Nuccio *et al.*, 2011). In sum, PPARγ appears to facilitate the survival and differentiation of OPC cells and enhance their antioxidant defenses and mitochondrial function (Bernardo *et al.*, 2009).

Despite the abovementioned evidence that PPARγ favors remyelination after injury, negative effects of PPARγ agonists on OPCs have also been observed. For example, 15d-PGJ2 treatment can induce apoptosis in early-stage mouse OPCs (Xiang *et al.*, 2007). Statins can also impede oligodendrocyte maturation and myelin formation *in vitro* (Miron *et al.*, 2007; Klopfleisch *et al.*, 2008). Statins may also hamper intrinsic myelin repair and maintenance in the cuprizone-induced animal model of demyelination (Klopfleisch *et al.*, 2008; Miron *et al.*, 2009). Furthermore, PPARβ, but not PPARγ, was shown to promote OPC differentiation in primary mixed glial cell cultures enriched in oligodendrocytes (Saluja *et al.*, 2001; Jana *et al.*, 2012). Activation of PPARβ also protects primary human oligodendrocytes against serum deprivation-induced cell death (Jana *et al.*, 2012). However, crosstalk between PPARβ and PPARγ may enhance OPC differentiation in undifferentiated C6 glioma cells (Leisewitz *et al.*, 2008). Therefore, further studies are needed to resolve these controversies and decipher the precise role of PPARγ in regulating developmental processes in cells of the oligodendrocyte lineage. Furthermore, as gene transcriptional activation is a subtle but dynamic process, there needs to be greater resolution of the temporal kinetics of gene expression after PPARγ activation. Other unresolved issues include identification of the

stage of OPC differentiation during which agonist-mediated PPARγ activation might be most effective, as well as the pharmacokinetics and optimal dosages of PPARγ agonists.

5.5 BBB repair and angiogenesis/revascularization

Angiogenesis plays important roles in tissue repair and functional recovery after various CNS injuries. Extensive studies have shown that newly formed microvessels improve tissue microperfusion around the ischemia boundary zone and promote functional recovery after stroke (Zhang *et al.*, 2000; Zhang and Chopp, 2002). PPARγ is highly expressed in vascular walls, including the endothelial lining, and is one of major transcription factors involved in the regulation of cerebrovascular structure and function (Culman *et al.*, 2007; Beyer *et al.*, 2008; Halabi *et al.*, 2008; Hamblin *et al.*, 2009). Beyer *et al.* examined vascular tone and function using heterozygous knock-in mice expressing dominant negative-PPARγ (Beyer *et al.*, 2008). They reported that endothelium-dependent agonist-induced dilation in cerebral blood vessels was significantly impaired in dominant negetive-PPARγ mice. The authors also concluded that interruptions in PPARγ signaling result in endothelial dysfunction through oxidative stress and cause vascular hypertrophy and inward remodeling.

Chu *et al.* investigated the effects of the PPARγ agonist RGZ on angiogenesis and neurological recovery after cerebral ischemia in the rat MCAO model (Chu *et al.*, 2006). The authors reported that RGZ-pretreated rats present not only with smaller infarct volumes but also with fewer initial neurologic deficits and superior recovery from day 1 through 5 weeks after cerebral ischemia. Notably, RGZ pretreatment also causes significant increases in $BrdU^+$ proliferating endothelial cells in the lesioned hemispheres. Furthermore, RGZ increased cerebral microvessels density, vascular branch points, and vascular surface areas in the ipsilateral hemisphere. The authors conclude that eNOS upregulation may be the main mechanism of RGZ-promoted angiogenesis after focal cerebral ischemia. Another recent study evaluated the role of PPARγ in regulating human pulmonary microvascular endothelial cell migration and angiogenesis (Vattulainen-Collanus *et al.*, 2016). In that study, loss of PPARγ attenuated angiogenesis and migration capacity of the cells through E2F transcription factor 1-mediated Wnt signaling. Using *in vivo* angiogenesis assays with subcutaneously placed matrigel plugs, Vattulainen-Collanus and colleagues also reported reductions in angiogenesis and mobilization of endothelial progenitor-like cells from the bone marrow in Tie2Cre-$PPAR\gamma^{flox/flox}$ mice with ablation of PPARγ in endothelial cells and osteoclasts (Vattulainen-Collanus *et al.*, 2016).

Taken together, these findings suggest that PPARγ activation enhances angiogenesis and functional recovery in rodent ischemic stroke models. The genomic studies discussed in Section 2.4 are consistent with the findings presented here, as they reveal PPREs in genes involved in Wnt signaling, cell growth and maintenance, and BBB integrity (Lemay and Hwang, 2006; Heinaniemi *et al.*, 2007).

6. PPARγ protects against comorbidities

Comorbidities are well known to exacerbate CNS injuries, either by precipitating their onset, or by directly accelerating the underlying pathologic process. Fortunately, many comorbidities, such as hyperglycemia, hypertension, atherosclerosis, and infection are

clinically modifiable. Modification of these comorbidities confers protective effects against CNS injury and alleviates disease severity, and is therefore practiced as standard clinical management. Notably, PPARγ serves as a target of many of these comorbid diseases. In this section, we will discuss the effects of modifiable comorbidities commonly associated with CNS injuries, as well as clinical and preclinical evidence favoring their PPARγ-dependent modulation.

6.1 Hyperglycemia

Metabolic syndrome and diabetes mellitus (DM) are known risk factors for stroke. The prevalence of hyperglycemia is 20%–50% in acute stroke, even in the absence of DM (Yu *et al.*, 2015). The second European Cooperative Acute Stroke Study (ECASS-II) followed 748 stroke patients and reported that blood glucose levels were associated with almost all outcomes, including 7-day neurological improvements, 30-day favorable functional outcomes, 90-day negligible dependence, all-cause mortality within 90 days, and hemorrhagic transformation within the first 7 days (Sugawara *et al.*, 2001). Concurrent hyperglycemia is an independent predictor for stroke outcome (Ghajar, 2000; Sarafidis and Lasaridis, 2006). According to the American Stroke Association guidelines, a target of <300 mg/dL blood glucose should be met (Writing Group *et al.*, 2016). Even non-cardiovascular, traumatic CNS injuries such as TBI and SCI are associated with hyperglycemia and severe TBI patients exhibit higher blood glucose levels compared with mild TBI patients (Elder *et al.*, 2004; Jeremitsky *et al.*, 2005). Hyperglycemia is positively correlated with mortality rate, and blood glucose levels are predictive of worse neurological outcomes (Jeremitsky *et al.*, 2005; Uruno *et al.*, 2011; Bevers *et al.*, 2017). Similar detrimental effects of hyperglycemia in SCI have been reported in mouse models as well as in humans (Writing Group *et al.*, 2016). Although impaired neurovascular coupling and reduced cerebral perfusion have been reported in DM patients (Duarte *et al.*, 2015), it is not known with certitude if hyperglycemia is the cause of detrimental effects in the clinic, or if it is a stress response and/or biomarker of injury (Tsai *et al.*, 2009).

TZD treatment is part of the standard of care for DM patients, as it significantly lowers blood glucose levels without elevating the risk of hypoglycemia (Nathan *et al.*, 2009). Not surprisingly, stroke preventive effects of TZD have also been reported. For example, the “Insulin resistance intervention after stroke trial of PGZ” (IRIS trial) (Inzucchi and Furie, 2016) revealed significant secondary stroke prevention, and this effect was more pronounced for the lacunar subtype. It is worth noting that delivery of insulin (and not oral hypoglycemics) is the drug of choice in the acute phase of stroke (Nakayama *et al.*, 1994). A metaanalysis suggests that administration of PPARγ agonists reduces the incidence of primary stroke and recurrent stroke (Liu and Wang, 2015). However, RGZ was reported to increase the risk of heart failure, according to the “Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes” (RECORD) trial (Home *et al.*, 2009), which led to dispensing restrictions by the U.S. Food and Drug Administration (FDA) in 2010. However, after further discussion at the joint meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee in 2013 (FDA, 2013), the RECORD trial was deemed to suffer from bias in identification of cardiovascular events and the restrictions were lifted in

2015 (FDA, 2015). There have been no clinical trials on use of PPARγ agonists in TBI or SCI patients thus far.

6.2 Hypertension

Hypertension is the most frequent comorbidity associated with CNS injuries (Abraham *et al.*, 2016; Qureshi and Qureshi, 2017). Hypertension is evident in up to 70% of stroke patients (Staessen *et al.*, 2003). Hypertensive patients experience a two-fold increase in the lifetime risk of stroke compared to subjects with normal blood pressure (BP <120/80 mmHg) (Writing Group *et al.*, 2016). PPARγ has been shown to downregulate BP. Aside from metabolic abnormalities, loss-of-function mutations of PPARγ in humans can lead to severe hypertension (Barroso *et al.*, 1999; Agostini *et al.*, 2006; Auclair *et al.*, 2013). Consistent with these clinical findings, a two-fold increase in PPARγ expression levels can decrease BP by ~2.8 mmHg in rodents (Tsai *et al.*, 2009). The angiotensin II pathway is known to result in hypertension and might be the target of PPARγ. TZDs have been shown to decrease the transcription of angiotensin II receptor type 1 in vascular smooth muscles *in vivo* (Sugawara *et al.*, 2001), in agreement with *in vitro* findings that PGZ suppresses angiotensin II-induced aldosterone expression (Uruno *et al.*, 2011). Accordingly, activation of PPARγ with PGZ can attenuate angiotensin II-induced hypertension (Yu *et al.*, 2015). Other mechanisms underlying PPARγ-mediated modulation of BP may include maintaining calcium levels, inhibiting smooth muscle cell proliferation, stabilizing renal function, and attenuating sympathetic over-activation (Sarafidis and Lasaridis, 2006). These findings indicate that PPARγ activation might be a therapeutic approach to lowering BP to prevent the development of stroke. However, BP control during acute stroke is challenging, as both high BP and low BP are independent prognostic factors for poor stroke outcomes (Willmot *et al.*, 2004). Furthermore, in TBI and SCI, intracranial pressure, rather than systemic BP, is one of the most important prognostic factors (Ghajar, 2000), and does not appear to be under direct regulation of systemic BP.

6.3 Dyslipidemia and atherosclerosis

Abnormality in lipid metabolism is an independent risk factor for stroke. Increases in triglycerides are associated with both ischemic stroke and ICH (Nakayama *et al.*, 1994; Ott *et al.*, 1999). In contrast, levels of high-density lipoprotein-cholesterol (HDL-C), a reverse cholesterol transporter, are negatively correlated with stroke risk, and this effect is even more pronounced in thromboembolic stroke (Curb *et al.*, 2004; Huxley *et al.*, 2011). In contrast, low-density lipoprotein (LDL) and peripheral macrophages may directly mediate atherosclerosis (AS) formation. Excessive oxidized LDL deposition induces accumulation of macrophages in the vascular wall. Macrophages engulf detrimental lipoproteins and convert into foam cells (Chistiakov *et al.*, 2016). Activated foam cells within the sclerotic plaques secrete various cytokines, such as IL-6 and TNF-α, which lead to endothelial malfunction (Ait-Oufella *et al.*, 2011), smooth muscle cell migration and proliferation, as well as extracellular matrix production, which may constrict the diameter of the vascular lumen (Wahl *et al.*, 1997). In late stages of AS, excessively narrow arteries limit cerebral blood flow. In addition, macrophages produce extracellular proteases, such as MMPs, which can rupture plaques (Gough *et al.*, 2006), thereby leading to thrombotic stroke (Mughal *et al.*, 2011).

PPARγ expression is high in macrophages within AS plaques (Wilson, 2010). PPARγ may regulate dyslipidemia and AS by modulating macrophage behavior in a number of ways. First, PPARγ promotes clearance of lipid deposition. In apolipoprotein E-knockout mice fed a high-fat diet, TGZ attenuated fatty streak lesion formation and increased HDL-C levels, and this was associated with increased CD36, the scavenger receptor that mediates LDL phagocytosis (Chen *et al.*, 2001). Second, PPARγ prevents excessive engulfment of LDL, thereby reducing macrophage activation. This view is supported by an elegant study showing that, although RGZ cannot inhibit foam-cell transformation induced by LDL *in vitro*, it can promote cholesterol efflux from macrophages via over-expression of the gene encoding ABCA1 (Chinetti *et al.*, 2001). Third, PPARγ inhibits macrophage-mediated release of inflammatory cytokines in both rodents and humans (Li *et al.*, 2000). PPARγ agonists RGZ and GW7845 strongly inhibit AS development in LDL receptor-deficient mice, and this is associated with decreased TNF-α (Li *et al.*, 2000). Consistent with these findings, RGZ administration in non-diabetic patients was associated with decreased inflammatory markers and adipokines, although no changes in HDL-C and total cholesterol levels were observed (Samaha *et al.*, 2006). Finally, PPARγ mediates growth arrest in vascular smooth muscle cells (Bruemmer *et al.*, 2003a; Bruemmer *et al.*, 2003b), which may serve as another mechanism whereby PPARγ inhibits AS, although this awaits confirmation.

6.4 Renal dysfunction

Renal dysfunction is a common comorbid disease associated with CNS injury and is a risk factor for both ischemic stroke and ICH. Renal dysfunction is apparent in up to one-third of stroke patients and significantly increases mortality (Rowat *et al.*, 2014). In patients with ICH, renal dysfunction is associated with larger lobar hematomas and poorer outcomes (Molshatzki *et al.*, 2011). In TBI, acute renal failure is one of the most common and serious complications, with incidence varying from 1.5% to 18.1% (Schirmer-Mikalsen *et al.*, 2007; Bagshaw *et al.*, 2008). In SCI, renal deterioration was the main cause of death until the introduction of methods that improve bladder emptying in the 1980s (Frankel *et al.*, 1998). SCI-induced renal failure occurs mainly due to increased risk of vesicoureteral reflux and upper urinary tract dilation (McGuire *et al.*, 1981). In a case-control long-term study conducted by Elmelund and colleagues, 26% of SCI patients eventually developed renal deterioration (Elmelund *et al.*, 2017).

A number of studies demonstrate favorable kidney-protective effects of TZDs. Constitutive expression of PPARγ has been detected in human and rodent kidneys, predominantly in the medullary collecting duct (Guan *et al.*, 1997; Yang *et al.*, 1999). In various rodent models of type 2 diabetes, TZD treatment ameliorates diabetic nephropathy and improves renal function, aside from exerting glycemic control (Baylis *et al.*, 2003; Okada *et al.*, 2006). In accordance with preclinical studies, TZD treatment in diabetics significantly decreases urinary albumin excretion in patients with normoalbuminuria, microalbuminuria, or proteinuria (Sarafidis *et al.*, 2010). Other than mitigating diabetic nephropathy, TZDs can also protect against renal dysfunction induced by cyclosporine (Chung *et al.*, 2005), puromycin aminonucleoside (Zuo *et al.*, 2012), aging (Yang *et al.*, 2009a), and polycystic kidney disease (Yoshihara *et al.*, 2011). Mechanisms underlying PPARγ-mediated renal protection include improved insulin resistance and glycemic control, cell-cycle-dependent

actions, upregulation of adiponectin expression, anti-inflammatory effects, anti-oxidative effects, prevention of renal lipid accumulation, lowering of BP, *etc*. (Yang *et al*., 2009b). However, there are no reports showing that PPARγ protects against renal dysfunction in the setting of CNS injury.

6.5 Infection

Infection is an established risk factor for stroke. Exposure to minor infections in the previous month is an independent risk factor for childhood ischemic stroke, and is evident in one third of cases (Hills *et al*., 2012). Of these cases, 80% are respiratory infections (Hills *et al*., 2014). Chronic infections such as periodontitis, chronic bronchitis, and infection with *Helicobacter pylori, Chlamydia pneumoniae*, and CMV are associated with stroke, although the causal relationship remains unclear (Grau *et al*., 2010). Infection is also a common complication associated with ischemia, especially in the elderly, and is recognized as an independent predictor of poor outcomes (Wartenberg *et al*., 2011). Notably, stroke itself may induce immune depression, thereby increasing the incidence of systemic infection (Urra *et al*., 2009). In addition, infection is associated with excessive ROS generation, which may exacerbate neuronal loss and initiate a self-amplifying cascade of tissue destruction (Berg *et al*., 2011). Perhaps for this reason, the sepsis death cluster coincides with the so-called “Stroke Belt,” which refers to a region of increased stroke mortality across Mississippi, Alabama, Georgia, Tennessee, Kentucky, North Carolina, and South Carolina (Borhani, 1965; Howard *et al*., 1995; Wang *et al*., 2010). This overlap may also suggest shared, unidentified etiology of stroke and sepsis, but this remains to be confirmed.

The effects of PPARγ in sepsis have been examined. PPARγ expression is reduced in the lung in a mouse sepsis model induced by LPS intraperitoneal injection, and 15dPGJ2 improves survival 6-fold (9% to 55%) (Kaplan *et al*., 2005). These effects are associated with reduced NF-κB and increased HSP70. In another sepsis model induced by cecal ligation and puncture, curcumin treatment increased PPARγ expression in the liver, and reduced mortality and serum TNF-α levels, and these effects were reversed by the PPARγ inhibitor GW9662 (Siddiqui *et al*., 2006). As far as the underlying mechanism, the PPARγ agonists 15d-PGJ2, BRL 49659, and ciglitazone have been shown to desensitize macrophages in cultures, thereby suppressing the oxidative burst (Von Knethen and Brune, 2001). In addition, 15d-PGJ2 and TGZ can inhibit increased NO production and IκB degradation induced by LPS or heat-killed *Escherichia coli* and *Staphylococcus aureus* in rat peritoneal macrophages (Von Knethen and Brune, 2001). Aside from macrophages, T cells are also targeted by PPARγ, as GW9662 inhibits T cell expression of IFN-γ by interfering with c-Jun activation (Cunard *et al*., 2004).

Whether or not the findings outlined in this section can be translated into CNS injury remains unknown. Furthermore, there exists some controversy, in that PPARγ ligands can induce some proinflammatory responses. For example, macrophagic uptake of oxidized LDL is strongly associated with a proinflammatory phenotype polarization, and this may be enhanced by PPARγ ligands (Tontonoz *et al*., 1998) (Section 6.3). Second, sepsis refers to a severe infection that disturbs systemic homeostasis. How PPARγ affects mild to moderate

infections remains unknown. Third, no reports have focused on the role of PPARγ against infections under conditions of CNS injury. Thus, there remain many gaps in the field.

7. Translational perspectives

A large body of preclinical and clinical work outlined above supports the view that PPARγ activation promotes functional recovery of the CNS by 1) reducing inflammation, 2) minimizing cell death in gray and white matter, and 3) engaging cell repair programs. A wide range of synthetic compounds functioning as PPAR ligands have recently been developed, with TZDs being the most prominent (Lalloyer and Staels, 2010). In addition, it seems likely that endogenous PPARγ activity is naturally increased after acute injuries to help restore homeostasis. Consistent with these views, a clinical study demonstrated that higher plasma concentrations of 15d-PGJ2, a natural PPARγ agonist, were negatively correlated with infarct size and positively correlated with better outcomes in patients with acute athero-thrombotic ischemic stroke (Blanco *et al.*, 2005).

Although there are no clinical reports on the therapeutic effects of PPARγ agonists in the acute stages of cerebral ischemia, the potential effects of PPARγ agonists in stroke prevention and recurrent stroke risk reduction in high-risk populations have been analyzed. We have summarized clinical studies on the therapeutic efficacy and safety of two FDA-approved PPARγ agonists—PGZ and RGZ—in ischemic stroke, and found that most report beneficial outcomes (Table 1). The results of several large-scale clinical trials favor the administration of PPARγ agonists: 1) the prospective PGZ clinical trial in macro-vascular events (PROactive), 2) insulin resistance intervention after stroke trial (IRIS), 3) RGZ evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD), and 4) bypass angioplasty revascularization investigation in type 2 diabetes (BARI2D) (Table 1). Consistent with these observations, a meta-analysis also suggests that administration of PPARγ agonists reduces the incidence of primary and recurrent stroke (Liu and Wang, 2015). Compared with RGZ, PGZ seems to be more favorable, with fewer safety issues and superior therapeutic effects (Liu and Wang, 2015). On the other hand, some of the studies we reviewed failed to show significant effects of PPARγ agonists in stroke prevention (Table 1). Furthermore, RGZ was shown to increase the risk of cardiovascular events and ischemic stroke in some studies, leading to post-marketing monitoring of its safety (FDA, 2015). The adverse effects were mostly found among patients who were elderly or displayed a higher risk of developing macro-vascular diseases (Table 1). In addition, TZDs have been suggested to increase the risk of heart failure, particularly in type 2 diabetics (Michalik and Wahli, 2006). An exacerbation of heart failure following PPARγ activation has also been reported in animal studies (Lygate *et al.*, 2003; Xu *et al.*, 2003). Nevertheless, considering all the clinical studies collectively, it appears that PGZ or RGZ might reduce the incidence of stroke and recurrent stroke, although the target population may need to be carefully selected, as the elderly and those with higher risk of macrovascular diseases might not benefit from such treatment. This type of selective testing of therapies only on the appropriate patient population is gaining acceptance, and future clinical treatments will likely be individualized more carefully based on pharmacogenomic approaches and personalized medicine (Di Sanzo *et al.*, 2017). In addition, BBB permeability and pharmacokinetic-pharmacodynamic properties will need to be carefully

considered in order to improve the therapeutic efficacy of PPARγ agonists in CNS diseases. For example, women, diabetic patients, and subjects with lower body weight and higher serum creatinine were found to exhibit lower clearance of the TZD drug rivoglitazone (Rohatagi *et al.*, 2008). For some PPARγ agonists, such as tesaglitazar, rapid absorption, high bioavailability and an elimination half-life of approximately 45 h were observed (Ericsson *et al.*, 2004), suggesting negligible first-pass metabolism. Furthermore, brain penetration of PPARγ agonists such as RGZ may be impaired if they are substrates of P-glycoprotein, a major drug efflux transporter in the BBB (Gold *et al.*, 2010). Given the structural similarities of RGZ and PGZ, the passage of PGZ through the BBB may also be limited (Chang *et al.*, 2015b). Thus, modifications of drug formulation, structure, or dose might be needed to further increase the passage of PPARγ agonists through the BBB. For example, the stereoselectivity of PGZ has been shown to increase its distribution in the CNS and improve its therapeutic efficacy in Alzheimer's disease (Chang *et al.*, 2015b). Another alternative is to boost the activation of endogenous PPARγ. For example, endogenous prostaglandin J2 activates PPARγ and elicits anti-inflammatory effects (Finch *et al.*, 2017).

8. Summary

PPARγ is a widely-expressed nuclear receptor that regulates the transcription of genes involved in fatty acid storage, glucose homeostasis, insulin sensitivity, anti-inflammatory effects, redox balance, and stem cell differentiation, among other roles. PPARγ regulates PPREs as well as other signaling pathways to elicit neuroprotection and tissue repair. The products of the genes that are modified by PPARγ are found in almost every subcellular compartment as well as the extracellular space. The remarkable breadth of its effects makes PPARγ an attractive therapeutic target for many disorders, including acute brain injury. The activation of Nrf2 and the inhibition of NF-κB are central to the anti-oxidative and anti-inflammatory effects of PPARγ. PPARγ can reduce expression of pro-inflammatory mediators such as IL-6, COX-2, iNOS, and TNF and increase expression of anti-inflammatory mediators such as IL-10 (Chen *et al.*, 2012), which collectively mitigate inflammation in a synergistic fashion. In the acute injury phase, PPARγ may protect against tissue damage by inhibiting neuronal death, demyelination, and BBB disruption. During the chronic recovery phase, PPARγ may facilitate CNS repair by promoting resolution of inflammation, debris clearance, neurogenesis, remyelination, and resealing the BBB. Figure 6 lists the hypothetical mechanisms underlying the protective and reparative effects of PPARγ. Furthermore, PPARγ appears to protect against systemic comorbidities, such as hyperglycemia, hypertension, AS, dyslipidemia, renal dysfunction, and infection, all of which may influence the progression of brain injuries. Many unresolved questions remain, however, including 1) how PPARγ balances the beneficial and destructive faces of neuroinflammation, 2) whether PPARγ directly inhibits demyelination, 3) how PPARγ affects OPC recruitment and differentiation, and 4) whether PPARγ promotes neurogenesis and neuroplasticity. Furthermore, there are serious challenges associated with the application of PPARγ agonists in CNS injury conditions, and some of the effects of PPARγ agonists (such as TZDs) may even be PPARγ-independent, which may cloud the interpretations of preclinical studies. Although preclinical and clinical work supports the therapeutic potential of PPARγ in ischemic stroke, whether PPARγ agonists will be effective in human TBI and

SCI is not clear, and this gap in our knowledge is deepened by the poor predictive validity of some of the rodent injury models. Furthermore, PPARγ agonists such as rosiglitazone are associated with weight gain, edema, heart failure, and anemia (Chen *et al.*, 2012). In this respect, however, PPARγ agonists are not unique—there are challenges and limitations of every drug available on the market today, in part due to a failure to account for the genotypic and phenotypic heterogeneity of human populations relative to inbred laboratory animals. At the least, our analysis of the clinical literature in Table 1 and the meta-analyses conducted by Liu and Wang specifically support the use of PPARγ agonists against primary and recurrent stroke in judiciously selected patient populations (Liu and Wang, 2015). Thus, we remain hopeful that identifying the mechanisms underlying the beneficial effects of PPARγ will reveal novel targets for future therapies, and that rational drug design based on PPARγ synthetic or endogenous ligands will lead to superior pharmacological agonists to treat diabetes, cardiovascular diseases, and acute brain disorders.

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Abbreviations

15d-PGJ2	15-deoxy-D12, 15 prostaglandin J2
15(S)-HETE	15(S)-hydroxyeicosatetraenoic acid
ADP	adenosine diphosphate
AGE	advanced glycan end product
AMPA	α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid
ARE	antioxidant response element
AS	atherosclerosis
BBB	blood-brain barrier
BDNF	brain-derived neurotrophic factor
CCI	controlled cortical impact
CDK	cyclin-dependent kinase
CGZ	ciglitazone
CTL	cytotoxic T lymphocyte
CMV	cytomegalovirus
CNS	central nervous system

COX	cyclooxygenase
DC	dendritic cell
DM	diabetes mellitus
EAE	encephalomyelitis
FDA	Food and Drug Administration
Galectin	galactose-specific lectin
GFAP	glial fibrillary acidic protein
GFP	green fluorescent protein
GLT	glutamate transporter
HDAC	histone deacetylase
HDL-C	high-density lipoprotein-cholesterol
HSP	heat shock protein
ICH	intracerebral hemorrhage
IFN	interferon
IGF	insulin-like growth factor
IL	interleukin
iNOS	inducible nitric oxide synthase
LDL	low-density lipoprotein
LPS	lipopolysaccharide
MBP	myelin basic protein
MCAO	middle cerebral artery occlusion
MCP	monocyte chemotactic protein
NCoR	nuclear receptor corepressor
NF	nuclear factor
NGF	nerve growth factor
NMDA	N-methyl-D-aspartic acid
NOX	nicotinamide adenine dinucleotide phosphate oxidase
NPC	neural progenitor cell
NR1C	nuclear receptor 1C

Nrf2	nuclear factor erythroid 2-related factor 2
NSC	neural stem cell
OGD	oxygen-glucose deprivation
OPC	oligodendrocyte precursor cell
PGZ	pioglitazone
PMN	polymorphonuclear neutrophil
PPAR	peroxisome proliferator-activated receptor
PPRE	peroxisome proliferator response element
RGZ	rosiglitazone
ROS	reactive oxygen species
RXR	retinoid X receptor
SAH	subarachnoid hemorrhage
SCI	spinal cord injury
SGZ	subgranular zone
SOD	superoxide dismutase
SVZ	subventricular zone
TAI	traumatic axonal injury
TBI	traumatic brain injury
TGF	transforming growth factor
TGZ	triglitazone
TLR	Toll-like receptor
TNF	tumor necrosis factor
Treg	regulatory T cell
TZD	thiazolidinedione

References

Abraham HM, Wolfson L, Moscufo N, Guttmann CR, Kaplan RF, White WB. Cardiovascular risk factors and small vessel disease of the brain: Blood pressure, white matter lesions, and functional decline in older persons. J Cereb Blood Flow Metab. 2016; 36:132–142. [PubMed: 26036933]

Agostini M, Schoenmakers E, Mitchell C, Szatmari I, Savage D, Smith A, Rajanayagam O, Semple R, Luan J, Bath L, Zalin A, Labib M, Kumar S, Simpson H, Blom D, Marais D, Schwabe J, Barroso I, Trembath R, Wareham N, Nagy L, Gurnell M, O'Rahilly S, Chatterjee K. Non-DNA binding,

dominant-negative, human PPARgamma mutations cause lipodystrophic insulin resistance. Cell Metab. 2006; 4:303–311. [PubMed: 17011503]

Ahmadian M, Suh JM, Hah N, Liddle C, Atkins AR, Downes M, Evans RM. PPARgamma signaling and metabolism: the good, the bad and the future. Nat Med. 2013; 19:557–566. [PubMed: 23652116]

Ait-Oufella H, Taleb S, Mallat Z, Tedgui A. Recent advances on the role of cytokines in atherosclerosis. Arterioscler Thromb Vasc Biol. 2011; 31:969–979. [PubMed: 21508343]

Aktas O, Ullrich O, Infante-Duarte C, Nitsch R, Zipp F. Neuronal damage in brain inflammation. Arch Neurol. 2007; 64:185–189. [PubMed: 17296833]

Allahtavakoli M, Moloudi R, Arababadi MK, Shamsizadeh A, Javanmardi K. Delayed post ischemic treatment with Rosiglitazone attenuates infarct volume, neurological deficits and neutrophilia after embolic stroke in rat. Brain Res. 2009; 1271:121–127. [PubMed: 19332033]

Anderson CL, Shen L, Eicher DM, Wewers MD, Gill JK. Phagocytosis mediated by three distinct Fc gamma receptor classes on human leukocytes. J Exp Med. 1990; 171:1333–1345. [PubMed: 2139103]

Aoun P, Simpkins JW, Agarwal N. Role of PPAR-gamma ligands in neuroprotection against glutamate-induced cytotoxicity in retinal ganglion cells. Invest Ophthalmol Vis Sci. 2003; 44:2999–3004. [PubMed: 12824244]

Appel S, Mirakaj V, Bringmann A, Weck MM, Grunebach F, Brossart P. PPAR-gamma agonists inhibit toll-like receptor-mediated activation of dendritic cells via the MAP kinase and NF-kappaB pathways. Blood. 2005; 106:3888–3894. [PubMed: 16105976]

Arbo BD, Bennetti F, Ribeiro MF. Astrocytes as a target for neuroprotection: Modulation by progesterone and dehydroepiandrosterone. Prog Neurobiol. 2016; 144:27–47. [PubMed: 27048624]

Armstrong RC, Mierzwa AJ, Marion CM, Sullivan GM. White matter involvement after TBI: Clues to axon and myelin repair capacity. Exp Neurol. 2016a; 275(Pt 3):328–333. [PubMed: 25697845]

Armstrong RC, Mierzwa AJ, Sullivan GM, Sanchez MA. Myelin and oligodendrocyte lineage cells in white matter pathology and plasticity after traumatic brain injury. Neuropharmacology. 2016b; 110:654–659. [PubMed: 25963414]

Aronowski J, Zhao X. Molecular pathophysiology of cerebral hemorrhage: secondary brain injury. Stroke. 2011; 42:1781–1786. [PubMed: 21527759]

Arvidsson A, Collin T, Kirik D, Kokaia Z, Lindvall O. Neuronal replacement from endogenous precursors in the adult brain after stroke. Nat Med. 2002; 8:963–970. [PubMed: 12161747]

Asano T. Oxyhemoglobin as the principal cause of cerebral vasospasm: a holistic view of its actions. Crit Rev Neurosurg. 1999; 9:303–318. [PubMed: 10525849]

Aspelund A, Antila S, Proulx ST, Karlsen TV, Karaman S, Detmar M, Wiig H, Alitalo K. A dural lymphatic vascular system that drains brain interstitial fluid and macromolecules. J Exp Med. 2015; 212:991–999. [PubMed: 26077718]

Attwell D, Mishra A, Hall CN, O'Farrell FM, Dalkara T. What is a pericyte? J Cereb Blood Flow Metab. 2016; 36:451–455. [PubMed: 26661200]

Auclair M, Vigouroux C, Boccara F, Capel E, Vigeral C, Guerci B, Lascols O, Capeau J, Caron-Debarle M. Peroxisome proliferator-activated receptor-gamma mutations responsible for lipodystrophy with severe hypertension activate the cellular renin-angiotensin system. Arterioscler Thromb Vasc Biol. 2013; 33:829–838. [PubMed: 23393388]

Azoulay L, Schneider-Lindner V, Dell'aniello S, Filion KB, Suissa S. Thiazolidinediones and the risk of incident strokes in patients with type 2 diabetes: a nested case-control study. Pharmacoepidemiol Drug Saf. 2010; 19:343–350. [PubMed: 19998318]

Bach RG, Brooks MM, Lombardero M, Genuth S, Donner TW, Garber A, Kennedy L, Monrad ES, Pop-Busui R, Kelsey SF, Frye RL, Investigators, B.D. Rosiglitazone and outcomes for patients with diabetes mellitus and coronary artery disease in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial. Circulation. 2013; 128:785–794. [PubMed: 23857320]

Bagshaw SM, George C, Gibney RT, Bellomo R. A multi-center evaluation of early acute kidney injury in critically ill trauma patients. Ren Fail. 2008; 30:581–589. [PubMed: 18661407]

Ballesteros I, Cuartero MI, Pradillo JM, de la Parra J, Perez-Ruiz A, Corbi A, Ricote M, Hamilton JA, Sobrado M, Vivancos J, Nombela F, Lizasoain I, Moro MA. Rosiglitazone-induced CD36 up-regulation resolves inflammation by PPARgamma and 5-LO-dependent pathways. J Leukoc Biol. 2014; 95:587–598. [PubMed: 24338629]

Barnabe-Heider F, Goritz C, Sabelstrom H, Takebayashi H, Pfrieger FW, Meletis K, Frisen J. Origin of new glial cells in intact and injured adult spinal cord. Cell Stem Cell. 2010; 7:470–482. [PubMed: 20887953]

Barroso I, Gurnell M, Crowley VE, Agostini M, Schwabe JW, Soos MA, Maslen GL, Williams TD, Lewis H, Schafer AJ, Chatterjee VK, O'Rahilly S. Dominant negative mutations in human PPARgamma associated with severe insulin resistance, diabetes mellitus and hypertension. Nature. 1999; 402:880–883. [PubMed: 10622252]

Bath PM, Appleton JP, Sprigg N. The Insulin Resistance Intervention after Stroke trial: A perspective on future practice and research. Int J Stroke. 2016; 11:741–743. [PubMed: 27405860]

Bauer S, Hay M, Amilhon B, Jean A, Moyse E. In vivo neurogenesis in the dorsal vagal complex of the adult rat brainstem. Neuroscience. 2005; 130:75–90. [PubMed: 15561426]

Baylis C, Atzpodien EA, Freshour G, Engels K. Peroxisome proliferator-activated receptor [gamma] agonist provides superior renal protection versus angiotensin-converting enzyme inhibition in a rat model of type 2 diabetes with obesity. J Pharmacol Exp Ther. 2003; 307:854–860. [PubMed: 14560039]

Bayly PV, Cohen TS, Leister EP, Ajo D, Leuthardt EC, Genin GM. Deformation of the human brain induced by mild acceleration. J Neurotrauma. 2005; 22:845–856. [PubMed: 16083352]

Benarroch EE. Oligodendrocytes: Susceptibility to injury and involvement in neurologic disease. Neurology. 2009; 72:1779–1785. [PubMed: 19451534]

Berg RM, Moller K, Bailey DM. Neuro-oxidative-nitrosative stress in sepsis. J Cereb Blood Flow Metab. 2011; 31:1532–1544. [PubMed: 21487413]

Berger J, Moller DE. The mechanisms of action of PPARs. Annu Rev Med. 2002; 53:409–435. [PubMed: 11818483]

Bernardo A, Bianchi D, Magnaghi V, Minghetti L. Peroxisome proliferator-activated receptor-gamma agonists promote differentiation and antioxidant defenses of oligodendrocyte progenitor cells. J Neuropathol Exp Neurol. 2009; 68:797–808. [PubMed: 19535992]

Bernardo A, Levi G, Minghetti L. Role of the peroxisome proliferator-activated receptor-gamma (PPAR-gamma) and its natural ligand 15-deoxy-Delta12, 14-prostaglandin J2 in the regulation of microglial functions. Eur J Neurosci. 2000; 12:2215–2223. [PubMed: 10947800]

Bernier PJ, Bedard A, Vinet J, Levesque M, Parent A. Newly generated neurons in the amygdala and adjoining cortex of adult primates. Proc Natl Acad Sci U S A. 2002; 99:11464–11469. [PubMed: 12177450]

Bevers MB, Vaishnav NH, Pham L, Battey TW, Kimberly WT. Hyperglycemia is associated with more severe cytotoxic injury after stroke. J Cereb Blood Flow Metab. 2017; 37:2577–2583. [PubMed: 27671250]

Beyer AM, Baumbach GL, Halabi CM, Modrick ML, Lynch CM, Gerhold TD, Ghoneim SM, de Lange WJ, Keen HL, Tsai YS, Maeda N, Sigmund CD, Faraci FM. Interference with PPARgamma signaling causes cerebral vascular dysfunction, hypertrophy, and remodeling. Hypertension. 2008; 51:867–871. [PubMed: 18285614]

Bhatt DL, Chew DP, Grines C, Mukherjee D, Leesar M, Gilchrist IC, Corbelli JC, Blankenship JC, Eres A, Steinhubl S, Tan WA, Resar JR, AlMahameed A, Abdel-Latif A, Tang WH, Brennan D, McErlean E, Hazen SL, Topol EJ. Peroxisome proliferator-activated receptor gamma agonists for the Prevention of Adverse events following percutaneous coronary Revascularization–results of the PPAR study. Am Heart J. 2007; 154:137–143. [PubMed: 17584566]

Blaiss CA, Yu TS, Zhang G, Chen J, Dimchev G, Parada LF, Powell CM, Kernie SG. Temporally specified genetic ablation of neurogenesis impairs cognitive recovery after traumatic brain injury. J Neurosci. 2011; 31:4906–4916. [PubMed: 21451029]

Blakemore WF. Pattern of remyelination in the CNS. Nature. 1974; 249:577–578. [PubMed: 4834082]

Blanco M, Moro MA, Davalos A, Leira R, Castellanos M, Serena J, Vivancos J, Rodriguez-Yanez M, Lizasoain I, Castillo J. Increased plasma levels of 15-deoxyDelta prostaglandin J2 are associated

with good outcome in acute atherothrombotic ischemic stroke. Stroke. 2005; 36:1189–1194. [PubMed: 15879329]

Boekhoff TM, Ensinger EM, Carlson R, Bock P, Baumgartner W, Rohn K, Tipold A, Stein VM. Microglial contribution to secondary injury evaluated in a large animal model of human spinal cord trauma. J Neurotrauma. 2012; 29:1000–1011. [PubMed: 21599492]

Borhani NO. Changes and Geographic Distribution of Mortality from Cerebrovascular Disease. Am J Public Health Nations Health. 1965; 55:673–681. [PubMed: 14287837]

Braissant O, Wahli W. Differential expression of peroxisome proliferator-activated receptor-alpha, -beta, and -gamma during rat embryonic development. Endocrinology. 1998; 139:2748–2754. [PubMed: 9607781]

Bruemmer D, Berger JP, Liu J, Kintscher U, Wakino S, Fleck E, Moller DE, Law RE. A non-thiazolidinedione partial peroxisome proliferator-activated receptor gamma ligand inhibits vascular smooth muscle cell growth. Eur J Pharmacol. 2003a; 466:225–234. [PubMed: 12694805]

Bruemmer D, Yin F, Liu J, Berger JP, Sakai T, Blaschke F, Fleck E, Van Herle AJ, Forman BM, Law RE. Regulation of the growth arrest and DNA damage-inducible gene 45 (GADD45) by peroxisome proliferator-activated receptor gamma in vascular smooth muscle cells. Circ Res. 2003b; 93:e38–47. [PubMed: 12881480]

Butt AM. Neurotransmitter-mediated calcium signalling in oligodendrocyte physiology and pathology. Glia. 2006; 54:666–675. [PubMed: 17006895]

Canton J, Neculai D, Grinstein S. Scavenger receptors in homeostasis and immunity. Nat Rev Immunol. 2013; 13:621–634. [PubMed: 23928573]

Carroll WM, Jennings AR, Ironside LJ. Identification of the adult resting progenitor cell by autoradiographic tracking of oligodendrocyte precursors in experimental CNS demyelination. Brain. 1998; 121(Pt 2):293–302. [PubMed: 9549507]

Carson MJ, Doose JM, Melchior B, Schmid CD, Ploix CC. CNS immune privilege: hiding in plain sight. Immunol Rev. 2006; 213:48–65. [PubMed: 16972896]

Chaitanya GV, Eeka P, Munker R, Alexander JS, Babu PP. Role of cytotoxic protease granzyme-b in neuronal degeneration during human stroke. Brain Pathol. 2011; 21:16–30. [PubMed: 20825413]

Chang CZ, Wu SC, Kwan AL. Glycyrrhizin Attenuates Proinflammatory Cytokines through a Peroxisome Proliferator-Activated Receptor-gamma-Dependent Mechanism and Experimental Vasospasm in a Rat Model. J Vasc Res. 2015a; 52:12–21. [PubMed: 25896311]

Chang KL, Pee HN, Yang S, Ho PC. Influence of drug transporters and stereoselectivity on the brain penetration of pioglitazone as a potential medicine against Alzheimer's disease. Sci Rep. 2015b; 5:9000. [PubMed: 25760794]

Charbonnel B, Dormandy J, Erdmann E, Massi-Benedetti M, Skene A, Group, P.R.S. The prospective pioglitazone clinical trial in macrovascular events (PROactive): can pioglitazone reduce cardiovascular events in diabetes? Study design and baseline characteristics of 5238 patients. Diabetes Care. 2004; 27:1647–1653. [PubMed: 15220241]

Chen H, Shi R, Luo B, Yang X, Qiu L, Xiong J, Jiang M, Liu Y, Zhang Z, Wu Y. Macrophage peroxisome proliferator-activated receptor gamma deficiency delays skin wound healing through impairing apoptotic cell clearance in mice. Cell Death Dis. 2015; 6:e1597. [PubMed: 25590807]

Chen Q, Shi X, Tan Q, Feng Z, Wang Y, Yuan Q, Tao Y, Zhang J, Tan L, Zhu G, Feng H, Chen Z. Simvastatin Promotes Hematoma Absorption and Reduces Hydrocephalus Following Intraventricular Hemorrhage in Part by Upregulating CD36. Transl Stroke Res. 2017

Chen S, Feng H, Sherchan P, Klebe D, Zhao G, Sun X, Zhang J, Tang J, Zhang JH. Controversies and evolving new mechanisms in subarachnoid hemorrhage. Prog Neurobiol. 2014; 115:64–91. [PubMed: 24076160]

Chen YC, Wu JS, Tsai HD, Huang CY, Chen JJ, Sun GY, Lin TN. Peroxisome proliferator-activated receptor gamma (PPAR-gamma) and neurodegenerative disorders. Mol Neurobiol. 2012; 46:114–124. [PubMed: 22434581]

Chen Z, Ishibashi S, Perrey S, Osuga J, Gotoda T, Kitamine T, Tamura Y, Okazaki H, Yahagi N, Iizuka Y, Shionoiri F, Ohashi K, Harada K, Shimano H, Nagai R, Yamada N. Troglitazone inhibits atherosclerosis in apolipoprotein E-knockout mice: pleiotropic effects on CD36 expression and HDL. Arterioscler Thromb Vasc Biol. 2001; 21:372–377. [PubMed: 11231916]

Chinetti G, Lestavel S, Bocher V, Remaley AT, Neve B, Torra IP, Teissier E, Minnich A, Jaye M, Duverger N, Brewer HB, Fruchart JC, Clavey V, Staels B. PPAR-alpha and PPAR-gamma activators induce cholesterol removal from human macrophage foam cells through stimulation of the ABCA1 pathway. Nat Med. 2001; 7:53–58. [PubMed: 11135616]

Ching J, Amiridis S, Stylli SS, Bjorksten AR, Kountouri N, Zheng T, Paradiso L, Luwor RB, Morokoff AP, O'Brien TJ, Kaye AH. The peroxisome proliferator activated receptor gamma agonist pioglitazone increases functional expression of the glutamate transporter excitatory amino acid transporter 2 (EAAT2) in human glioblastoma cells. Oncotarget. 2015; 6:21301–21314. [PubMed: 26046374]

Chistiakov DA, Bobryshev YV, Orekhov AN. Macrophage-mediated cholesterol handling in atherosclerosis. J Cell Mol Med. 2016; 20:17–28. [PubMed: 26493158]

Cho HY, Gladwell W, Wang X, Chorley B, Bell D, Reddy SP, Kleeberger SR. Nrf2-regulated PPAR{gamma} expression is critical to protection against acute lung injury in mice. Am J Respir Crit Care Med. 2010; 182:170–182. [PubMed: 20224069]

Choi JH, Banks AS, Estall JL, Kajimura S, Bostrom P, Laznik D, Ruas JL, Chalmers MJ, Kamenecka TM, Bluher M, Griffin PR, Spiegelman BM. Anti-diabetic drugs inhibit obesity-linked phosphorylation of PPARgamma by Cdk5. Nature. 2010; 466:451–456. [PubMed: 20651683]

Choi JH, Banks AS, Kamenecka TM, Busby SA, Chalmers MJ, Kumar N, Kuruvilla DS, Shin Y, He Y, Bruning JB, Marciano DP, Cameron MD, Laznik D, Jurczak MJ, Schurer SC, Vidovic D, Shulman GI, Spiegelman BM, Griffin PR. Antidiabetic actions of a non-agonist PPARgamma ligand blocking Cdk5-mediated phosphorylation. Nature. 2011; 477:477–481. [PubMed: 21892191]

Choi YS, Cho HY, Hoyt KR, Naegele JR, Obrietan K. IGF-1 receptor-mediated ERK/MAPK signaling couples status epilepticus to progenitor cell proliferation in the subgranular layer of the dentate gyrus. Glia. 2008; 56:791–800. [PubMed: 18338791]

Chu K, Lee ST, Koo JS, Jung KH, Kim EH, Sinn DI, Kim JM, Ko SY, Kim SJ, Song EC, Kim M, Roh JK. Peroxisome proliferator-activated receptor-gamma-agonist, rosiglitazone, promotes angiogenesis after focal cerebral ischemia. Brain Res. 2006; 1093:208–218. [PubMed: 16696956]

Chung BH, Li C, Sun BK, Lim SW, Ahn KO, Yang JH, Choi YH, Yoon KH, Sugawara A, Ito S, Kim J, Yang CW. Rosiglitazone protects against cyclosporine-induced pancreatic and renal injury in rats. Am J Transplant. 2005; 5:1856–1867. [PubMed: 15996232]

Cipolletta D, Feuerer M, Li A, Kamei N, Lee J, Shoelson SE, Benoist C, Mathis D. PPAR-gamma is a major driver of the accumulation and phenotype of adipose tissue Treg cells. Nature. 2012; 486:549–553. [PubMed: 22722857]

Clark RB, Bishop-Bailey D, Estrada-Hernandez T, Hla T, Puddington L, Padula SJ. The nuclear receptor PPAR gamma and immunoregulation: PPAR gamma mediates inhibition of helper T cell responses. J Immunol. 2000; 164:1364–1371. [PubMed: 10640751]

Clark RK, Lee EV, Fish CJ, White RF, Price WJ, Jonak ZL, Feuerstein GZ, Barone FC. Development of tissue damage, inflammation and resolution following stroke: an immunohistochemical and quantitative planimetric study. Brain Res Bull. 1993; 31:565–572. [PubMed: 8495380]

Clark RS, Schiding JK, Kaczorowski SL, Marion DW, Kochanek PM. Neutrophil accumulation after traumatic brain injury in rats: comparison of weight drop and controlled cortical impact models. J Neurotrauma. 1994; 11:499–506. [PubMed: 7861443]

Clarkson BD, Heninger E, Harris MG, Lee J, Sandor M, Fabry Z. Innate-adaptive crosstalk: how dendritic cells shape immune responses in the CNS. Adv Exp Med Biol. 2012; 946:309–333. [PubMed: 21948376]

Clarner T, Diederichs F, Berger K, Denecke B, Gan L, van der Valk P, Beyer C, Amor S, Kipp M. Myelin debris regulates inflammatory responses in an experimental demyelination animal model and multiple sclerosis lesions. Glia. 2012; 60:1468–1480. [PubMed: 22689449]

Clelland CD, Choi M, Romberg C, Clemenson GD Jr, Fragniere A, Tyers P, Jessberger S, Saksida LM, Barker RA, Gage FH, Bussey TJ. A functional role for adult hippocampal neurogenesis in spatial pattern separation. Science. 2009; 325:210–213. [PubMed: 19590004]

Collino M, Aragno M, Mastrocola R, Gallicchio M, Rosa AC, Dianzani C, Danni O, Thiemermann C, Fantozzi R. Modulation of the oxidative stress and inflammatory response by PPAR-gamma

agonists in the hippocampus of rats exposed to cerebral ischemia/reperfusion. Eur J Pharmacol. 2006; 530:70–80. [PubMed: 16386242]

Compe E, Drane P, Laurent C, Diderich K, Braun C, Hoeijmakers JH, Egly JM. Dysregulation of the peroxisome proliferator-activated receptor target genes by XPD mutations. Mol Cell Biol. 2005; 25:6065–6076. [PubMed: 15988019]

Conti AC, Raghupathi R, Trojanowski JQ, McIntosh TK. Experimental brain injury induces regionally distinct apoptosis during the acute and delayed post-traumatic period. J Neurosci. 1998; 18:5663–5672. [PubMed: 9671657]

Cuartero MI, Ballesteros I, Moraga A, Nombela F, Vivancos J, Hamilton JA, Corbi AL, Lizasoain I, Moro MA. N2 neutrophils, novel players in brain inflammation after stroke: modulation by the PPARgamma agonist rosiglitazone. Stroke. 2013; 44:3498–3508. [PubMed: 24135932]

Cullingford TE, Bhakoo K, Peuchen S, Dolphin CT, Patel R, Clark JB. Distribution of mRNAs encoding the peroxisome proliferator-activated receptor alpha, beta, and gamma and the retinoid X receptor alpha, beta, and gamma in rat central nervous system. J Neurochem. 1998; 70:1366–1375. [PubMed: 9523552]

Culman J, Zhao Y, Gohlke P, Herdegen T. PPAR-gamma: therapeutic target for ischemic stroke. Trends Pharmacol Sci. 2007; 28:244–249. [PubMed: 17416424]

Cunard R, Eto Y, Muljadi JT, Glass CK, Kelly CJ, Ricote M. Repression of IFN-gamma expression by peroxisome proliferator-activated receptor gamma. J Immunol. 2004; 172:7530–7536. [PubMed: 15187132]

Curb JD, Abbott RD, Rodriguez BL, Masaki KH, Chen R, Popper JS, Petrovitch H, Ross GW, Schatz IJ, Belleau GC, Yano K. High density lipoprotein cholesterol and the risk of stroke in elderly men: the Honolulu heart program. Am J Epidemiol. 2004; 160:150–157. [PubMed: 15234936]

da Rocha Junior LF, Dantas AT, Duarte AL, de Melo Rego MJ, Pitta Ida R, Pitta MG. PPARgamma Agonists in Adaptive Immunity: What Do Immune Disorders and Their Models Have to Tell Us? PPAR Res. 2013; 2013:519724. [PubMed: 23983678]

Dawson MR, Polito A, Levine JM, Reynolds R. NG2-expressing glial progenitor cells: an abundant and widespread population of cycling cells in the adult rat CNS. Mol Cell Neurosci. 2003; 24:476–488. [PubMed: 14572468]

Dayer AG, Cleaver KM, Abouantoun T, Cameron HA. New GABAergic interneurons in the adult neocortex and striatum are generated from different precursors. J Cell Biol. 2005; 168:415–427. [PubMed: 15684031]

De Nuccio C, Bernardo A, De Simone R, Mancuso E, Magnaghi V, Visentin S, Minghetti L. Peroxisome proliferator-activated receptor gamma agonists accelerate oligodendrocyte maturation and influence mitochondrial functions and oscillatory Ca(2+) waves. J Neuropathol Exp Neurol. 2011; 70:900–912. [PubMed: 21937914]

de Wit NM, Vanmol J, Kamermans A, Hendriks J, de Vries HE. Inflammation at the blood-brain barrier: The role of liver X receptors. Neurobiol Dis. 2017

Dekkers JF, van der Ent CK, Kalkhoven E, Beekman JM. PPARgamma as a therapeutic target in cystic fibrosis. Trends Mol Med. 2012; 18:283–291. [PubMed: 22494945]

Delerive P, Furman C, Teissier E, Fruchart J, Duriez P, Staels B. Oxidized phospholipids activate PPARalpha in a phospholipase A2-dependent manner. FEBS Lett. 2000; 471:34–38. [PubMed: 10760508]

Dello Russo C, Gavrilyuk V, Weinberg G, Almeida A, Bolanos JP, Palmer J, Pelligrino D, Galea E, Feinstein DL. Peroxisome proliferator-activated receptor gamma thiazolidinedione agonists increase glucose metabolism in astrocytes. J Biol Chem. 2003; 278:5828–5836. [PubMed: 12486128]

Desmond DW. Cognition and white matter lesions. Cerebrovasc Dis. 2002; 13(Suppl 2):53–57. [PubMed: 11901244]

Dhawan, V. Studies on Respiratory DisordersSpringer; 2014Reactive Oxygen and Nitrogen Species: General Considerations; 27-47

Di Sanzo M, Fineschi V, Borro M, La Russa R, Santurro A, Scopetti M, Simmaco M, Frati P. Clinical applications of Personalized Medicine: a new paradigm and challenge. Curr Pharm Biotechnol. 2017

Dirnagl U, Iadecola C, Moskowitz MA. Pathobiology of ischaemic stroke: an integrated view. Trends Neurosci. 1999; 22:391–397. [PubMed: 10441299]

Doetsch F, Garcia-Verdugo JM, Alvarez-Buylla A. Cellular composition and three-dimensional organization of the subventricular germinal zone in the adult mammalian brain. J Neurosci. 1997; 17:5046–5061. [PubMed: 9185542]

Donnan GA, Fisher M, Macleod M, Davis SM. Stroke. Lancet. 2008; 371:1612–1623. [PubMed: 18468545]

Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, Skene AM, Tan MH, Lefebvre PJ, Murray GD, Standl E, Wilcox RG, Wilhelmsen L, Betteridge J, Birkeland K, Golay A, Heine RJ, Koranyi L, Laakso M, Mokan M, Norkus A, Pirags V, Podar T, Scheen A, Scherbaum W, Schernthaner G, Schmitz O, Skrha J, Smith U, Taton J, Investigators, P.R. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet. 2005; 366:1279–1289. [PubMed: 16214598]

Duan H, Song W, Zhao W, Gao Y, Yang Z, Li X. Endogenous neurogenesis in adult mammals after spinal cord injury. Sci China Life Sci. 2016; 59:1313–1318. [PubMed: 27796638]

Duan SZ, Usher MG, Mortensen RM. Peroxisome proliferator-activated receptor-gamma-mediated effects in the vasculature. Circ Res. 2008; 102:283–294. [PubMed: 18276926]

Duarte JV, Pereira JM, Quendera B, Raimundo M, Moreno C, Gomes L, Carrilho F, Castelo-Branco M. Early disrupted neurovascular coupling and changed event level hemodynamic response function in type 2 diabetes: an fMRI study. J Cereb Blood Flow Metab. 2015; 35:1671–1680. [PubMed: 26058698]

Dustin ML. Complement Receptors in Myeloid Cell Adhesion and Phagocytosis. Microbiol Spectr. 2016; 4

Duvanel CB, Honegger P, Pershadsingh H, Feinstein D, Matthieu JM. Inhibition of glial cell proinflammatory activities by peroxisome proliferator-activated receptor gamma agonist confers partial protection during antimyelin oligodendrocyte glycoprotein demyelination in vitro. J Neurosci Res. 2003; 71:246–255. [PubMed: 12503087]

Elbrecht A, Chen Y, Cullinan CA, Hayes N, Leibowitz M, Moller DE, Berger J. Molecular cloning, expression and characterization of human peroxisome proliferator activated receptors gamma 1 and gamma 2. Biochem Biophys Res Commun. 1996; 224:431–437. [PubMed: 8702406]

Elder CP, Apple DF, Bickel CS, Meyer RA, Dudley GA. Intramuscular fat and glucose tolerance after spinal cord injury–a cross-sectional study. Spinal Cord. 2004; 42:711–716. [PubMed: 15303112]

Elmelund M, Klarskov N, Bagi P, Oturai PS, Biering-Sorensen F. Renal deterioration after spinal cord injury is associated with length of detrusor contractions during cystometry-A study with a median of 41 years follow-up. Neurourol Urodyn. 2017

Elting JW, de Jager AE, Teelken AW, Schaaf MJ, Maurits NM, van der Naalt J, Sibinga CT, Sulter GA, De Keyser J. Comparison of serum S-100 protein levels following stroke and traumatic brain injury. J Neurol Sci. 2000; 181:104–110. [PubMed: 11099719]

Erdmann E, Harding S, Lam H, Perez A. Ten-year observational follow-up of PROactive: a randomized cardiovascular outcomes trial evaluating pioglitazone in type 2 diabetes. Diabetes Obes Metab. 2016; 18:266–273. [PubMed: 26592506]

Erdmann E, Song E, Spanheimer R, van Troostenburg de Bruyn AR, Perez A. Observational follow-up of the PROactive study: a 6-year update. Diabetes Obes Metab. 2014; 16:63–74. [PubMed: 23859428]

Erdmann E, Spanheimer R, Charbonnel B, Investigators, P.R.S. Pioglitazone and the risk of cardiovascular events in patients with Type 2 diabetes receiving concomitant treatment with nitrates, renin-angiotensin system blockers, or insulin: results from the PROactive study (PROactive 20). J Diabetes. 2010; 2:212–220. [PubMed: 20923486]

Ericsson H, Hamren B, Bergstrand S, Elebring M, Fryklund L, Heijer M, Ohman KP. Pharmacokinetics and metabolism of tesaglitazar, a novel dual-acting peroxisome proliferator-activated receptor alpha/gamma agonist, after a single oral and intravenous dose in humans. Drug Metab Dispos. 2004; 32:923–929. [PubMed: 15319332]

Eriksson PS, Perfilieva E, Bjork-Eriksson T, Alborn AM, Nordborg C, Peterson DA, Gage FH. Neurogenesis in the adult human hippocampus. Nat Med. 1998; 4:1313–1317. [PubMed: 9809557]

Ezekowitz RA, Sastry K, Bailly P, Warner A. Molecular characterization of the human macrophage mannose receptor: demonstration of multiple carbohydrate recognition-like domains and phagocytosis of yeasts in Cos-1 cells. J Exp Med. 1990; 172:1785–1794. [PubMed: 2258707]

Fadok VA, Warner ML, Bratton DL, Henson PM. CD36 is required for phagocytosis of apoptotic cells by human macrophages that use either a phosphatidylserine receptor or the vitronectin receptor (alpha v beta 3). J Immunol. 1998; 161:6250–6257. [PubMed: 9834113]

Fajas L, Auboeuf D, Raspe E, Schoonjans K, Lefebvre AM, Saladin R, Najib J, Laville M, Fruchart JC, Deeb S, Vidal-Puig A, Flier J, Briggs MR, Staels B, Vidal H, Auwerx J. The organization, promoter analysis, and expression of the human PPARgamma gene. J Biol Chem. 1997; 272:18779–18789. [PubMed: 9228052]

Fancy SP, Zhao C, Franklin RJ. Increased expression of Nkx2.2 and Olig2 identifies reactive oligodendrocyte progenitor cells responding to demyelination in the adult CNS. Mol Cell Neurosci. 2004; 27:247–254. [PubMed: 15519240]

Fang H, Chen J, Lin S, Wang P, Wang Y, Xiong X, Yang Q. CD36-mediated hematoma absorption following intracerebral hemorrhage: negative regulation by TLR4 signaling. J Immunol. 2014; 192:5984–5992. [PubMed: 24808360]

Faveeuw C, Fougeray S, Angeli V, Fontaine J, Chinetti G, Gosset P, Delerive P, Maliszewski C, Capron M, Staels B, Moser M, Trottein F. Peroxisome proliferator-activated receptor gamma activators inhibit interleukin-12 production in murine dendritic cells. FEBS Lett. 2000; 486:261–266. [PubMed: 11119715]

FDA. FDA Drug Safety Communication: FDA requires removal of some prescribing and dispensing restrictions for rosiglitazone-containing diabetes medicines. 2013

FDA. FDA Drug Safety Communication: FDA eliminates the Risk Evaluation and Mitigation Strategy (REMS) for rosiglitazone-containing diabetes medicines. 2015

Feddersen RM, Van Ness BG. Single copy gene detection requiring minimal cell numbers. Biotechniques. 1989; 7:44–49. [PubMed: 2629832]

Feinstein DL, Galea E, Gavrilyuk V, Brosnan CF, Whitacre CC, Dumitrescu-Ozimek L, Landreth GE, Pershadsingh HA, Weinberg G, Heneka MT. Peroxisome proliferator-activated receptor-gamma agonists prevent experimental autoimmune encephalomyelitis. Ann Neurol. 2002; 51:694–702. [PubMed: 12112074]

Ferguson LB, Most D, Blednov YA, Harris RA. PPAR agonists regulate brain gene expression: relationship to their effects on ethanol consumption. Neuropharmacology. 2014; 86:397–407. [PubMed: 25036611]

Finch ER, Tukaramrao DB, Goodfield LL, Quickel MD, Paulson RF, Prabhu KS. Activation of PPARgamma by endogenous prostaglandin J2 mediates the antileukemic effect of selenium in murine leukemia. Blood. 2017; 129:1802–1810. [PubMed: 28115365]

Floyd ZE, Wang ZQ, Kilroy G, Cefalu WT. Modulation of peroxisome proliferator-activated receptor gamma stability and transcriptional activity in adipocytes by resveratrol. Metabolism. 2008; 57:S32–38.

Flygt J, Djupsjo A, Lenne F, Marklund N. Myelin loss and oligodendrocyte pathology in white matter tracts following traumatic brain injury in the rat. Eur J Neurosci. 2013; 38:2153–2165. [PubMed: 23458840]

Forman BM, Tontonoz P, Chen J, Brun RP, Spiegelman BM, Evans RM. 15-Deoxy-delta 12, 14-prostaglandin J2 is a ligand for the adipocyte determination factor PPAR gamma. Cell. 1995; 83:803–812. [PubMed: 8521497]

Frankel HL, Coll JR, Charlifue SW, Whiteneck GG, Gardner BP, Jamous MA, Krishnan KR, Nuseibeh I, Savic G, Sett P. Long-term survival in spinal cord injury: a fifty year investigation. Spinal Cord. 1998; 36:266–274. [PubMed: 9589527]

Franklin RJ, Ffrench-Constant C. Remyelination in the CNS: from biology to therapy. Nat Rev Neurosci. 2008; 9:839–855. [PubMed: 18931697]

Freeman SA, Grinstein S. Phagocytosis: receptors, signal integration, and the cytoskeleton. Immunol Rev. 2014; 262:193–215. [PubMed: 25319336]

Funfschilling U, Supplie LM, Mahad D, Boretius S, Saab AS, Edgar J, Brinkmann BG, Kassmann CM, Tzvetanova ID, Mobius W, Diaz F, Meijer D, Suter U, Hamprecht B, Sereda MW, Moraes CT, Frahm J, Goebbels S, Nave KA. Glycolytic oligodendrocytes maintain myelin and long-term axonal integrity. Nature. 2012; 485:517–521. [PubMed: 22622581]

Gaetani P, Marzatico F, Rodriguez y Baena R, Pacchiarini L, Vigano T, Grignani G, Crivellari MT, Benzi G. Arachidonic acid metabolism and pathophysiologic aspects of subarachnoid hemorrhage in rats. Stroke. 1990; 21:328–332. [PubMed: 2106176]

Galeffi F, Degan S, Britz G, Turner DA. Dysregulation of oxygen hemodynamic responses to synaptic train stimulation in a rat hippocampal model of subarachnoid hemorrhage. J Cereb Blood Flow Metab. 2016; 36:696–701. [PubMed: 26721394]

Gan Y, Liu Q, Wu W, Yin JX, Bai XF, Shen R, Wang Y, Chen J, La Cava A, Poursine-Laurent J, Yokoyama W, Shi FD. Ischemic neurons recruit natural killer cells that accelerate brain infarction. Proc Natl Acad Sci U S A. 2014; 111:2704–2709. [PubMed: 24550298]

Garcia-Bueno B, Caso JR, Perez-Nievas BG, Lorenzo P, Leza JC. Effects of peroxisome proliferator-activated receptor gamma agonists on brain glucose and glutamate transporters after stress in rats. Neuropsychopharmacology. 2007; 32:1251–1260. [PubMed: 17119541]

Gelderblom M, Leypoldt F, Steinbach K, Behrens D, Choe CU, Siler DA, Arumugam TV, Orthey E, Gerloff C, Tolosa E, Magnus T. Temporal and spatial dynamics of cerebral immune cell accumulation in stroke. Stroke. 2009; 40:1849–1857. [PubMed: 19265055]

Gennarelli TA. Mechanisms of brain injury. J Emerg Med. 1993; 11(Suppl 1):5–11. [PubMed: 8445204]

Genovese T, Esposito E, Mazzon E, Di Paola R, Muia C, Meli R, Bramanti P, Cuzzocrea S. Effect of cyclopentanone prostaglandin 15-deoxy-delta12, 14PGJ2 on early functional recovery from experimental spinal cord injury. Shock. 2008; 30:142–152. [PubMed: 18628687]

Gensert JM, Goldman JE. Endogenous progenitors remyelinate demyelinated axons in the adult CNS. Neuron. 1997; 19:197–203. [PubMed: 9247275]

Ghajar J. Traumatic brain injury. Lancet. 2000; 356:923–929. [PubMed: 11036909]

Ghirnikar RS, Lee YL, Eng LF. Inflammation in traumatic brain injury: role of cytokines and chemokines. Neurochem Res. 1998; 23:329–340. [PubMed: 9482245]

Gillespie W, Tyagi N, Tyagi SC. Role of PPARgamma, a nuclear hormone receptor in neuroprotection. Indian J Biochem Biophys. 2011; 48:73–81. [PubMed: 21682137]

Girnun GD, Domann FE, Moore SA, Robbins ME. Identification of a functional peroxisome proliferator-activated receptor response element in the rat catalase promoter. Mol Endocrinol. 2002; 16:2793–2801. [PubMed: 12456800]

Glass CK, Ogawa S. Combinatorial roles of nuclear receptors in inflammation and immunity. Nat Rev Immunol. 2006; 6:44–55. [PubMed: 16493426]

Gold M, Alderton C, Zvartau-Hind M, Egginton S, Saunders AM, Irizarry M, Craft S, Landreth G, Linnamagi U, Sawchak S. Rosiglitazone monotherapy in mild-to-moderate Alzheimer's disease: results from a randomized, double-blind, placebo-controlled phase III study. Dement Geriatr Cogn Disord. 2010; 30:131–146. [PubMed: 20733306]

Gong C, Hoff JT, Keep RF. Acute inflammatory reaction following experimental intracerebral hemorrhage in rat. Brain Res. 2000; 871:57–65. [PubMed: 10882783]

Gosset P, Charbonnier AS, Delerive P, Fontaine J, Staels B, Pestel J, Tonnel AB, Trottein F. Peroxisome proliferator-activated receptor gamma activators affect the maturation of human monocyte-derived dendritic cells. Eur J Immunol. 2001; 31:2857–2865. [PubMed: 11592060]

Gough PJ, Gomez IG, Wille PT, Raines EW. Macrophage expression of active MMP-9 induces acute plaque disruption in apoE-deficient mice. J Clin Invest. 2006; 116:59–69. [PubMed: 16374516]

Goverman J. Autoimmune T cell responses in the central nervous system. Nat Rev Immunol. 2009; 9:393–407. [PubMed: 19444307]

Graham DJ, Ouellet-Hellstrom R, MaCurdy TE, Ali F, Sholley C, Worrall C, Kelman JA. Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. JAMA. 2010; 304:411–418. [PubMed: 20584880]

Grau AJ, Urbanek C, Palm F. Common infections and the risk of stroke. Nat Rev Neurol. 2010; 6:681–694. [PubMed: 21060340]

Greene ME, Blumberg B, McBride OW, Yi HF, Kronquist K, Kwan K, Hsieh L, Greene G, Nimer SD. Isolation of the human peroxisome proliferator activated receptor gamma cDNA: expression in hematopoietic cells and chromosomal mapping. Gene Expr. 1995; 4:281–299. [PubMed: 7787419]

Greenhalgh AD, David S. Differences in the phagocytic response of microglia and peripheral macrophages after spinal cord injury and its effects on cell death. J Neurosci. 2014; 34:6316–6322. [PubMed: 24790202]

Griggs RB, Donahue RR, Morgenweck J, Grace PM, Sutton A, Watkins LR, Taylor BK. Pioglitazone rapidly reduces neuropathic pain through astrocyte and nongenomic PPARgamma mechanisms. Pain. 2015; 156:469–482. [PubMed: 25599238]

Grommes C, Karlo JC, Caprariello A, Blankenship D, Dechant A, Landreth GE. The PPARgamma agonist pioglitazone crosses the blood-brain barrier and reduces tumor growth in a human xenograft model. Cancer Chemother Pharmacol. 2013; 71:929–936. [PubMed: 23358645]

Groves AK, Barnett SC, Franklin RJ, Crang AJ, Mayer M, Blakemore WF, Noble M. Repair of demyelinated lesions by transplantation of purified O-2A progenitor cells. Nature. 1993; 362:453–455. [PubMed: 8464477]

Grygiel-Gorniak B. Peroxisome proliferator-activated receptors and their ligands: nutritional and clinical implications–a review. Nutr J. 2014; 13:17. [PubMed: 24524207]

Guan LM, Zhao J, Scandalios JG. Cis-elements and trans-factors that regulate expression of the maize Cat1 antioxidant gene in response to ABA and osmotic stress: H2O2 is the likely intermediary signaling molecule for the response. Plant J. 2000; 22:87–95. [PubMed: 10792824]

Guan Y, Zhang Y, Davis L, Breyer MD. Expression of peroxisome proliferator-activated receptors in urinary tract of rabbits and humans. Am J Physiol. 1997; 273:F1013–1022. [PubMed: 9435691]

Habib ZA, Tzogias L, Havstad SL, Wells K, Divine G, Lanfear DE, Tang J, Krajenta R, Pladevall M, Williams LK. Relationship between thiazolidinedione use and cardiovascular outcomes and all-cause mortality among patients with diabetes: a time-updated propensity analysis. Pharmacoepidemiol Drug Saf. 2009; 18:437–447. [PubMed: 19235778]

Hacke W, Schwab S, Horn M, Spranger M, De Georgia M, von Kummer R. 'Malignant' middle cerebral artery territory infarction: clinical course and prognostic signs. Arch Neurol. 1996; 53:309–315. [PubMed: 8929152]

Halabi CM, Beyer AM, de Lange WJ, Keen HL, Baumbach GL, Faraci FM, Sigmund CD. Interference with PPAR gamma function in smooth muscle causes vascular dysfunction and hypertension. Cell Metab. 2008; 7:215–226. [PubMed: 18316027]

Hamblin M, Chang L, Fan Y, Zhang J, Chen YE. PPARs and the cardiovascular system. Antioxid Redox Signal. 2009; 11:1415–1452. [PubMed: 19061437]

Hamming AM, Wermer MJ, Umesh Rudrapatna S, Lanier C, van Os HJ, van den Bergh WM, Ferrari MD, van der Toorn A, van den Maagdenberg AM, Stowe AM, Dijkhuizen RM. Spreading depolarizations increase delayed brain injury in a rat model of subarachnoid hemorrhage. J Cereb Blood Flow Metab. 2016; 36:1224–1231. [PubMed: 26661246]

Han L, Cai W, Mao L, Liu J, Li P, Leak RK, Xu Y, Hu X, Chen J. Rosiglitazone Promotes White Matter Integrity and Long-Term Functional Recovery After Focal Cerebral Ischemia. Stroke. 2015; 46:2628–2636. [PubMed: 26243225]

Harrison BM, Gledhill RF, McDonald WJ. Remyelination after transient compression of the spinal cord. Proc Aust Assoc Neurol. 1975; 12:117–122. [PubMed: 1215377]

Hawkins CP, Mackenzie F, Tofts P, du Boulay EP, McDonald WI. Patterns of blood-brain barrier breakdown in inflammatory demyelination. Brain. 1991; 114(Pt 2):801–810. [PubMed: 2043950]

He F, Doucet JA, Stephens JM. Caspase-mediated degradation of PPARgamma proteins in adipocytes. Obesity (Silver Spring). 2008; 16:1735–1741. [PubMed: 18497737]

Heinaniemi M, Uski JO, Degenhardt T, Carlberg C. Meta-analysis of primary target genes of peroxisome proliferator- activated receptors. Genome Biol. 2007; 8:R147. [PubMed: 17650321]

Heneka MT, Feinstein DL, Galea E, Gleichmann M, Wullner U, Klockgether T. Peroxisome proliferator-activated receptor gamma agonists protect cerebellar granule cells from cytokine-

induced apoptotic cell death by inhibition of inducible nitric oxide synthase. J Neuroimmunol. 1999; 100:156–168. [PubMed: 10695726]

Henson PM, Hume DA. Apoptotic cell removal in development and tissue homeostasis. Trends Immunol. 2006; 27:244–250. [PubMed: 16584921]

Heppner FL, Ransohoff RM, Becher B. Immune attack: the role of inflammation in Alzheimer disease. Nat Rev Neurosci. 2015; 16:358–372. [PubMed: 25991443]

Hesp ZC, Goldstein EZ, Miranda CJ, Kaspar BK, McTigue DM. Chronic oligodendrogenesis and remyelination after spinal cord injury in mice and rats. J Neurosci. 2015; 35:1274–1290. [PubMed: 25609641]

Hickenbottom SL, Grotta JC, Strong R, Denner LA, Aronowski J. Nuclear factor-kappaB and cell death after experimental intracerebral hemorrhage in rats. Stroke. 1999; 30:2472–2477. discussion 2477-2478. [PubMed: 10548686]

Hills NK, Johnston SC, Sidney S, Zielinski BA, Fullerton HJ. Recent trauma and acute infection as risk factors for childhood arterial ischemic stroke. Ann Neurol. 2012; 72:850–858. [PubMed: 23280836]

Hills NK, Sidney S, Fullerton HJ. Timing and number of minor infections as risk factors for childhood arterial ischemic stroke. Neurology. 2014; 83:890–897. [PubMed: 25142897]

Hind WH, Tufarelli C, Neophytou M, Anderson SI, England TJ, O'Sullivan SE. Endocannabinoids modulate human blood-brain barrier permeability in vitro. Br J Pharmacol. 2015; 172:3015–3027. [PubMed: 25651941]

Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, Jones NP, Komajda M, McMurray JJ, Team, R.S. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet. 2009; 373:2125–2135. [PubMed: 19501900]

Hovelmeyer N, Hao Z, Kranidioti K, Kassiotis G, Buch T, Frommer F, von Hoch L, Kramer D, Minichiello L, Kollias G, Lassmann H, Waisman A. Apoptosis of oligodendrocytes via Fas and TNF-R1 is a key event in the induction of experimental autoimmune encephalomyelitis. J Immunol. 2005; 175:5875–5884. [PubMed: 16237080]

Howard G, Evans GW, Pearce K, Howard VJ, Bell RA, Mayer EJ, Burke GL. Is the stroke belt disappearing? An analysis of racial, temporal, and age effects. Stroke. 1995; 26:1153–1158. [PubMed: 7604406]

Hsiao FY, Huang WF, Wen YW, Chen PF, Kuo KN, Tsai YW. Thiazolidinediones and cardiovascular events in patients with type 2 diabetes mellitus: a retrospective cohort study of over 473,000 patients using the National Health Insurance database in Taiwan. Drug Saf. 2009; 32:675–690. [PubMed: 19591532]

Hu E, Kim JB, Sarraf P, Spiegelman BM. Inhibition of adipogenesis through MAP kinase-mediated phosphorylation of PPARgamma. Science. 1996; 274:2100–2103. [PubMed: 8953045]

Hu X, Leak RK, Shi Y, Suenaga J, Gao Y, Zheng P, Chen J. Microglial and macrophage polarization-new prospects for brain repair. Nat Rev Neurol. 2015; 11:56–64. [PubMed: 25385337]

Hu X, Li P, Guo Y, Wang H, Leak RK, Chen S, Gao Y, Chen J. Microglia/macrophage polarization dynamics reveal novel mechanism of injury expansion after focal cerebral ischemia. Stroke. 2012; 43:3063–3070. [PubMed: 22933588]

Huria T, Beeraka NM, Al-Ghamdi B, Fern R. Premyelinated central axons express neurotoxic NMDA receptors: relevance to early developing white-matter injury. J Cereb Blood Flow Metab. 2015; 35:543–553. [PubMed: 25515212]

Husain J, Juurlink BH. Oligodendroglial precursor cell susceptibility to hypoxia is related to poor ability to cope with reactive oxygen species. Brain Res. 1995; 698:86–94. [PubMed: 8581507]

Huxley RR, Barzi F, Lam TH, Czernichow S, Fang X, Welborn T, Shaw J, Ueshima H, Zimmet P, Jee SH, Patel JV, Caterson I, Perkovic V, Woodward M, Asia Pacific Cohort Studies, C; the Obesity in Asia, C. Isolated low levels of high-density lipoprotein cholesterol are associated with an increased risk of coronary heart disease: an individual participant data meta-analysis of 23 studies in the Asia-Pacific region. Circulation. 2011; 124:2056–2064. [PubMed: 21986289]

Iankova I, Petersen RK, Annicotte JS, Chavey C, Hansen JB, Kratchmarova I, Sarruf D, Benkirane M, Kristiansen K, Fajas L. Peroxisome proliferator-activated receptor gamma recruits the positive

transcription elongation factor b complex to activate transcription and promote adipogenesis. Mol Endocrinol. 2006; 20:1494–1505. [PubMed: 16484339]

Ikeda Y, Sugawara A, Taniyama Y, Uruno A, Igarashi K, Arima S, Ito S, Takeuchi K. Suppression of rat thromboxane synthase gene transcription by peroxisome proliferator-activated receptor gamma in macrophages via an interaction with NRF2. J Biol Chem. 2000; 275:33142–33150. [PubMed: 10930400]

Imamoto E, Yoshida N, Uchiyama K, Kuroda M, Kokura S, Ichikawa H, Naito Y, Tanigawa T, Yoshikawa T. Inhibitory effect of pioglitazone on expression of adhesion molecules on neutrophils and endothelial cells. Biofactors. 2004; 20:37–47. [PubMed: 15096659]

Inzucchi SE, Furie KL. The IRIS (Insulin Resistance Intervention after Stroke) trial: A new perspective on pioglitazone. J Diabetes. 2016; 8:607–609. [PubMed: 27125599]

Irvine KA, Blakemore WF. Remyelination protects axons from demyelination-associated axon degeneration. Brain. 2008; 131:1464–1477. [PubMed: 18490361]

Ishii T, Itoh K, Ruiz E, Leake DS, Unoki H, Yamamoto M, Mann GE. Role of Nrf2 in the regulation of CD36 and stress protein expression in murine macrophages: activation by oxidatively modified LDL and 4-hydroxynonenal. Circ Res. 2004; 94:609–616. [PubMed: 14752028]

Issemann I, Green S. Activation of a member of the steroid hormone receptor superfamily by peroxisome proliferators. Nature. 1990; 347:645–650. [PubMed: 2129546]

Iwai S, Maeda T, Kiguchi N, Kobayashi Y, Fukazawa Y, Ozaki M, Kishioka S. Pioglitazone attenuates tactile allodynia and microglial activation in mice with peripheral nerve injury. Drug Discov Ther. 2008; 2:353–356. [PubMed: 22504745]

Izawa Y, Takahashi S, Suzuki N. Pioglitazone enhances pyruvate and lactate oxidation in cultured neurons but not in cultured astroglia. Brain Res. 2009; 1305:64–73. [PubMed: 19800324]

Jackson SM, Parhami F, Xi XP, Berliner JA, Hsueh WA, Law RE, Demer LL. Peroxisome proliferator-activated receptor activators target human endothelial cells to inhibit leukocyte-endothelial cell interaction. Arterioscler Thromb Vasc Biol. 1999; 19:2094–2104. [PubMed: 10479650]

Jana M, Mondal S, Gonzalez FJ, Pahan K. Gemfibrozil, a lipid-lowering drug, increases myelin genes in human oligodendrocytes via peroxisome proliferator-activated receptor-beta. J Biol Chem. 2012; 287:34134–34148. [PubMed: 22879602]

Janani C, Ranjitha Kumari BD. PPAR gamma gene–a review. Diabetes Metab Syndr. 2015; 9:46–50. [PubMed: 25450819]

Jeffery ND, Blakemore WF. Locomotor deficits induced by experimental spinal cord demyelination are abolished by spontaneous remyelination. Brain. 1997; 120(Pt 1):27–37. [PubMed: 9055795]

Jennewein C, Kuhn AM, Schmidt MV, Meilladec-Jullig V, von Knethen A, Gonzalez FJ, Brune B. Sumoylation of peroxisome proliferator-activated receptor gamma by apoptotic cells prevents lipopolysaccharide-induced NCoR removal from kappaB binding sites mediating transrepression of proinflammatory cytokines. J Immunol. 2008; 181:5646–5652. [PubMed: 18832723]

Jeremitsky E, Omert LA, Dunham CM, Wilberger J, Rodriguez A. The impact of hyperglycemia on patients with severe brain injury. J Trauma. 2005; 58:47–50. [PubMed: 15674149]

Jia HB, Wang XM, Qiu LL, Liu XY, Shen JC, Ji Q, Yang JJ. Spinal neuroimmune activation inhibited by repeated administration of pioglitazone in rats after L5 spinal nerve transection. Neurosci Lett. 2013; 543:130–135. [PubMed: 23583338]

Jiang X, Pu H, Hu X, Wei Z, Hong D, Zhang W, Gao Y, Chen J, Shi Y. A Post-stroke Therapeutic Regimen with Omega-3 Polyunsaturated Fatty Acids that Promotes White Matter Integrity and Beneficial Microglial Responses after Cerebral Ischemia. Transl Stroke Res. 2016; 7:548–561. [PubMed: 27714669]

Jin K, Wang X, Xie L, Mao XO, Greenberg DA. Transgenic ablation of doublecortin-expressing cells suppresses adult neurogenesis and worsens stroke outcome in mice. Proc Natl Acad Sci U S A. 2010a; 107:7993–7998. [PubMed: 20385829]

Jin R, Yang G, Li G. Inflammatory mechanisms in ischemic stroke: role of inflammatory cells. J Leukoc Biol. 2010b; 87:779–789. [PubMed: 20130219]

Jin WN, Shi SX, Li Z, Li M, Wood K, Gonzales RJ, Liu Q. Depletion of microglia exacerbates postischemic inflammation and brain injury. J Cereb Blood Flow Metab. 2017; 37:2224–2236. [PubMed: 28273719]

Johansson CB, Momma S, Clarke DL, Risling M, Lendahl U, Frisen J. Identification of a neural stem cell in the adult mammalian central nervous system. Cell. 1999; 96:25–34. [PubMed: 9989494]

Johnstone JT, Morton PD, Jayakumar AR, Johnstone AL, Gao H, Bracchi-Ricard V, Pearse DD, Norenberg MD, Bethea JR. Inhibition of NADPH oxidase activation in oligodendrocytes reduces cytotoxicity following trauma. PLoS One. 2013; 8:e80975. [PubMed: 24260524]

Jordan JE, Zhao ZQ, Vinten-Johansen J. The role of neutrophils in myocardial ischemia-reperfusion injury. Cardiovasc Res. 1999; 43:860–878. [PubMed: 10615413]

Joseph MJ, Caliaperumal J, Schlichter LC. After Intracerebral Hemorrhage, Oligodendrocyte Precursors Proliferate and Differentiate Inside White-Matter Tracts in the Rat Striatum. Transl Stroke Res. 2016; 7:192–208. [PubMed: 26743212]

Jurkunas UV, Bitar MS, Funaki T, Azizi B. Evidence of oxidative stress in the pathogenesis of fuchs endothelial corneal dystrophy. Am J Pathol. 2010; 177:2278–2289. [PubMed: 20847286]

Juurlink BH. Response of glial cells to ischemia: roles of reactive oxygen species and glutathione. Neurosci Biobehav Rev. 1997; 21:151–166. [PubMed: 9062938]

Kanakasabai S, Pestereva E, Chearwae W, Gupta SK, Ansari S, Bright JJ. PPARgamma agonists promote oligodendrocyte differentiation of neural stem cells by modulating stemness and differentiation genes. PLoS One. 2012; 7:e50500. [PubMed: 23185633]

Kane CJ, Phelan KD, Han L, Smith RR, Xie J, Douglas JC, Drew PD. Protection of neurons and microglia against ethanol in a mouse model of fetal alcohol spectrum disorders by peroxisome proliferator-activated receptor-gamma agonists. Brain Behav Immun. 2011; 25(Suppl 1):S137–145. [PubMed: 21376806]

Kapadia R, Yi JH, Vemuganti R. Mechanisms of anti-inflammatory and neuroprotective actions of PPAR-gamma agonists. Front Biosci. 2008; 13:1813–1826. [PubMed: 17981670]

Kaplan JM, Cook JA, Hake PW, O'Connor M, Burroughs TJ, Zingarelli B. 15-Deoxy-delta(12,14)-prostaglandin J(2) (15D-PGJ(2)), a peroxisome proliferator activated receptor gamma ligand, reduces tissue leukosequestration and mortality in endotoxic shock. Shock. 2005; 24:59–65. [PubMed: 15988322]

Katzan I. Can add-on pioglitazone prevent recurrent stroke in patients with type 2 diabetes? Nat Clin Pract Neurol. 2007; 3:486–487. [PubMed: 17637729]

Kaundal RK, Sharma SS. Peroxisome proliferator-activated receptor gamma agonists as neuroprotective agents. Drug News Perspect. 2010; 23:241–256. [PubMed: 20520853]

Kawabori M, Yenari MA. Inflammatory responses in brain ischemia. Curr Med Chem. 2015; 22:1258–1277. [PubMed: 25666795]

Kernan WN, Viscoli CM, Furie KL, Young LH, Inzucchi SE, Gorman M, Guarino PD, Lovejoy AM, Peduzzi PN, Conwit R, Brass LM, Schwartz GG, Adams HP Jr, Berger L, Carolei A, Clark W, Coull B, Ford GA, Kleindorfer D, O'Leary JR, Parsons MW, Ringleb P, Sen S, Spence JD, Tanne D, Wang D, Winder TR, Investigators, I.T. Pioglitazone after Ischemic Stroke or Transient Ischemic Attack. N Engl J Med. 2016; 374:1321–1331. [PubMed: 26886418]

Khandoudi N, Delerive P, Berrebi-Bertrand I, Buckingham RE, Staels B, Bril A. Rosiglitazone, a peroxisome proliferator-activated receptor-gamma, inhibits the Jun NH(2)-terminal kinase/activating protein 1 pathway and protects the heart from ischemia/reperfusion injury. Diabetes. 2002; 51:1507–1514. [PubMed: 11978649]

Kheir WA, Gevrey JC, Yamaguchi H, Isaac B, Cox D. A WAVE2-Abi1 complex mediates CSF-1-induced F-actin-rich membrane protrusions and migration in macrophages. J Cell Sci. 2005; 118:5369–5379. [PubMed: 16280551]

Kielian T, Syed MM, Liu S, Phulwani NK, Phillips N, Wagoner G, Drew PD, Esen N. The synthetic peroxisome proliferator-activated receptor-gamma agonist ciglitazone attenuates neuroinflammation and accelerates encapsulation in b0Oacterial brain abscesses. J Immunol. 2008; 180:5004–5016. [PubMed: 18354226]

Kim TH, Kim MY, Jo SH, Park JM, Ahn YH. Modulation of the transcriptional activity of peroxisome proliferator-activated receptor gamma by protein-protein interactions and post-translational modifications. Yonsei Med J. 2013; 54:545–559. [PubMed: 23549795]

Kivisakk P, Imitola J, Rasmussen S, Elyaman W, Zhu B, Ransohoff RM, Khoury SJ. Localizing central nervous system immune surveillance: meningeal antigen-presenting cells activate T cells during

experimental autoimmune encephalomyelitis. Ann Neurol. 2009; 65:457–469. [PubMed: 18496841]

Klopfleisch S, Merkler D, Schmitz M, Kloppner S, Schedensack M, Jeserich G, Althaus HH, Bruck W. Negative impact of statins on oligodendrocytes and myelin formation in vitro and in vivo. J Neurosci. 2008; 28:13609–13614. [PubMed: 19074034]

Klotz L, Burgdorf S, Dani I, Saijo K, Flossdorf J, Hucke S, Alferink J, Nowak N, Beyer M, Mayer G, Langhans B, Klockgether T, Waisman A, Eberl G, Schultze J, Famulok M, Kolanus W, Glass C, Kurts C, Knolle PA. The nuclear receptor PPAR gamma selectively inhibits Th17 differentiation in a T cell-intrinsic fashion and suppresses CNS autoimmunity. J Exp Med. 2009; 206:2079–2089. [PubMed: 19737866]

Koenigsknecht-Talboo J, Landreth GE. Microglial phagocytosis induced by fibrillar beta-amyloid and IgGs are differentially regulated by proinflammatory cytokines. J Neurosci. 2005; 25:8240–8249. [PubMed: 16148231]

Koizumi S, Shigemoto-Mogami Y, Nasu-Tada K, Shinozaki Y, Ohsawa K, Tsuda M, Joshi BV, Jacobson KA, Kohsaka S, Inoue K. UDP acting at P2Y6 receptors is a mediator of microglial phagocytosis. Nature. 2007; 446:1091–1095. [PubMed: 17410128]

Kokoeva MV, Yin H, Flier JS. Neurogenesis in the hypothalamus of adult mice: potential role in energy balance. Science. 2005; 310:679–683. [PubMed: 16254185]

Krueger M, Bechmann I, Immig K, Reichenbach A, Hartig W, Michalski D. Blood-brain barrier breakdown involves four distinct stages of vascular damage in various models of experimental focal cerebral ischemia. J Cereb Blood Flow Metab. 2015; 35:292–303. [PubMed: 25425076]

Kumari R, Willing LB, Patel SD, Krady JK, Zavadoski WJ, Gibbs EM, Vannucci SJ, Simpson IA. The PPAR-654 gamma agonist, darglitazone, restores acute inflammatory responses to cerebral hypoxia-ischemia in the diabetic ob/ob mouse. J Cereb Blood Flow Metab. 2010; 30:352–360. [PubMed: 19861974]

Lai TW, Zhang S, Wang YT. Excitotoxicity and stroke: identifying novel targets for neuroprotection. Prog Neurobiol. 2014; 115:157–188. [PubMed: 24361499]

Lalloyer F, Staels B. Fibrates, glitazones, and peroxisome proliferator-activated receptors. Arterioscler Thromb Vasc Biol. 2010; 30:894–899. [PubMed: 20393155]

Lan LF, Zheng L, Yang X, Ji XT, Fan YH, Zeng JS. Peroxisome proliferator-activated receptor-gamma agonist pioglitazone ameliorates white matter lesion and cognitive impairment in hypertensive rats. CNS Neurosci Ther. 2015; 21:410–416. [PubMed: 25611692]

Lee-Liu D, Edwards-Faret G, Tapia VS, Larrain J. Spinal cord regeneration: lessons for mammals from non-mammalian vertebrates. Genesis. 2013; 51:529–544. [PubMed: 23760835]

Lee J, Reding M. Effects of thiazolidinediones on stroke recovery: a case-matched controlled study. Neurochem Res. 2007; 32:635–638. [PubMed: 16960755]

Lee TM, Chou TF. Troglitazone administration limits infarct size by reduced phosphorylation of canine myocardial connexin43 proteins. Am J Physiol Heart Circ Physiol. 2003; 285:H1650–1659. [PubMed: 12969882]

Lee Y, Morrison BM, Li Y, Lengacher S, Farah MH, Hoffman PN, Liu Y, Tsingalia A, Jin L, Zhang PW, Pellerin L, Magistretti PJ, Rothstein JD. Oligodendroglia metabolically support axons and contribute to neurodegeneration. Nature. 2012; 487:443–448. [PubMed: 22801498]

Leesnitzer LM, Parks DJ, Bledsoe RK, Cobb JE, Collins JL, Consler TG, Davis RG, Hull-Ryde EA, Lenhard JM, Patel L, Plunket KD, Shenk JL, Stimmel JB, Therapontos C, Willson TM, Blanchard SG. Functional consequences of cysteine modification in the ligand binding sites of peroxisome proliferator activated receptors by GW9662. Biochemistry. 2002; 41:6640–6650. [PubMed: 12022867]

Lehmann JM, Moore LB, Smith-Oliver TA, Wilkison WO, Willson TM, Kliewer SA. An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor gamma (PPAR gamma). J Biol Chem. 1995; 270:12953–12956. [PubMed: 7768881]

Leisewitz AV, Urrutia CR, Martinez GR, Loyola G, Bronfman M. A PPARs cross-talk concertedly commits C6 glioma cells to oligodendrocytes and induces enzymes involved in myelin synthesis. J Cell Physiol. 2008; 217:367–376. [PubMed: 18543250]

Lemay DG, Hwang DH. Genome-wide identification of peroxisome proliferator response elements using integrated computational genomics. J Lipid Res. 2006; 47:1583–1587. [PubMed: 16585784]

Li AC, Brown KK, Silvestre MJ, Willson TM, Palinski W, Glass CK. Peroxisome proliferator-activated receptor gamma ligands inhibit development of atherosclerosis in LDL receptor-deficient mice. J Clin Invest. 2000; 106:523–531. [PubMed: 10953027]

Li X, Du J, Xu S, Lin X, Ling Z. Peroxisome proliferator-activated receptor-gamma agonist rosiglitazone reduces secondary damage in experimental spinal cord injury. J Int Med Res. 2013; 41:153–161. [PubMed: 23569141]

Li X, Melief E, Postupna N, Montine KS, Keene CD, Montine TJ. Prostaglandin E2 receptor subtype 2 regulation of scavenger receptor CD36 modulates microglial Abeta42 phagocytosis. Am J Pathol. 2015; 185:230–239. [PubMed: 25452117]

Liebetanz D, Merkler D. Effects of commissural de- and remyelination on motor skill behaviour in the cuprizone mouse model of multiple sclerosis. Exp Neurol. 2006; 202:217–224. [PubMed: 16857191]

Liesz A, Dalpke A, Mracsko E, Antoine DJ, Roth S, Zhou W, Yang H, Na SY, Akhisaroglu M, Fleming T, Eigenbrod T, Nawroth PP, Tracey KJ, Veltkamp R. DAMP signaling is a key pathway inducing immune modulation after brain injury. J Neurosci. 2015; 35:583–598. [PubMed: 25589753]

Lin TN, Cheung WM, Wu JS, Chen JJ, Lin H, Chen JJ, Liou JY, Shyue SK, Wu KK. 15d-prostaglandin J2 protects brain from ischemia-reperfusion injury. Arterioscler Thromb Vasc Biol. 2006; 26:481–487. [PubMed: 16385084]

Lin W, Harding HP, Ron D, Popko B. Endoplasmic reticulum stress modulates the response of myelinating oligodendrocytes to the immune cytokine interferon-gamma. J Cell Biol. 2005; 169:603–612. [PubMed: 15911877]

Lindvall O, Kokaia Z. Neurogenesis following Stroke Affecting the Adult Brain. Cold Spring Harb Perspect Biol. 2015; 7

Liu H, Rose ME, Culver S, Ma X, Dixon CE, Graham SH. Rosiglitazone attenuates inflammation and CA3 neuronal loss following traumatic brain injury in rats. Biochem Biophys Res Commun. 2016; 472:648–655. [PubMed: 26947332]

Liu HR, Tao L, Gao E, Lopez BL, Christopher TA, Willette RN, Ohlstein EH, Yue TL, Ma XL. Anti-apoptotic effects of rosiglitazone in hypercholesterolemic rabbits subjected to myocardial ischemia and reperfusion. Cardiovasc Res. 2004; 62:135–144. [PubMed: 15023560]

Liu J, Wang LN. Peroxisome proliferator-activated receptor gamma agonists for preventing recurrent stroke and other vascular events in patients with stroke or transient ischaemic attack. Cochrane Database Syst Rev. 2015:CD010693. [PubMed: 26511368]

Liu SH, Yang CN, Pan HC, Sung YJ, Liao KK, Chen WB, Lin WZ, Sheu ML. IL-13 downregulates PPAR-gamma/heme oxygenase-1 via ER stress-stimulated calpain activation: aggravation of activated microglia death. Cell Mol Life Sci. 2010; 67:1465–1476. [PubMed: 20221786]

Lo Verme J, Fu J, Astarita G, La Rana G, Russo R, Calignano A, Piomelli D. The nuclear receptor peroxisome proliferator-activated receptor-alpha mediates the anti-inflammatory actions of palmitoylethanolamide. Mol Pharmacol. 2005; 67:15–19. [PubMed: 15465922]

Losy J, Zaremba J, Skrobanski P. CXCL1 (GRO-alpha) chemokine in acute ischaemic stroke patients. Folia Neuropathol. 2005; 43:97–102. [PubMed: 16012911]

Louveau A, Smirnov I, Keyes TJ, Eccles JD, Rouhani SJ, Peske JD, Derecki NC, Castle D, Mandell JW, Lee KS, Harris TH, Kipnis J. Structural and functional features of central nervous system lymphatic vessels. Nature. 2015; 523:337–341. [PubMed: 26030524]

Lu CJ, Sun Y, Muo CH, Chen RC, Chen PC, Hsu CY. Risk of stroke with thiazolidinediones: a ten-year nationwide population-based cohort study. Cerebrovasc Dis. 2013; 36:145–151. [PubMed: 24029780]

Luna-Medina R, Cortes-Canteli M, Alonso M, Santos A, Martinez A, Perez-Castillo A. Regulation of inflammatory response in neural cells in vitro by thiadiazolidinones derivatives through peroxisome proliferator-activated receptor gamma activation. J Biol Chem. 2005; 280:21453–21462. [PubMed: 15817469]

Luo Y, Yin W, Signore AP, Zhang F, Hong Z, Wang S, Graham SH, Chen J. Neuroprotection against focal ischemic brain injury by the peroxisome proliferator-activated receptor-gamma agonist rosiglitazone. J Neurochem. 2006; 97:435–448. [PubMed: 16539667]

Luzzati F, De Marchis S, Fasolo A, Peretto P. Neurogenesis in the caudate nucleus of the adult rabbit. J Neurosci. 2006; 26:609–621. [PubMed: 16407559]

Lygate CA, Hulbert K, Monfared M, Cole MA, Clarke K, Neubauer S. The PPARgamma-activator rosiglitazone does not alter remodeling but increases mortality in rats post-myocardial infarction. Cardiovasc Res. 2003; 58:632–637. [PubMed: 12798436]

Mahaffey KW, Hafley G, Dickerson S, Burns S, Tourt-Uhlig S, White J, Newby LK, Komajda M, McMurray J, Bigelow R, Home PD, Lopes RD. Results of a reevaluation of cardiovascular outcomes in the RECORD trial. Am Heart J. 2013; 166:240–249 e241. [PubMed: 23895806]

Majai G, Sarang Z, Csomos K, Zahuczky G, Fesus L. PPARgamma-dependent regulation of human macrophages in phagocytosis of apoptotic cells. Eur J Immunol. 2007; 37:1343–1354. [PubMed: 17407194]

Mandai K, Matsumoto M, Kitagawa K, Matsushita K, Ohtsuki T, Mabuchi T, Colman DR, Kamada T, Yanagihara T. Ischemic damage and subsequent proliferation of oligodendrocytes in focal cerebral ischemia. Neuroscience. 1997; 77:849–861. [PubMed: 9070757]

Mandrekar-Colucci S, Sauerbeck A, Popovich PG, McTigue DM. PPAR agonists as therapeutics for CNS trauma and neurological diseases. ASN Neuro. 2013; 5:e00129. [PubMed: 24215544]

Marklund N, Clausen F, Lewander T, Hillered L. Monitoring of reactive oxygen species production after traumatic brain injury in rats with microdialysis and the 4-hydroxybenzoic acid trapping method. J Neurotrauma. 2001; 18:1217–1227. [PubMed: 11721740]

Marx N, Mach F, Sauty A, Leung JH, Sarafi MN, Ransohoff RM, Libby P, Plutzky J, Luster AD. Peroxisome proliferator-activated receptor-gamma activators inhibit IFN-gamma-induced expression of the T cell-active CXC chemokines IP-10, Mig, and I-TAC in human endothelial cells. J Immunol. 2000; 164:6503–6508. [PubMed: 10843708]

Masuda T, Isobe Y, Aihara N, Furuyama F, Misumi S, Kim TS, Nishino H, Hida H. Increase in neurogenesis and neuroblast migration after a small intracerebral hemorrhage in rats. Neurosci Lett. 2007; 425:114–119. [PubMed: 17826909]

Matute C, Alberdi E, Domercq M, Sanchez-Gomez MV, Perez-Samartin A, Rodriguez-Antiguedad A, Perez-Cerda F. Excitotoxic damage to white matter. J Anat. 2007; 210:693–702. [PubMed: 17504270]

McGuire EJ, Woodside JR, Borden TA, Weiss RM. Prognostic value of urodynamic testing in myelodysplastic patients. J Urol. 1981; 126:205–209. [PubMed: 7196460]

McKee CA, Lukens JR. Emerging Roles for the Immune System in Traumatic Brain Injury. Front Immunol. 2016; 7:556. [PubMed: 27994591]

McTigue DM. Potential Therapeutic Targets for PPARgamma after Spinal Cord Injury. PPAR Res. 2008; 2008:517162. [PubMed: 18401444]

McTigue DM, Tripathi R, Wei P, Lash AT. The PPAR gamma agonist Pioglitazone improves anatomical and locomotor recovery after rodent spinal cord injury. Exp Neurol. 2007; 205:396–406. [PubMed: 17433295]

Meletis K, Barnabe-Heider F, Carlen M, Evergren E, Tomilin N, Shupliakov O, Frisen J. Spinal cord injury reveals multilineage differentiation of ependymal cells. PLoS Biol. 2008; 6:e182. [PubMed: 18651793]

Meng B, Zhang Q, Huang C, Zhang HT, Tang T, Yang HL. Effects of a single dose of methylprednisolone versus three doses of rosiglitazone on nerve growth factor levels after spinal cord injury. J Int Med Res. 2011; 39:805–814. [PubMed: 21819712]

Michalik L, Wahli W. Involvement of PPAR nuclear receptors in tissue injury and wound repair. J Clin Invest. 2006; 116:598–606. [PubMed: 16511592]

Mierzwa AJ, Marion CM, Sullivan GM, McDaniel DP, Armstrong RC. Components of myelin damage and repair in the progression of white matter pathology after mild traumatic brain injury. J Neuropathol Exp Neurol. 2015; 74:218–232. [PubMed: 25668562]

Migaud M, Batailler M, Segura S, Duittoz A, Franceschini I, Pillon D. Emerging new sites for adult neurogenesis in the mammalian brain: a comparative study between the hypothalamus and the classical neurogenic zones. Eur J Neurosci. 2010; 32:2042–2052. [PubMed: 21143659]

Min LJ, Mogi M, Shudou M, Jing F, Tsukuda K, Ohshima K, Iwanami J, Horiuchi M. Peroxisome proliferator- activated receptor-gamma activation with angiotensin II type 1 receptor blockade is pivotal for the prevention of blood-brain barrier impairment and cognitive decline in type 2 diabetic mice. Hypertension. 2012; 59:1079–1088. [PubMed: 22454480]

Ming X, Ding M, Zhai B, Xiao L, Piao T, Liu M. Biochanin A inhibits lipopolysaccharide-induced inflammation in human umbilical vein endothelial cells. Life Sci. 2015; 136:36–41. [PubMed: 26141992]

Miron VE, Rajasekharan S, Jarjour AA, Zamvil SS, Kennedy TE, Antel JP. Simvastatin regulates oligodendroglial process dynamics and survival. Glia. 2007; 55:130–143. [PubMed: 17078030]

Miron VE, Zehntner SP, Kuhlmann T, Ludwin SK, Owens T, Kennedy TE, Bedell BJ, Antel JP. Statin therapy inhibits remyelination in the central nervous system. Am J Pathol. 2009; 174:1880–1890. [PubMed: 19349355]

Molina-Holgado E, Molina-Holgado F. Mending the broken brain: neuroimmune interactions in neurogenesis. J Neurochem. 2010; 114:1277–1290. [PubMed: 20534007]

Molshatzki N, Orion D, Tsabari R, Schwammenthal Y, Merzeliak O, Toashi M, Tanne D. Chronic kidney disease in patients with acute intracerebral hemorrhage: association with large hematoma volume and poor outcome. Cerebrovasc Dis. 2011; 31:271–277. [PubMed: 21178352]

Moreno S, Farioli-Vecchioli S, Ceru MP. Immunolocalization of peroxisome proliferator-activated receptors and retinoid X receptors in the adult rat CNS. Neuroscience. 2004; 123:131–145. [PubMed: 14667448]

Morganti-Kossmann MC, Rancan M, Otto VI, Stahel PF, Kossmann T. Role of cerebral inflammation after traumatic brain injury: a revisited concept. Shock. 2001; 16:165–177. [PubMed: 11531017]

Mracsko E, Liesz A, Stojanovic A, Lou WP, Osswald M, Zhou W, Karcher S, Winkler F, Martin-Villalba A, Cerwenka A, Veltkamp R. Antigen dependently activated cluster of differentiation 8-positive T cells cause perforin-mediated neurotoxicity in experimental stroke. J Neurosci. 2014; 34:16784–16795. [PubMed: 25505331]

Mughal MM, Khan MK, DeMarco JK, Majid A, Shamoun F, Abela GS. Symptomatic and asymptomatic carotid artery plaque. Expert Rev Cardiovasc Ther. 2011; 9:1315–1330. [PubMed: 21985544]

Mukohda M, Stump M, Ketsawatsomkron P, Hu C, Quelle FW, Sigmund CD. Endothelial PPAR-gamma provides vascular protection from IL-1 beta-induced oxidative stress. Am J Physiol Heart Circ Physiol. 2016; 310:H39–48. [PubMed: 26566726]

Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. Lancet. 1997; 349:1498–1504. [PubMed: 9167458]

Nakayama H, Jorgensen HS, Raaschou HO, Olsen TS. Recovery of upper extremity function in stroke patients: the Copenhagen Stroke Study. Arch Phys Med Rehabil. 1994; 75:394–398. [PubMed: 8172497]

Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zinman B, American Diabetes, A; European Association for Study of, D. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2009; 32:193–203. [PubMed: 18945920]

Neschen S, Morino K, Dong J, Wang-Fischer Y, Cline GW, Romanelli AJ, Rossbacher JC, Moore IK, Regittnig W, Munoz DS, Kim JH, Shulman GI. n-3 Fatty acids preserve insulin sensitivity in vivo in a peroxisome proliferator-activated receptor-alpha-dependent manner. Diabetes. 2007; 56:1034–1041. [PubMed: 17251275]

Neumann J, Sauerzweig S, Ronicke R, Gunzer F, Dinkel K, Ullrich O, Gunzer M, Reymann KG. Microglia cells protect neurons by direct engulfment of invading neutrophil granulocytes: a new mechanism of CNS immune privilege. J Neurosci. 2008; 28:5965–5975. [PubMed: 18524901]

Ni W, Mao S, Xi G, Keep RF, Hua Y. Role of Erythrocyte CD47 in Intracerebral Hematoma Clearance. Stroke. 2016; 47:505–511. [PubMed: 26732568]

Niino M, Iwabuchi K, Kikuchi S, Ato M, Morohashi T, Ogata A, Tashiro K, Onoe K. Amelioration of experimental autoimmune encephalomyelitis in C57BL/6 mice by an agonist of peroxisome proliferator-activated receptor-gamma. J Neuroimmunol. 2001; 116:40–48. [PubMed: 11311328]

Nissen SE, Wolski K. Rosiglitazone revisited: an updated meta-analysis of risk for myocardial infarction and cardiovascular mortality. Arch Intern Med. 2010; 170:1191–1201. [PubMed: 20656674]

Okada T, Wada J, Hida K, Eguchi J, Hashimoto I, Baba M, Yasuhara A, Shikata K, Makino H. Thiazolidinediones ameliorate diabetic nephropathy via cell cycle-dependent mechanisms. Diabetes. 2006; 55:1666–1677. [PubMed: 16731829]

Ormerod BK, Hanft SJ, Asokan A, Haditsch U, Lee SW, Palmer TD. PPARgamma activation prevents impairments in spatial memory and neurogenesis following transient illness. Brain Behav Immun. 2013; 29:28–38. [PubMed: 23108061]

Ott A, Stolk RP, van Harskamp F, Pols HA, Hofman A, Breteler MM. Diabetes mellitus and the risk of dementia: The Rotterdam Study. Neurology. 1999; 53:1937–1942. [PubMed: 10599761]

Ou Z, Zhao X, Labiche LA, Strong R, Grotta JC, Herrmann O, Aronowski J. Neuronal expression of peroxisome proliferator-activated receptor-gamma (PPARgamma) and 15d-prostaglandin J2–mediated protection of brain after experimental cerebral ischemia in rat. Brain Res. 2006; 1096:196–203. [PubMed: 16725118]

Ouyang YB, Xu L, Liu S, Giffard RG. Role of Astrocytes in Delayed Neuronal Death: GLT-1 and its Novel Regulation by MicroRNAs. Adv Neurobiol. 2014; 11:171–188. [PubMed: 25236729]

Owens J, Wyper DJ, Patterson J, Brown DR, Elliott AT, Teasdale GM, McCulloch J. First SPET images of glutamate (NMDA) receptor activation in vivo in cerebral ischaemia. Nucl Med Commun. 1997; 18:149–158. [PubMed: 9076771]

Oyinbo CA. Secondary injury mechanisms in traumatic spinal cord injury: a nugget of this multiply cascade. Acta Neurobiol Exp (Wars). 2011; 71:281–299. [PubMed: 21731081]

Padilla J, Kaur K, Cao HJ, Smith TJ, Phipps RP. Peroxisome proliferator activator receptor-gamma agonists and 15-deoxy-Delta(12,14)(12,14)-PGJ(2) induce apoptosis in normal and malignant B-lineage cells. J Immunol. 2000; 165:6941–6948. [PubMed: 11120820]

Paintlia AS, Paintlia MK, Khan M, Vollmer T, Singh AK, Singh I. HMG-CoA reductase inhibitor augments survival and differentiation of oligodendrocyte progenitors in animal model of multiple sclerosis. FASEB J. 2005; 19:1407–1421. [PubMed: 16126908]

Paintlia AS, Paintlia MK, Singh AK, Orak JK, Singh I. Activation of PPAR-gamma and PTEN cascade participates in lovastatin-mediated accelerated differentiation of oligodendrocyte progenitor cells. Glia. 2010; 58:1669–1685. [PubMed: 20578043]

Paintlia AS, Paintlia MK, Singh AK, Singh I. Inhibition of rho family functions by lovastatin promotes myelin repair in ameliorating experimental autoimmune encephalomyelitis. Mol Pharmacol. 2008; 73:1381–1393. [PubMed: 18239032]

Pan HC, Yang CN, Hung YW, Lee WJ, Tien HR, Shen CC, Sheehan J, Chou CT, Sheu ML. Reciprocal modulation of C/EBP-alpha and C/EBP-beta by IL-13 in activated microglia prevents neuronal death. Eur J Immunol. 2013; 43:2854–2865. [PubMed: 23881867]

Pang Y, Cai Z, Rhodes PG. Effect of tumor necrosis factor-alpha on developing optic nerve oligodendrocytes in culture. J Neurosci Res. 2005; 80:226–234. [PubMed: 15765524]

Pantoni L, Garcia JH, Gutierrez JA. Cerebral white matter is highly vulnerable to ischemia. Stroke. 1996; 27:1641–1646. discussion 1647. [PubMed: 8784142]

Park BV, Pan F. The role of nuclear receptors in regulation of Th17/Treg biology and its implications for diseases. Cell Mol Immunol. 2015; 12:533–542. [PubMed: 25958843]

Park EJ, Park SY, Joe EH, Jou I. 15d-PGJ2 and rosiglitazone suppress Janus kinase-STAT inflammatory signaling through induction of suppressor of cytokine signaling 1 (SOCS1) and SOCS3 in glia. J Biol Chem. 2003; 278:14747–14752. [PubMed: 12584205]

Park EY, Cho IJ, Kim SG. Transactivation of the PPAR-responsive enhancer module in chemopreventive glutathione S-transferase gene by the peroxisome proliferator-activated receptor-gamma and retinoid X receptor heterodimer. Cancer Res. 2004a; 64:3701–3713. [PubMed: 15150131]

Park KS, Lee RD, Kang SK, Han SY, Park KL, Yang KH, Song YS, Park HJ, Lee YM, Yun YP, Oh KW, Kim DJ, Yun YW, Hwang SJ, Lee SE, Hong JT. Neuronal differentiation of embryonic midbrain cells by upregulation of peroxisome proliferator-activated receptor-gamma via the JNK-dependent pathway. Exp Cell Res. 2004b; 297:424–433. [PubMed: 15212945]

Pasceri V, Wu HD, Willerson JT, Yeh ET. Modulation of vascular inflammation in vitro and in vivo by peroxisome proliferator-activated receptor-gamma activators. Circulation. 2000; 101:235–238. [PubMed: 10645917]

Pascual G, Fong AL, Ogawa S, Gamliel A, Li AC, Perissi V, Rose DW, Willson TM, Rosenfeld MG, Glass CK. A SUMOylation-dependent pathway mediates transrepression of inflammatory response genes by PPAR-gamma. Nature. 2005; 437:759–763. [PubMed: 16127449]

Patel AR, Ritzel R, McCullough LD, Liu F. Microglia and ischemic stroke: a double-edged sword. Int J Physiol Pathophysiol Pharmacol. 2013; 5:73–90. [PubMed: 23750306]

Patel PC, Harrison RE. Membrane ruffles capture C3bi-opsonized particles in activated macrophages. Mol Biol Cell. 2008; 19:4628–4639. [PubMed: 18768756]

Patel SN, Serghides L, Smith TG, Febbraio M, Silverstein RL, Kurtz TW, Pravenec M, Kain KC. CD36 mediates the phagocytosis of Plasmodium falciparum-infected erythrocytes by rodent macrophages. J Infect Dis. 2004; 189:204–213. [PubMed: 14722884]

Paterniti I, Impellizzeri D, Crupi R, Morabito R, Campolo M, Esposito E, Cuzzocrea S. Molecular evidence for the involvement of PPAR-delta and PPAR-gamma in anti-inflammatory and neuroprotective activities of palmitoylethanolamide after spinal cord trauma. J Neuroinflammation. 2013; 10:20. [PubMed: 23374874]

Pedersen WA, McMillan PJ, Kulstad JJ, Leverenz JB, Craft S, Haynatzki GR. Rosiglitazone attenuates learning and memory deficits in Tg2576 Alzheimer mice. Exp Neurol. 2006; 199:265–273. [PubMed: 16515786]

Pennypacker KR, Offner H. The role of the spleen in ischemic stroke. J Cereb Blood Flow Metab. 2015; 35:186–187. [PubMed: 25465042]

Piantadosi CA, Zhang J. Mitochondrial generation of reactive oxygen species after brain ischemia in the rat. Stroke. 1996; 27:327–331. discussion 332. [PubMed: 8571432]

Picard F, Kurtev M, Chung N, Topark-Ngarm A, Senawong T, Machado De Oliveira R, Leid M, McBurney MW, Guarente L. Sirt1 promotes fat mobilization in white adipocytes by repressing PPAR-gamma. Nature. 2004; 429:771–776. [PubMed: 15175761]

Pierce AA, Xu AW. De novo neurogenesis in adult hypothalamus as a compensatory mechanism to regulate energy balance. J Neurosci. 2010; 30:723–730. [PubMed: 20071537]

Pittet JF, Lee H, Morabito D, Howard MB, Welch WJ, Mackersie RC. Serum levels of Hsp 72 measured early after trauma correlate with survival. J Trauma. 2002; 52:611–617. discussion 617. [PubMed: 11956372]

Polvani S, Tarocchi M, Galli A. PPARgamma and Oxidative Stress: Con(beta) Catenating NRF2 and FOXO. PPAR Res. 2012; 2012:641087. [PubMed: 22481913]

Pourcet B, Pineda-Torra I, Derudas B, Staels B, Glineur C. SUMOylation of human peroxisome proliferator-activated receptor alpha inhibits its trans-activity through the recruitment of the nuclear corepressor NCoR. J Biol Chem. 2010; 285:5983–5992. [PubMed: 19955185]

Puyal J, Ginet V, Clarke PG. Multiple interacting cell death mechanisms in the mediation of excitotoxicity and ischemic brain damage: a challenge for neuroprotection. Prog Neurobiol. 2013; 105:24–48. [PubMed: 23567504]

Qi L, Jacob A, Wang P, Wu R. Peroxisome proliferator activated receptor-gamma and traumatic brain injury. Int J Clin Exp Med. 2010; 3:283–292. [PubMed: 21072262]

Quinones-Hinojosa A, Sanai N, Soriano-Navarro M, Gonzalez-Perez O, Mirzadeh Z, Gil-Perotin S, Romero-Rodriguez R, Berger MS, Garcia-Verdugo JM, Alvarez-Buylla A. Cellular composition and cytoarchitecture of the adult human subventricular zone: a niche of neural stem cells. J Comp Neurol. 2006; 494:415–434. [PubMed: 16320258]

Qureshi AI, Mendelow AD, Hanley DF. Intracerebral haemorrhage. Lancet. 2009; 373:1632–1644. [PubMed: 19427958]

Qureshi AI, Qureshi MH. Acute hypertensive response in patients with intracerebral hemorrhage pathophysiology and treatment. J Cereb Blood Flow Metab. 2017:271678X17725431.

Qureshi AI, Tuhrim S, Broderick JP, Batjer HH, Hondo H, Hanley DF. Spontaneous intracerebral hemorrhage. N Engl J Med. 2001; 344:1450–1460. [PubMed: 11346811]

Ramirez-Amaya V, Marrone DF, Gage FH, Worley PF, Barnes CA. Integration of new neurons into functional neural networks. J Neurosci. 2006; 26:12237–12241. [PubMed: 17122048]

Randall RD, Thayer SA. Glutamate-induced calcium transient triggers delayed calcium overload and neurotoxicity in rat hippocampal neurons. J Neurosci. 1992; 12:1882–1895. [PubMed: 1349638]

Redondo-Castro E, Hernandez J, Mahy N, Navarro X. Phagocytic microglial phenotype induced by glibenclamide improves functional recovery but worsens hyperalgesia after spinal cord injury in adult rats. Eur J Neurosci. 2013; 38:3786–3798. [PubMed: 24112298]

Ricote M, Li AC, Willson TM, Kelly CJ, Glass CK. The peroxisome proliferator-activated receptor-gamma is a negative regulator of macrophage activation. Nature. 1998; 391:79–82. [PubMed: 9422508]

Riyahi TY, Frese F, Steinert M, Omosigho NN, Glockner G, Eichinger L, Orabi B, Williams RS, Noegel AA. RpkA, a highly conserved GPCR with a lipid kinase domain, has a role in phagocytosis and anti-bacterial defense. PLoS One. 2011; 6:e27311. [PubMed: 22073313]

Robinson MB. The family of sodium-dependent glutamate transporters: a focus on the GLT-1/EAAT2 subtype. Neurochem Int. 1998; 33:479–491. [PubMed: 10098717]

Rohatagi S, Carrothers TJ, Jin J, Jusko WJ, Khariton T, Walker J, Truitt K, Salazar DE. Model-based development of a PPARgamma agonist, rivoglitazone, to aid dose selection and optimize clinical trial designs. J Clin Pharmacol. 2008; 48:1420–1429. [PubMed: 18936283]

Rolland M, Li X, Sellier Y, Martin H, Perez-Berezo T, Rauwel B, Benchoua A, Bessieres B, Aziza J, Cenac N, Luo M, Casper C, Peschanski M, Gonzalez-Dunia D, Leruez-Ville M, Davrinche C, Chavanas S. PPARgamma Is Activated during Congenital Cytomegalovirus Infection and Inhibits Neuronogenesis from Human Neural Stem Cells. PLoS Pathog. 2016; 12:e1005547. [PubMed: 27078877]

Romera C, Hurtado O, Mallolas J, Pereira MP, Morales JR, Romera A, Serena J, Vivancos J, Nombela F, Lorenzo P, Lizasoain I, Moro MA. Ischemic preconditioning reveals that GLT1/EAAT2 glutamate transporter is a novel PPARgamma target gene involved in neuroprotection. J Cereb Blood Flow Metab. 2007; 27:1327–1338. [PubMed: 17213861]

Rosenberg GA. Inflammation and white matter damage in vascular cognitive impairment. Stroke. 2009; 40:S20–23. [PubMed: 19064797]

Rosenberg GA. Vascular cognitive impairment: Biomarkers in diagnosis and molecular targets in therapy. J Cereb Blood Flow Metab. 2016; 36:4–5. [PubMed: 26667984]

Rosenbluth J. Redundant myelin sheaths and other ultrastructural features of the toad cerebellum. J Cell Biol. 1966; 28:73–93. [PubMed: 5901501]

Ross GD, Reed W, Dalzell JG, Becker SE, Hogg N. Macrophage cytoskeleton association with CR3 and CR4 regulates receptor mobility and phagocytosis of iC3b-opsonized erythrocytes. J Leukoc Biol. 1992; 51:109–117. [PubMed: 1358992]

Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990s. Nature. 1993; 362:801–809. [PubMed: 8479518]

Ross R. Atherosclerosis–an inflammatory disease. N Engl J Med. 1999; 340:115–126. [PubMed: 9887164]

Roth AD, Leisewitz AV, Jung JE, Cassina P, Barbeito L, Inestrosa NC, Bronfman M. PPAR gamma activators induce growth arrest and process extension in B12 oligodendrocyte-like cells and terminal differentiation of cultured oligodendrocytes. J Neurosci Res. 2003; 72:425–435. [PubMed: 12704804]

Rotshenker S. Microglia and macrophage activation and the regulation of complement-receptor-3 (CR3/MAC-1)-mediated myelin phagocytosis in injury and disease. J Mol Neurosci. 2003; 21:65–72. [PubMed: 14500997]

Rotshenker S. The role of Galectin-3/MAC-2 in the activation of the innate-immune function of phagocytosis in microglia in injury and disease. J Mol Neurosci. 2009; 39:99–103. [PubMed: 19253007]

Rowat A, Graham C, Dennis M. Renal dysfunction in stroke patients: a hospital-based cohort study and systematic review. Int J Stroke. 2014; 9:633–639. [PubMed: 24621343]

Rushmore TH, Morton MR, Pickett CB. The antioxidant responsive element. Activation by oxidative stress and identification of the DNA consensus sequence required for functional activity. J Biol Chem. 1991; 266:11632–11639. [PubMed: 1646813]

Rushmore TH, Pickett CB. Transcriptional regulation of the rat glutathione S-transferase Ya subunit gene. Characterization of a xenobiotic-responsive element controlling inducible expression by phenolic antioxidants. J Biol Chem. 1990; 265:14648–14653. [PubMed: 2387873]

Sahay A, Scobie KN, Hill AS, O'Carroll CM, Kheirbek MA, Burghardt NS, Fenton AA, Dranovsky A, Hen R. Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation. Nature. 2011; 472:466–470. [PubMed: 21460835]

Salehi A, Zhang JH, Obenaus A. Response of the cerebral vasculature following traumatic brain injury. J Cereb Blood Flow Metab. 2017; 37:2320–2339. [PubMed: 28378621]

Salter MG, Fern R. NMDA receptors are expressed in developing oligodendrocyte processes and mediate injury. Nature. 2005; 438:1167–1171. [PubMed: 16372012]

Saluja I, Granneman JG, Skoff RP. PPAR delta agonists stimulate oligodendrocyte differentiation in tissue culture. Glia. 2001; 33:191–204. [PubMed: 11241737]

Samaha FF, Szapary PO, Iqbal N, Williams MM, Bloedon LT, Kochar A, Wolfe ML, Rader DJ. Effects of rosiglitazone on lipids, adipokines, and inflammatory markers in nondiabetic patients with low high-density lipoprotein cholesterol and metabolic syndrome. Arterioscler Thromb Vasc Biol. 2006; 26:624–630. [PubMed: 16357312]

Sarafidis PA, Lasaridis AN. Actions of peroxisome proliferator-activated receptors-gamma agonists explaining a possible blood pressure-lowering effect. Am J Hypertens. 2006; 19:646–653. [PubMed: 16733240]

Sarafidis PA, Stafylas PC, Georgianos PI, Saratzis AN, Lasaridis AN. Effect of thiazolidinediones on albuminuria and proteinuria in diabetes: a meta-analysis. Am J Kidney Dis. 2010; 55:835–847. [PubMed: 20110146]

Sasaki M, Jordan P, Welbourne T, Minagar A, Joh T, Itoh M, Elrod JW, Alexander JS. Troglitazone, a PPAR-gamma activator prevents endothelial cell adhesion molecule expression and lymphocyte adhesion mediated by TNF-alpha. BMC Physiol. 2005; 5:3. [PubMed: 15694007]

Sauer S. Ligands for the Nuclear Peroxisome Proliferator-Activated Receptor Gamma. Trends Pharmacol Sci. 2015; 36:688–704. [PubMed: 26435213]

Scheen AJ. Outcomes and lessons from the PROactive study. Diabetes Res Clin Pract. 2012; 98:175–186. [PubMed: 23020930]

Schilling M, Besselmann M, Muller M, Strecker JK, Ringelstein EB, Kiefer R. Predominant phagocytic activity of resident microglia over hematogenous macrophages following transient focal cerebral ischemia: an investigation using green fluorescent protein transgenic bone marrow chimeric mice. Exp Neurol. 2005; 196:290–297. [PubMed: 16153641]

Schirmer-Mikalsen K, Vik A, Gisvold SE, Skandsen T, Hynne H, Klepstad P. Severe head injury: control of physiological variables, organ failure and complications in the intensive care unit. Acta Anaesthesiol Scand. 2007; 51:1194–1201. [PubMed: 17711565]

Schousboe A, Waagepetersen HS. Role of astrocytes in glutamate homeostasis: implications for excitotoxicity. Neurotox Res. 2005; 8:221–225. [PubMed: 16371316]

Schulz MK, Wang LP, Tange M, Bjerre P. Cerebral microdialysis monitoring: determination of normal and ischemic cerebral metabolisms in patients with aneurysmal subarachnoid hemorrhage. J Neurosurg. 2000; 93:808–814. [PubMed: 11059662]

Semple RK, Chatterjee VK, O'Rahilly S. PPAR gamma and human metabolic disease. J Clin Invest. 2006; 116:581–589. [PubMed: 16511590]

Seri B, Garcia-Verdugo JM, McEwen BS, Alvarez-Buylla A. Astrocytes give rise to new neurons in the adult mammalian hippocampus. J Neurosci. 2001; 21:7153–7160. [PubMed: 11549726]

Shao D, Rangwala SM, Bailey ST, Krakow SL, Reginato MJ, Lazar MA. Interdomain communication regulating ligand binding by PPAR-gamma. Nature. 1998; 396:377–380. [PubMed: 9845075]

Sharma SK, Naidu G. The role of danger-associated molecular patterns (DAMPs) in trauma and infections. J Thorac Dis. 2016; 8:1406–1409. [PubMed: 27500853]

Shattil SJ, Kim C, Ginsberg MH. The final steps of integrin activation: the end game. Nat Rev Mol Cell Biol. 2010; 11:288–300. [PubMed: 20308986]

Shaya FT, Lu Z, Sohn K, Weir MR. Thiazolidinediones and cardiovascular events in high-risk patients with type-2 diabetes mellitus: a comparison with other oral antidiabetic agents. P T. 2009; 34:490–501. [PubMed: 20140111]

Shen J, Xie L, Mao X, Zhou Y, Zhan R, Greenberg DA, Jin K. Neurogenesis after primary intracerebral hemorrhage in adult human brain. J Cereb Blood Flow Metab. 2008; 28:1460–1468. [PubMed: 18446166]

Shereen A, Nemkul N, Yang D, Adhami F, Dunn RS, Hazen ML, Nakafuku M, Ning G, Lindquist DM, Kuan CY. Ex vivo diffusion tensor imaging and neuropathological correlation in a murine model of hypoxia-ischemia-induced thrombotic stroke. J Cereb Blood Flow Metab. 2011; 31:1155–1169. [PubMed: 21139628]

Shevach EM. Mechanisms of foxp3+ T regulatory cell-mediated suppression. Immunity. 2009; 30:636–645. [PubMed: 19464986]

Shevach EM, DiPaolo RA, Andersson J, Zhao DM, Stephens GL, Thornton AM. The lifestyle of naturally occurring CD4+ CD25+ Foxp3+ regulatory T cells. Immunol Rev. 2006; 212:60–73. [PubMed: 16903906]

Shi H, Hu X, Leak RK, Shi Y, An C, Suenaga J, Chen J, Gao Y. Demyelination as a rational therapeutic target for ischemic or traumatic brain injury. Exp Neurol. 2015; 272:17–25. [PubMed: 25819104]

Shi Y, Leak RK, Keep RF, Chen J. Translational Stroke Research on Blood-Brain Barrier Damage: Challenges, Perspectives, and Goals. Transl Stroke Res. 2016a; 7:89–92. [PubMed: 26757714]

Shi Y, Zhang L, Pu H, Mao L, Hu X, Jiang X, Xu N, Stetler RA, Zhang F, Liu X, Leak RK, Keep RF, Ji X, Chen J. Rapid endothelial cytoskeletal reorganization enables early blood-brain barrier disruption and long-term ischaemic reperfusion brain injury. Nat Commun. 2016b; 7:10523. [PubMed: 26813496]

Shih AY, Imbeault S, Barakauskas V, Erb H, Jiang L, Li P, Murphy TH. Induction of the Nrf2-driven antioxidant response confers neuroprotection during mitochondrial stress in vivo. J Biol Chem. 2005; 280:22925–22936. [PubMed: 15840590]

Shiomi T, Tsutsui H, Hayashidani S, Suematsu N, Ikeuchi M, Wen J, Ishibashi M, Kubota T, Egashira K, Takeshita A. Pioglitazone, a peroxisome proliferator-activated receptor-gamma agonist, attenuates left ventricular remodeling and failure after experimental myocardial infarction. Circulation. 2002; 106:3126–3132. [PubMed: 12473562]

Siddiqui AM, Cui X, Wu R, Dong W, Zhou M, Hu M, Simms HH, Wang P. The anti-inflammatory effect of curcumin in an experimental model of sepsis is mediated by up-regulation of peroxisome proliferator-activated receptor-gamma. Crit Care Med. 2006; 34:1874–1882. [PubMed: 16715036]

Sidell RJ, Cole MA, Draper NJ, Desrois M, Buckingham RE, Clarke K. Thiazolidinedione treatment normalizes insulin resistance and ischemic injury in the zucker Fatty rat heart. Diabetes. 2002; 51:1110–1117. [PubMed: 11916933]

Sim FJ, Lang JK, Ali TA, Roy NS, Vates GE, Pilcher WH, Goldman SA. Statin treatment of adult human glial progenitors induces PPAR gamma-mediated oligodendrocytic differentiation. Glia. 2008; 56:954–962. [PubMed: 18383345]

Sim FJ, Zhao C, Penderis J, Franklin RJ. The age-related decrease in CNS remyelination efficiency is attributable to an impairment of both oligodendrocyte progenitor recruitment and differentiation. J Neurosci. 2002; 22:2451–2459. [PubMed: 11923409]

Simoni J, Feola M, Canizaro PC. Generation of free oxygen radicals and the toxicity of hemoglobin solutions. Biomater Artif Cells Artif Organs. 1990; 18:189–202. [PubMed: 2369646]

Smith KJ, Blakemore WF, McDonald WI. Central remyelination restores secure conduction. Nature. 1979; 280:395–396. [PubMed: 460414]

Soares HD, Hicks RR, Smith D, McIntosh TK. Inflammatory leukocytic recruitment and diffuse neuronal degeneration are separate pathological processes resulting from traumatic brain injury. J Neurosci. 1995; 15:8223–8233. [PubMed: 8613756]

Staessen JA, Kuznetsova T, Stolarz K. Hypertension prevalence and stroke mortality across populations. JAMA. 2003; 289:2420–2422. [PubMed: 12746368]

Stephen RL, Gustafsson MC, Jarvis M, Tatoud R, Marshall BR, Knight D, Ehrenborg E, Harris AL, Wolf CR, Palmer CN. Activation of peroxisome proliferator-activated receptor delta stimulates the proliferation of human breast and prostate cancer cell lines. Cancer Res. 2004; 64:3162–3170. [PubMed: 15126355]

Storer PD, Xu J, Chavis JA, Drew PD. Cyclopentenone prostaglandins PGA2 and 15-deoxy-delta12, 14 PGJ2 suppress activation of murine microglia and astrocytes: implications for multiple sclerosis. J Neurosci Res. 2005; 80:66–74. [PubMed: 15723383]

Streilein JW. Unraveling immune privilege. Science. 1995; 270:1158–1159. [PubMed: 7502038]

Sugawara A, Takeuchi K, Uruno A, Ikeda Y, Arima S, Kudo M, Sato K, Taniyama Y, Ito S. Transcriptional suppression of type 1 angiotensin II receptor gene expression by peroxisome proliferator-activated receptor-gamma in vascular smooth muscle cells. Endocrinology. 2001; 142:3125–3134. [PubMed: 11416035]

Sullivan GM, Mierzwa AJ, Kijpaisalratana N, Tang H, Wang Y, Song SK, Selwyn R, Armstrong RC. Oligodendrocyte lineage and subventricular zone response to traumatic axonal injury in the corpus callosum. J Neuropathol Exp Neurol. 2013; 72:1106–1125. [PubMed: 24226267]

Sundararajan S, Landreth GE. Antiinflammatory properties of PPARgamma agonists following ischemia. Drug News Perspect. 2004; 17:229–236. [PubMed: 15334171]

Taheri M, Salamian A, Ghaedi K, Peymani M, Izadi T, Nejati AS, Atefi A, Nematollahi M, Ahmadi Ghahrizjani F, Esmaeili M, Kiani Esfahani A, Irani S, Baharvand H, Nasr-Esfahani MH. A ground state of PPARgamma activity and expression is required for appropriate neural differentiation of hESCs. Pharmacol Rep. 2015; 67:1103–1114. [PubMed: 26481528]

Takeuchi H, Jin S, Wang J, Zhang G, Kawanokuchi J, Kuno R, Sonobe Y, Mizuno T, Suzumura A. Tumor necrosis factor-alpha induces neurotoxicity via glutamate release from hemichannels of activated microglia in an autocrine manner. J Biol Chem. 2006; 281:21362–21368. [PubMed: 16720574]

Tanaka R, Yamashiro K, Okuma Y, Shimura H, Nakamura S, Ueno Y, Tanaka Y, Miyamoto N, Tomizawa Y, Nakahara T, Furukawa Y, Watada H, Kawamori R, Hattori N, Urabe T. Effects of Pioglitazone for Secondary Stroke Prevention in Patients with Impaired Glucose Tolerance and Newly Diagnosed Diabetes: The J-SPIRIT Study. J Atheroscler Thromb. 2015; 22:1305–1316. [PubMed: 26269002]

Tang Y, Le W. Differential Roles of M1 and M2 Microglia in Neurodegenerative Diseases. Mol Neurobiol. 2016; 53:1181–1194. [PubMed: 25598354]

Tekkok SB, Goldberg MP. Ampa/kainate receptor activation mediates hypoxic oligodendrocyte death and axonal injury in cerebral white matter. J Neurosci. 2001; 21:4237–4248. [PubMed: 11404409]

Terasaki Y, Liu Y, Hayakawa K, Pham LD, Lo EH, Ji X, Arai K. Mechanisms of neurovascular dysfunction in acute ischemic brain. Curr Med Chem. 2014; 21:2035–2042. [PubMed: 24372202]

Tesfamariam B, DeFelice AF. Endothelial injury in the initiation and progression of vascular disorders. Vascul Pharmacol. 2007; 46:229–237. [PubMed: 17218160]

Thal SC, Heinemann M, Luh C, Pieter D, Werner C, Engelhard K. Pioglitazone reduces secondary brain damage after experimental brain trauma by PPAR-gamma-independent mechanisms. J Neurotrauma. 2011; 28:983–993. [PubMed: 21501066]

Thal SC, Neuhaus W. The blood-brain barrier as a target in traumatic brain injury treatment. Arch Med Res. 2014; 45:698–710. [PubMed: 25446615]

Thal SC, Wyschkon S, Pieter D, Engelhard K, Werner C. Selection of endogenous control genes for normalization of gene expression analysis after experimental brain trauma in mice. J Neurotrauma. 2008; 25:785–794. [PubMed: 18627256]

Tholance Y, Barcelos G, Dailler F, Perret-Liaudet A, Renaud B. Clinical Neurochemistry of Subarachnoid Hemorrhage: Toward Predicting Individual Outcomes via Biomarkers of Brain Energy Metabolism. ACS Chem Neurosci. 2015; 6:1902–1905. [PubMed: 26595414]

Tontonoz P, Nagy L, Alvarez JG, Thomazy VA, Evans RM. PPARgamma promotes monocyte/macrophage differentiation and uptake of oxidized LDL. Cell. 1998; 93:241–252. [PubMed: 9568716]

Trang T, Beggs S, Salter MW. Brain-derived neurotrophic factor from microglia: a molecular substrate for neuropathic pain. Neuron Glia Biol. 2011; 7:99–108. [PubMed: 22613083]

Tripathi R, McTigue DM. Prominent oligodendrocyte genesis along the border of spinal contusion lesions. Glia. 2007; 55:698–711. [PubMed: 17330874]

Tsai YS, Xu L, Smithies O, Maeda N. Genetic variations in peroxisome proliferator-activated receptor gamma expression affect blood pressure. Proc Natl Acad Sci U S A. 2009; 106:19084–19089. [PubMed: 19884495]

Tymianski M, Charlton MP, Carlen PL, Tator CH. Secondary Ca2+ overload indicates early neuronal injury which precedes staining with viability indicators. Brain Res. 1993; 607:319–323. [PubMed: 7683241]

Urra X, Obach V, Chamorro A. Stroke induced immunodepression syndrome: from bench to bedside. Curr Mol Med. 2009; 9:195–202. [PubMed: 19275627]

Uruno A, Matsuda K, Noguchi N, Yoshikawa T, Kudo M, Satoh F, Rainey WE, Hui XG, Akahira J, Nakamura Y, Sasano H, Okamoto H, Ito S, Sugawara A. Peroxisome proliferator-activated receptor-{gamma} suppresses CYP11B2 expression and aldosterone production. J Mol Endocrinol. 2011; 46:37–49. [PubMed: 21106862]

Vallarino C, Perez A, Fusco G, Liang H, Bron M, Manne S, Joseph G, Yu S. Comparing pioglitazone to insulin with respect to cancer, cardiovascular and bone fracture endpoints, using propensity score weights. Clin Drug Investig. 2013; 33:621–631.

Vanasse A, Carpentier AC, Courteau J, Asghari S. Stroke and cardiovascular morbidity and mortality associated with rosiglitazone use in elderly diabetic patients. Diab Vasc Dis Res. 2009; 6:87–93. [PubMed: 20368198]

Vattulainen-Collanus S, Akinrinade O, Li M, Koskenvuo M, Li CG, Rao SP, de Jesus Perez V, Yuan K, Sawada H, Koskenvuo JW, Alvira C, Rabinovitch M, Alastalo TP. Loss of PPARgamma in endothelial cells leads to impaired angiogenesis. J Cell Sci. 2016; 129:693–705. [PubMed: 26743080]

Venkatesan C, Chrzaszcz M, Choi N, Wainwright MS. Chronic upregulation of activated microglia immunoreactive for galectin-3/Mac-2 and nerve growth factor following diffuse axonal injury. J Neuroinflammation. 2010; 7:32. [PubMed: 20507613]

Verrier E, Wang L, Wadham C, Albanese N, Hahn C, Gamble JR, Chatterjee VK, Vadas MA, Xia P. PPARgamma agonists ameliorate endothelial cell activation via inhibition of diacylglycerol-protein kinase C signaling pathway: role of diacylglycerol kinase. Circ Res. 2004; 94:1515–1522. [PubMed: 15117825]

Victor NA, Wanderi EW, Gamboa J, Zhao X, Aronowski J, Deininger K, Lust WD, Landreth GE, Sundararajan S. Altered PPARgamma expression and activation after transient focal ischemia in rats. Eur J Neurosci. 2006; 24:1653–1663. [PubMed: 17004929]

Viola HM, Hool LC. Role of the cytoskeleton in communication between L-type Ca(2+) channels and mitochondria. Clin Exp Pharmacol Physiol. 2013; 40:295–304. [PubMed: 23551128]

Viscoli CM, Brass LM, Carolei A, Conwit R, Ford GA, Furie KL, Gorman M, Guarino PD, Inzucchi SE, Lovejoy AM, Parsons MW, Peduzzi PN, Ringleb PA, Schwartz GG, Spence JD, Tanne D, Young LH, Kernan WN, investigators, I.T. Pioglitazone for secondary prevention after ischemic stroke and transient ischemic attack: rationale and design of the Insulin Resistance Intervention after Stroke Trial. Am Heart J. 2014; 168:823–829 e826. [PubMed: 25458644]

Von Knethen AA, Brune B. Delayed activation of PPARgamma by LPS and IFN-gamma attenuates the oxidative burst in macrophages. FASEB J. 2001; 15:535–544. [PubMed: 11156969]

Wada K, Nakajima A, Katayama K, Kudo C, Shibuya A, Kubota N, Terauchi Y, Tachibana M, Miyoshi H, Kamisaki Y, Mayumi T, Kadowaki T, Blumberg RS. Peroxisome proliferator-activated receptor gamma-mediated regulation of neural stem cell proliferation and differentiation. J Biol Chem. 2006; 281:12673–12681. [PubMed: 16524877]

Wahl LM, Shankavaram U, Zhang Y. Role of macrophages in vascular tissue remodelling. Transpl Immunol. 1997; 5:173–176. [PubMed: 9402681]

Waite KJ, Floyd ZE, Arbour-Reily P, Stephens JM. Interferon-gamma-induced regulation of peroxisome proliferator- activated receptor gamma and STATs in adipocytes. J Biol Chem. 2001; 276:7062–7068. [PubMed: 11106650]

Wan Ibrahim WN, Tofighi R, Onishchenko N, Rebellato P, Bose R, Uhlen P, Ceccatelli S. Perfluorooctane sulfonate induces neuronal and oligodendrocytic differentiation in neural stem cells and alters the expression of PPARgamma in vitro and in vivo. Toxicol Appl Pharmacol. 2013; 269:51–60. [PubMed: 23500012]

Wang CY, Wang ZY, Xie JW, Cai JH, Wang T, Xu Y, Wang X, An L. CD36 upregulation mediated by intranasal LV-NRF2 treatment mitigates hypoxia-induced progression of Alzheimer's-like pathogenesis. Antioxid Redox Signal. 2014; 21:2208–2230. [PubMed: 24702189]

Wang G, Zhang J, Hu X, Zhang L, Mao L, Jiang X, Liou AK, Leak RK, Gao Y, Chen J. Microglia/macrophage polarization dynamics in white matter after traumatic brain injury. J Cereb Blood Flow Metab. 2013; 33:1864–1874. [PubMed: 23942366]

Wang HE, Devereaux RS, Yealy DM, Safford MM, Howard G. National variation in United States sepsis mortality: a descriptive study. Int J Health Geogr. 2010; 9:9. [PubMed: 20156361]

Wang J, Rogove AD, Tsirka AE, Tsirka SE. Protective role of tuftsin fragment 1-3 in an animal model of intracerebral hemorrhage. Ann Neurol. 2003a; 54:655–664. [PubMed: 14595655]

Wang J, Tsirka SE. Tuftsin fragment 1-3 is beneficial when delivered after the induction of intracerebral hemorrhage. Stroke. 2005; 36:613–618. [PubMed: 15692122]

Wang N, Verna L, Chen NG, Chen J, Li H, Forman BM, Stemerman MB. Constitutive activation of peroxisome proliferator-activated receptor-gamma suppresses pro-inflammatory adhesion molecules in human vascular endothelial cells. J Biol Chem. 2002a; 277:34176–34181. [PubMed: 12107164]

Wang SH, Sun ZL, Guo YJ, Yuan Y, Li L. PPARgamma-mediated advanced glycation end products regulation of neural stem cells. Mol Cell Endocrinol. 2009; 307:176–184. [PubMed: 19524138]

Wang X, Mao X, Xie L, Sun F, Greenberg DA, Jin K. Conditional depletion of neurogenesis inhibits long-term recovery after experimental stroke in mice. PLoS One. 2012a; 7:e38932. [PubMed: 22723908]

Wang Y, Huang J, Li Y, Yang GY. Roles of chemokine CXCL12 and its receptors in ischemic stroke. Curr Drug Targets. 2012b; 13:166–172. [PubMed: 22204316]

Wang Y, Liao J, Tang SJ, Shu J, Zhang W. HIV-1 gp120 Upregulates Brain-Derived Neurotrophic Factor (BDNF) Expression in BV2 Cells via the Wnt/beta-Catenin Signaling Pathway. J Mol Neurosci. 2017; 62:199–208. [PubMed: 28560687]

Wang Y, Liu G, Hong D, Chen F, Ji X, Cao G. White matter injury in ischemic stroke. Prog Neurobiol. 2016; 141:45–60. [PubMed: 27090751]

Wang YL, Frauwirth KA, Rangwala SM, Lazar MA, Thompson CB. Thiazolidinedione activation of peroxisome proliferator-activated receptor gamma can enhance mitochondrial potential and promote cell survival. J Biol Chem. 2002b; 277:31781–31788. [PubMed: 12082115]

Wang YX, Lee CH, Tiep S, Yu RT, Ham J, Kang H, Evans RM. Peroxisome-proliferator-activated receptor delta activates fat metabolism to prevent obesity. Cell. 2003b; 113:159–170. [PubMed: 12705865]

Warden A, Truitt J, Merriman M, Ponomareva O, Jameson K, Ferguson LB, Mayfield RD, Harris RA. Localization of PPAR isotypes in the adult mouse and human brain. Sci Rep. 2016; 6:27618. [PubMed: 27283430]

Wardyn JD, Ponsford AH, Sanderson CM. Dissecting molecular cross-talk between Nrf2 and NF-kappaB response pathways. Biochem Soc Trans. 2015; 43:621–626. [PubMed: 26551702]

Wartenberg KE, Stoll A, Funk A, Meyer A, Schmidt JM, Berrouschot J. Infection after acute ischemic stroke: risk factors, biomarkers, and outcome. Stroke Res Treat. 2011; 2011:830614. [PubMed: 21789273]

Wasserman JK, Schlichter LC. White matter injury in young and aged rats after intracerebral hemorrhage. Exp Neurol. 2008; 214:266–275. [PubMed: 18848934]

Wayman NS, Hattori Y, McDonald MC, Mota-Filipe H, Cuzzocrea S, Pisano B, Chatterjee PK, Thiemermann C. Ligands of the peroxisome proliferator-activated receptors (PPAR-gamma and PPAR-alpha) reduce myocardial infarct size. FASEB J. 2002; 16:1027–1040. [PubMed: 12087064]

Weiss N, Miller F, Cazaubon S, Couraud PO. The blood-brain barrier in brain homeostasis and neurological diseases. Biochim Biophys Acta. 2009; 1788:842–857. [PubMed: 19061857]

Wilcox R, Bousser MG, Betteridge DJ, Schernthaner G, Pirags V, Kupfer S, Dormandy J, Investigators, P.R. Effects of pioglitazone in patients with type 2 diabetes with or without previous stroke: results from PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events 04). Stroke. 2007; 38:865–873. [PubMed: 17290029]

Willmot M, Leonardi-Bee J, Bath PM. High blood pressure in acute stroke and subsequent outcome: a systematic review. Hypertension. 2004; 43:18–24. [PubMed: 14662649]

Wilson HM. Macrophages heterogeneity in atherosclerosis - implications for therapy. J Cell Mol Med. 2010; 14:2055–2065. [PubMed: 20629993]

Winkelmayer WC, Setoguchi S, Levin R, Solomon DH. Comparison of cardiovascular outcomes in elderly patients with diabetes who initiated rosiglitazone vs pioglitazone therapy. Arch Intern Med. 2008; 168:2368–2375. [PubMed: 19029503]

Wohlfert EA, Nichols FC, Nevius E, Clark RB. Peroxisome proliferator-activated receptor gamma (PPARgamma) and immunoregulation: enhancement of regulatory T cells through PPARgamma-dependent and -independent mechanisms. J Immunol. 2007; 178:4129–4135. [PubMed: 17371968]

Wolinski P, Glabinski A. Chemokines and neurodegeneration in the early stage of experimental ischemic stroke. Mediators Inflamm. 2013; 2013:727189. [PubMed: 24324296]

Woo MS, Yang J, Beltran C, Cho S. Cell Surface CD36 Protein in Monocyte/Macrophage Contributes to Phagocytosis during the Resolution Phase of Ischemic Stroke in Mice. J Biol Chem. 2016; 291:23654–23661. [PubMed: 27646002]

Writing Group, M; Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Despres JP, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jimenez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER 3rd, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Rosamond W, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Woo D, Yeh RW, Turner MB, American Heart Association Statistics, C; Stroke Statistics, S. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. Circulation. 2016; 133:e38–360. [PubMed: 26673558]

Wu G, Wu J, Jiao Y, Wang L, Wang F, Zhang Y. Rosiglitazone infusion therapy following minimally invasive surgery for intracerebral hemorrhage evacuation decreases matrix metalloproteinase-9 and blood-brain barrier disruption in rabbits. BMC Neurol. 2015; 15:37. [PubMed: 26021445]

Wu JS, Cheung WM, Tsai YS, Chen YT, Fong WH, Tsai HD, Chen YC, Liou JY, Shyue SK, Chen JJ, Chen YE, Maeda N, Wu KK, Lin TN. Ligand-activated peroxisome proliferator-activated receptor-gamma protects against ischemic cerebral infarction and neuronal apoptosis by 14-3-3 epsilon upregulation. Circulation. 2009; 119:1124–1134. [PubMed: 19221220]

Wu JS, Tsai HD, Cheung WM, Hsu CY, Lin TN. PPAR-gamma Ameliorates Neuronal Apoptosis and Ischemic Brain Injury via Suppressing NF-kappaB-Driven p22phox Transcription. Mol Neurobiol. 2016; 53:3626–3645. [PubMed: 26108185]

Xiang Z, Lin T, Reeves SA. 15d-PGJ2 induces apoptosis of mouse oligodendrocyte precursor cells. J Neuroinflammation. 2007; 4:18. [PubMed: 17634127]

Xu R, Wang S, Li W, Liu Z, Tang J, Tang X. Activation of peroxisome proliferator-activated receptor-gamma by a 12/15-lipoxygenase product of arachidonic acid: a possible neuroprotective effect in the brain after experimental intracerebral hemorrhage. J Neurosurg. 2016:1–10.

Xu Y, Lu L, Greyson C, Lee J, Gen M, Kinugawa K, Long CS, Schwartz GG. Deleterious effects of acute treatment with a peroxisome proliferator-activated receptor-gamma activator in myocardial ischemia and reperfusion in pigs. Diabetes. 2003; 52:1187–1194. [PubMed: 12716751]

Xu Y, Tamamaki N, Noda T, Kimura K, Itokazu Y, Matsumoto N, Dezawa M, Ide C. Neurogenesis in the ependymal layer of the adult rat 3rd ventricle. Exp Neurol. 2005; 192:251–264. [PubMed: 15755543]

Xue M, Del Bigio MR. Intracerebral injection of autologous whole blood in rats: time course of inflammation and cell death. Neurosci Lett. 2000; 283:230–232. [PubMed: 10754230]

Yamanaka M, Ishikawa T, Griep A, Axt D, Kummer MP, Heneka MT. PPARgamma/RXRalpha-induced and CD36- mediated microglial amyloid-beta phagocytosis results in cognitive

improvement in amyloid precursor protein/presenilin 1 mice. J Neurosci. 2012; 32:17321–17331. [PubMed: 23197723]

Yamashita D, Yamaguchi T, Shimizu M, Nakata N, Hirose F, Osumi T. The transactivating function of peroxisome proliferator-activated receptor gamma is negatively regulated by SUMO conjugation in the amino-terminal domain. Genes Cells. 2004; 9:1017–1029. [PubMed: 15507114]

Yang HC, Deleuze S, Zuo Y, Potthoff SA, Ma LJ, Fogo AB. The PPARgamma agonist pioglitazone ameliorates aging-related progressive renal injury. J Am Soc Nephrol. 2009a; 20:2380–2388. [PubMed: 19797472]

Yang J, Zhang D, Li J, Zhang X, Fan F, Guan Y. Role of PPARgamma in renoprotection in Type 2 diabetes: molecular mechanisms and therapeutic potential. Clin Sci (Lond). 2009b; 116:17–26. [PubMed: 19037881]

Yang T, Michele DE, Park J, Smart AM, Lin Z, Brosius FC 3rd, Schnermann JB, Briggs JP. Expression of peroxisomal proliferator-activated receptors and retinoid X receptors in the kidney. Am J Physiol. 1999; 277:F966–973. [PubMed: 10600944]

Yang T, Sun Y, Lu Z, Leak RK, Zhang F. The impact of cerebrovascular aging on vascular cognitive impairment and dementia. Ageing Res Rev. 2017; 34:15–29. [PubMed: 27693240]

Yang, T., Sun, Y., Zhang, F. Non-Neuronal Mechanisms of Brain Damage and Repair After StrokeSpringer; 2016The Role of Nonneuronal Nrf2 Pathway in Ischemic Stroke: Damage Control and Potential Tissue Repair; 377-397

Yao J, Zheng K, Zhang X. Rosiglitazone exerts neuroprotective effects via the suppression of neuronal autophagy and apoptosis in the cortex following traumatic brain injury. Mol Med Rep. 2015; 12:6591–6597. [PubMed: 26351751]

Yessoufou A, Wahli W. Multifaceted roles of peroxisome proliferator-activated receptors (PPARs) at the cellular and whole organism levels. Swiss Med Wkly. 2010; 140:w13071. [PubMed: 20842602]

Yi JH, Park SW, Brooks N, Lang BT, Vemuganti R. PPARgamma agonist rosiglitazone is neuroprotective after traumatic brain injury via anti-inflammatory and anti-oxidative mechanisms. Brain Res. 2008; 1244:164–172. [PubMed: 18948087]

Yilmaz G, Granger DN. Cell adhesion molecules and ischemic stroke. Neurol Res. 2008; 30:783–793. [PubMed: 18826804]

Yin KJ, Deng Z, Hamblin M, Xiang Y, Huang H, Zhang J, Jiang X, Wang Y, Chen YE. Peroxisome proliferator-activated receptor delta regulation of miR-15a in ischemia-induced cerebral vascular endothelial injury. J Neurosci. 2010; 30:6398–6408. [PubMed: 20445066]

Yin KJ, Fan Y, Hamblin M, Zhang J, Zhu T, Li S, Hawse JR, Subramaniam M, Song CZ, Urrutia R, Lin JD, Chen YE. KLF11 mediates PPARgamma cerebrovascular protection in ischaemic stroke. Brain. 2013; 136:1274–1287. [PubMed: 23408111]

Yin KJ, Hamblin M, Chen YE. Non-coding RNAs in cerebral endothelial pathophysiology: emerging roles in stroke. Neurochem Int. 2014; 77:9–16. [PubMed: 24704794]

Yoo HY, Chang MS, Rho HM. Induction of the rat Cu/Zn superoxide dismutase gene through the peroxisome proliferator-responsive element by arachidonic acid. Gene. 1999; 234:87–91. [PubMed: 10393242]

Yoshihara D, Kurahashi H, Morita M, Kugita M, Hiki Y, Aukema HM, Yamaguchi T, Calvet JP, Wallace DP, Nagao S. PPAR-gamma agonist ameliorates kidney and liver disease in an orthologous rat model of human autosomal recessive polycystic kidney disease. Am J Physiol Renal Physiol. 2011; 300:F465–474. [PubMed: 21147840]

Yoshii H, Onuma T, Yamazaki T, Watada H, Matsuhisa M, Matsumoto M, Kitagawa K, Kitakaze M, Yamasaki Y, Kawamori R, Group, P.J.S. Effects of pioglitazone on macrovascular events in patients with type 2 diabetes mellitus at high risk of stroke: the PROFIT-J study. J Atheroscler Thromb. 2014; 21:563–573. [PubMed: 24477028]

Yu Y, Xue BJ, Wei SG, Zhang ZH, Beltz TG, Guo F, Johnson AK, Felder RB. Activation of central PPAR-gamma attenuates angiotensin II-induced hypertension. Hypertension. 2015; 66:403–411. [PubMed: 26101342]

Yue Tl TL, Chen J, Bao W, Narayanan PK, Bril A, Jiang W, Lysko PG, Gu JL, Boyce R, Zimmerman DM, Hart TK, Buckingham RE, Ohlstein EH. In vivo myocardial protection from ischemia/

reperfusion injury by the peroxisome proliferator-activated receptor-gamma agonist rosiglitazone. Circulation. 2001; 104:2588–2594. [PubMed: 11714655]

Zelko IN, Mariani TJ, Folz RJ. Superoxide dismutase multigene family: a comparison of the CuZn-SOD (SOD1), Mn- SOD (SOD2), and EC-SOD (SOD3) gene structures, evolution, and expression. Free Radic Biol Med. 2002; 33:337–349. [PubMed: 12126755]

Zhang M, An C, Gao Y, Leak RK, Chen J, Zhang F. Emerging roles of Nrf2 and phase II antioxidant enzymes in neuroprotection. Prog Neurobiol. 2013; 100:30–47. [PubMed: 23025925]

Zhang Q, Hu W, Meng B, Tang T. PPARgamma agonist rosiglitazone is neuroprotective after traumatic spinal cord injury via anti-inflammatory in adult rats. Neurol Res. 2010; 32:852–859. [PubMed: 20350367]

Zhang X, Rodriguez-Galan MC, Subleski JJ, Ortaldo JR, Hodge DL, Wang JM, Shimozato O, Reynolds DA, Young HA. Peroxisome proliferator-activated receptor-gamma and its ligands attenuate biologic functions of human natural killer cells. Blood. 2004a; 104:3276–3284. [PubMed: 15265789]

Zhang Y, Wang H, Li J, Jimenez DA, Levitan ES, Aizenman E, Rosenberg PA. Peroxynitrite-induced neuronal apoptosis is mediated by intracellular zinc release and 12-lipoxygenase activation. J Neurosci. 2004b; 24:10616–10627. [PubMed: 15564577]

Zhang Z, Chopp M. Vascular endothelial growth factor and angiopoietins in focal cerebral ischemia. Trends Cardiovasc Med. 2002; 12:62–66. [PubMed: 11852252]

Zhang ZG, Zhang L, Jiang Q, Zhang R, Davies K, Powers C, Bruggen N, Chopp M. VEGF enhances angiogenesis and promotes blood-brain barrier leakage in the ischemic brain. J Clin Invest. 2000; 106:829–838. [PubMed: 11018070]

Zhao, X., Aronowski, J. Immunological Mechanisms and Therapies in Brain Injuries and StrokeSpringer; 2014The Role of PPARγ in Stroke; 301-320

Zhao X, Grotta J, Gonzales N, Aronowski J. Hematoma resolution as a therapeutic target: the role of microglia/macrophages. Stroke. 2009a; 40:S92–94. [PubMed: 19064796]

Zhao X, Strong R, Zhang J, Sun G, Tsien JZ, Cui Z, Grotta JC, Aronowski J. Neuronal PPARgamma deficiency increases susceptibility to brain damage after cerebral ischemia. J Neurosci. 2009b; 29:6186–6195. [PubMed: 19439596]

Zhao X, Sun G, Ting SM, Song S, Zhang J, Edwards NJ, Aronowski J. Cleaning up after ICH: the role of Nrf2 in modulating microglia function and hematoma clearance. J Neurochem. 2015a; 133:144–152. [PubMed: 25328080]

Zhao X, Sun G, Zhang J, Strong R, Song W, Gonzales N, Grotta JC, Aronowski J. Hematoma resolution as a target for intracerebral hemorrhage treatment: role for peroxisome proliferator-activated receptor gamma in microglia/macrophages. Ann Neurol. 2007; 61:352–362. [PubMed: 17457822]

Zhao X, Zhang Y, Strong R, Grotta JC, Aronowski J. 15d-Prostaglandin J2 activates peroxisome proliferator-activated receptor-gamma, promotes expression of catalase, and reduces inflammation, behavioral dysfunction, and neuronal loss after intracerebral hemorrhage in rats. J Cereb Blood Flow Metab. 2006; 26:811–820. [PubMed: 16208315]

Zhao XR, Gonzales N, Aronowski J. Pleiotropic role of PPARgamma in intracerebral hemorrhage: an intricate system involving Nrf2, RXR, and NF-kappaB. CNS Neurosci Ther. 2015b; 21:357–366. [PubMed: 25430543]

Zhao Z, Alam S, Oppenheim RW, Prevette DM, Evenson A, Parsadanian A. Overexpression of glial cell line-derived neurotrophic factor in the CNS rescues motoneurons from programmed cell death and promotes their long-term survival following axotomy. Exp Neurol. 2004; 190:356–372. [PubMed: 15530875]

Zhou K, Zhong Q, Wang YC, Xiong XY, Meng ZY, Zhao T, Zhu WY, Liao MF, Wu LR, Yang YR, Liu J, Duan CM, Li J, Gong QW, Liu L, Yang MH, Xiong A, Wang J, Yang QW. Regulatory T cells ameliorate intracerebral hemorrhage-induced inflammatory injury by modulating microglia/macrophage polarization through the IL- 10/GSK3beta/PTEN axis. J Cereb Blood Flow Metab. 2017; 37:967–979. [PubMed: 27174997]

Zhu Y, Qi C, Korenberg JR, Chen XN, Noya D, Rao MS, Reddy JK. Structural organization of mouse peroxisome proliferator-activated receptor gamma (mPPAR gamma) gene: alternative promoter

use and different splicing yield two mPPAR gamma isoforms. Proc Natl Acad Sci U S A. 1995; 92:7921–7925. [PubMed: 7644514]

Zoete V, Grosdidier A, Michielin O. Peroxisome proliferator-activated receptor structures: ligand specificity, molecular switch and interactions with regulators. Biochim Biophys Acta. 2007; 1771:915–925. [PubMed: 17317294]

Zuhayra M, Zhao Y, von Forstner C, Henze E, Gohlke P, Culman J, Lutzen U. Activation of cerebral peroxisome proliferator-activated receptors gamma (PPARgamma) reduces neuronal damage in the substantia nigra after transient focal cerebral ischaemia in the rat. Neuropathol Appl Neurobiol. 2011; 37:738–752. [PubMed: 21366664]

Zuo Y, Yang HC, Potthoff SA, Najafian B, Kon V, Ma LJ, Fogo AB. Protective effects of PPARgamma agonist in acute nephrotic syndrome. Nephrol Dial Transplant. 2012; 27:174–181. [PubMed: 21565943]

Highlights

- PPARγ is a master gatekeeper of cell fate decisions
- PPARγ controls inflammation and oxidative stress and limits acute brain injury
- PPARγ fosters tissue repair and facilitates long-term functional recovery
- PPARγ may reduce the risk for stroke in humans
- PPARγ should be further investigated for its therapeutic potential in acute brain injuries

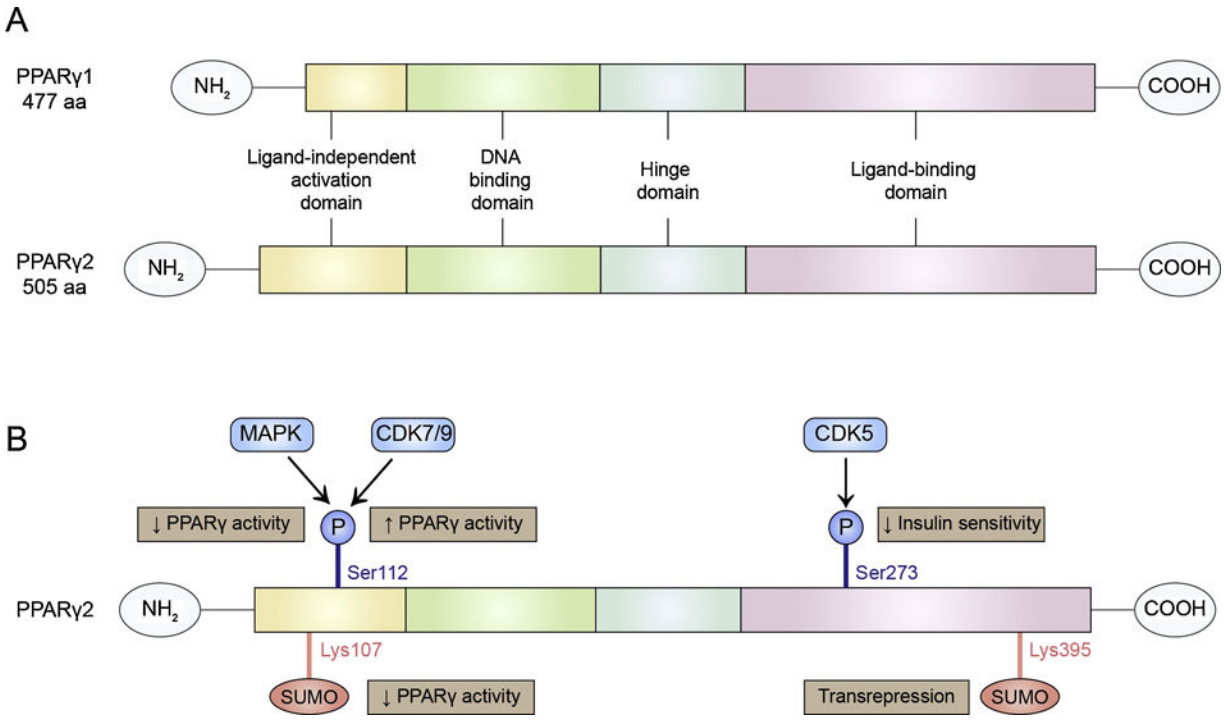

Figure 1.

PPARγ structure and post-translational modifications (PTMs). (A) Human PPARγ consists of two isoforms, PPARγ1 (477 aa) and PPARγ2 (505 aa). Like all other nuclear receptors, PPARγ has four functional domains: a ligand-independent activation domain, a DNA binding domain, a hinge domain, and a ligand-binding domain. (B) PPARγ activity is regulated by PTMs. Ser112 phosphorylation results in different transcriptional outcomes depending on the kinases involved. CDK7/9 mediated Ser112 phosphorylation leads to increased PPARγ activity whereas MAPK elicits the opposite effect. Lys107 SUMOylation is associated with increases in PPARγ activity. Ser273 phosphorylation results in decreased insulin sensitivity. SUMOylation of Lys395 mediates transrepression. Abbreviations: Mitogen-activated protein kinases (MAPKs), cyclin-dependent kinase (CDK).

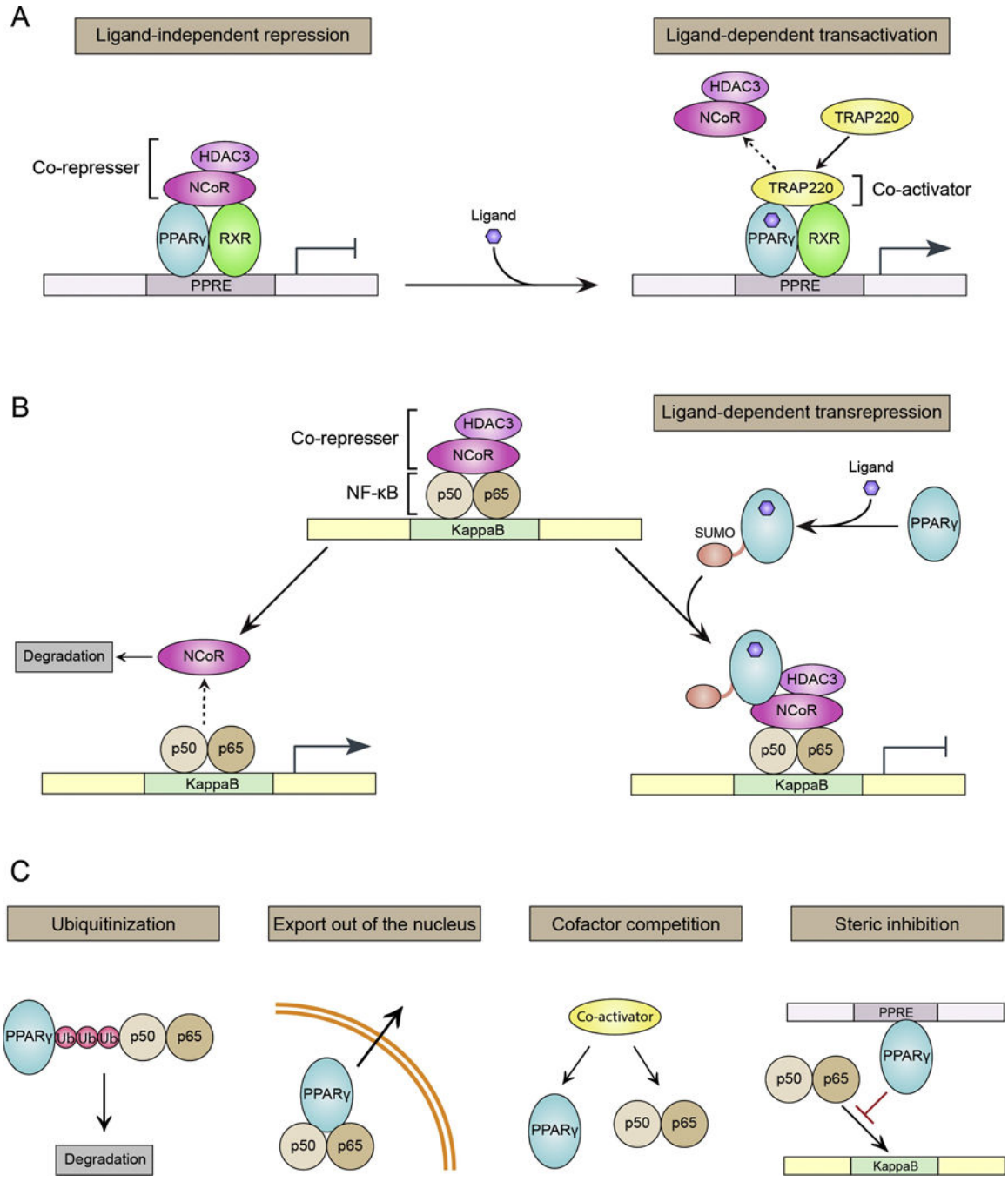

Figure 2.

Functional patterns of PPARγ. (A) Ligand-independent repression and ligand-dependent transactivation. Under resting conditions, the PPARγ/RXR heterodimer is connected to co-repressor (HDAC and NCoR), which blocks PPRE target gene transcription. After binding to the PPARy ligand, conformational changes lead to dissociation of the co-repressor and recruitment of a co-activator (*e.g.* TRAP220), which triggers transcription of PPRE target genes. (B) Ligand-dependent transrepression. Binding to its ligand leads to SUMOylation of PPARγ, which stabilizes the co-repressor of NF-κB, leading to blockade of NF-κB target

gene expression. (C) PPARγ can also inhibit NF-κB target genes by 1) mediating NF-κB degradation, 2) facilitating NF-κB export out of the nucleus, 3) cofactor competition with NF-κB, and 4) steric inhibition of NF-κB binding. Abbreviations: retinoid X receptor (RXR), histone deacetylase (HCAC), nuclear receptor corepressor (NCoR), thyroid hormone-associated protein 220 (TRAP220), peroxisome proliferator response elements (PPREs), ubiquitin (Ub), nuclear factor-κB (NF-κB).

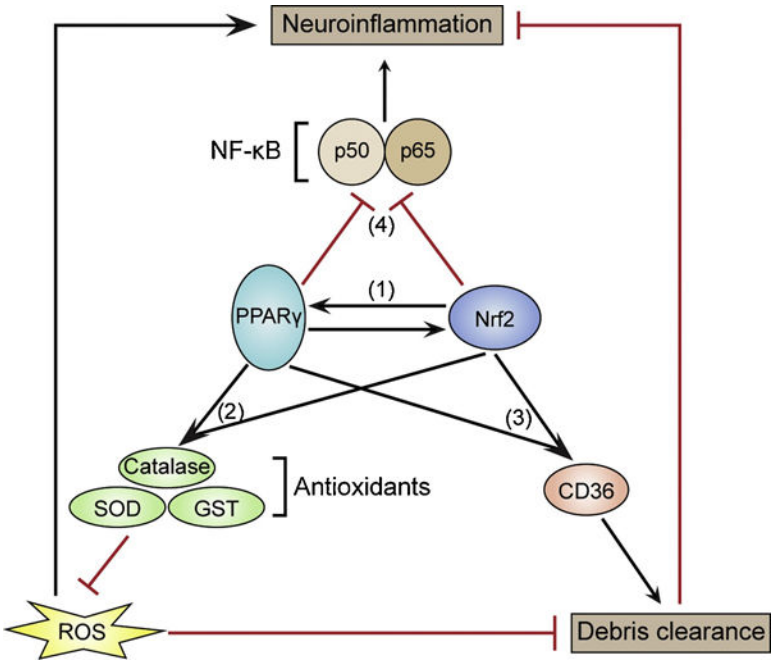

Figure 3.

Interactions between PPARγ and Nrf2 pathways. (1) A bidirectional loop exists between PPARγ and Nrf2. PPARγ can upregulate Nrf2 expression and vice versa. (2) PPARγ and Nrf2 synergistically increase the expression of some antioxidants, including catalase, SOD, and GST, which have both PPRE and ARE elements in their genes. These proteins inhibit the generation of ROS, thereby mitigating neuroinflammation and improving debris clearance. (3) Microglial CD36 is regulated by both PPARγ and Nrf2. CD36 is critical for microglial phagocytosis and subsequent debris clearance, both of which facilitate the resolution of neuroinflammation. (4) PPARγ and Nrf2 synergistically inhibit NF-κB, the major proinflammatory pathway. Abbreviations: nuclear factor erythroid 2-related factor 2 (Nrf2), glutathione S-transferase (GST), reactive oxygen species (ROS), superoxide dismutase (SOD).

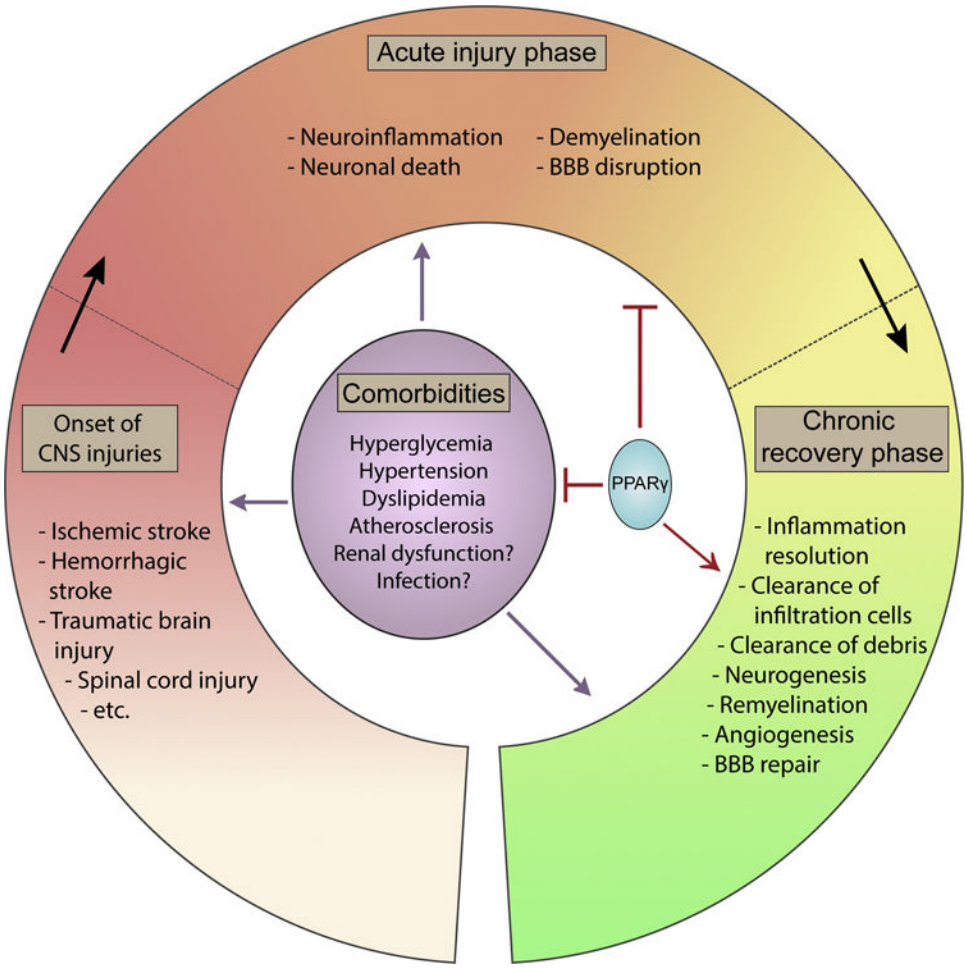

Figure 4.

Pathophysiology of CNS injuries and summary of PPARγ effects. The acute phase of CNS injuries (*e.g.* stroke, TBI, SCI, *etc.*) is characterized by neuroinflammation, neuronal death, demyelination, and BBB disruption. In the chronic recovery phase, repair processes are initiated, such as resolution of inflammation, clearance of debris and infiltrating cells, neurogenesis, remyelination, angiogenesis, and BBB repair. Comorbidities affect the risk of CNS injuries, and influence the course of the injury and self-reparatory activities. PPARγ inhibits the detrimental effects of injuries, promotes repair, and mitigates comorbidities. Abbreviations: blood brain barrier (BBB).

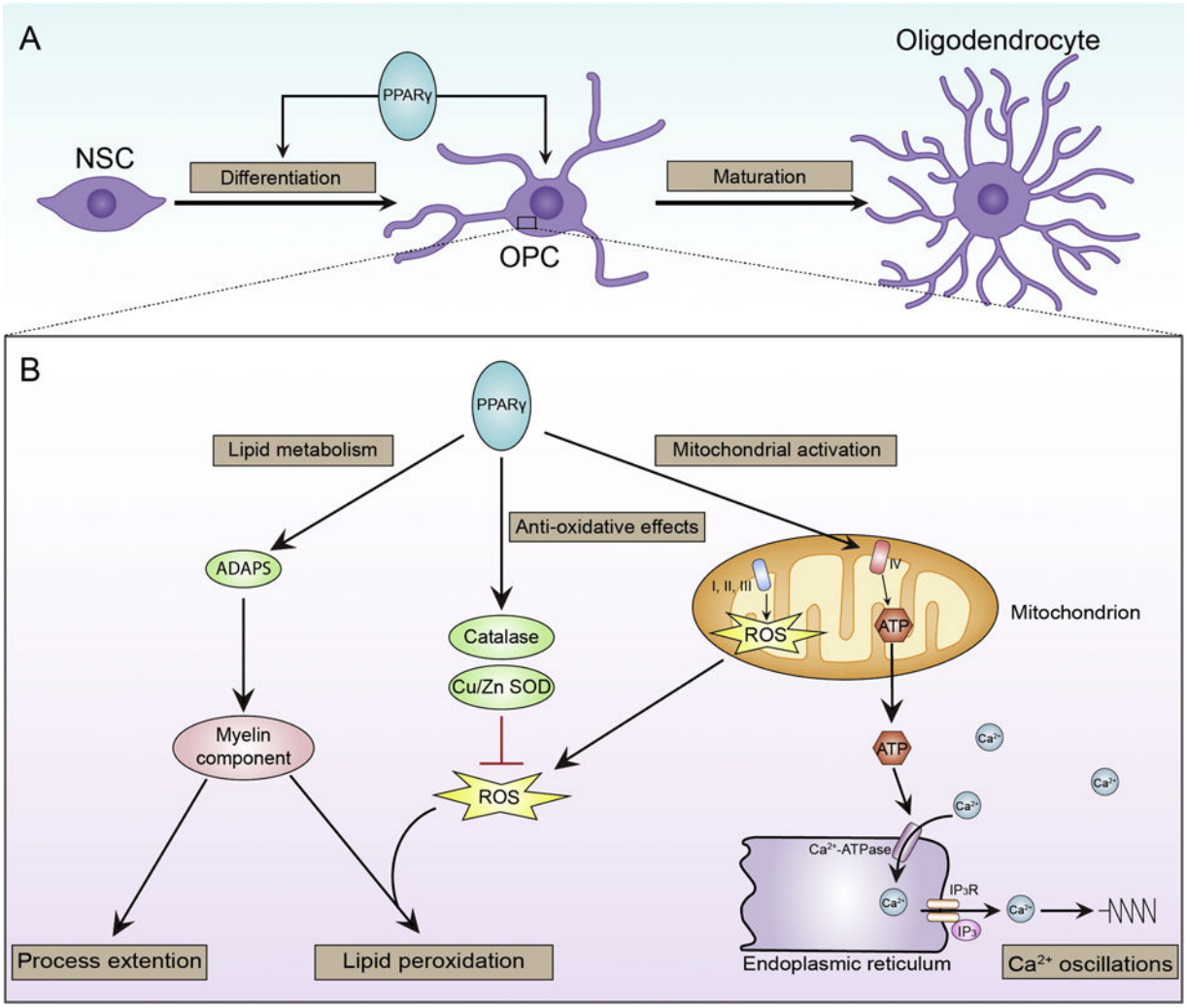

Figure 5.

PPARγ promotes regeneration and maturation of cells of the oligodendrocyte lineage. (A) PPARγ promotes differentiation of neural stem cells (NSCs) into oligodendrocyte precursor cells (OPCs), and enhances further maturation of OPCs into mature, myelinating oligodendrocytes. (B) Signaling pathways involved in OPC maturation: (1) PPARγ enhances the formation of myelin components (*e.g.*, lipid plasmalogen) by increasing ADAPS expression, which in turn promotes OPC process extension. (2) Rapid lipid metabolism results in oxidative stress and lipid peroxidation, but this is counteracted by PPARγ-mediated upregulation of antioxidants such as catalase and Cu/Zn SOD. (3) PPARγ enhances mitochondrial activation by increasing activity of mitochondrial respiratory chain complex IV and upregulating ATP-induced Ca^{2+} oscillations. Abbreviations: neural stem cell (NSC), oligodendrocyte precursor cell (OPC), alkyl-dihydroxyacetone phosphate synthase (ADAPS), superoxide dismutase (SOD), reactive oxygen species (ROS), respiratory chain complex I, II, III, and IV, adenosine 5′-triphosphate (ATP), inositol 1,4,5-trisphosphate (IP3), inositol 1,4,5-trisphosphate receptor (IP_3R).

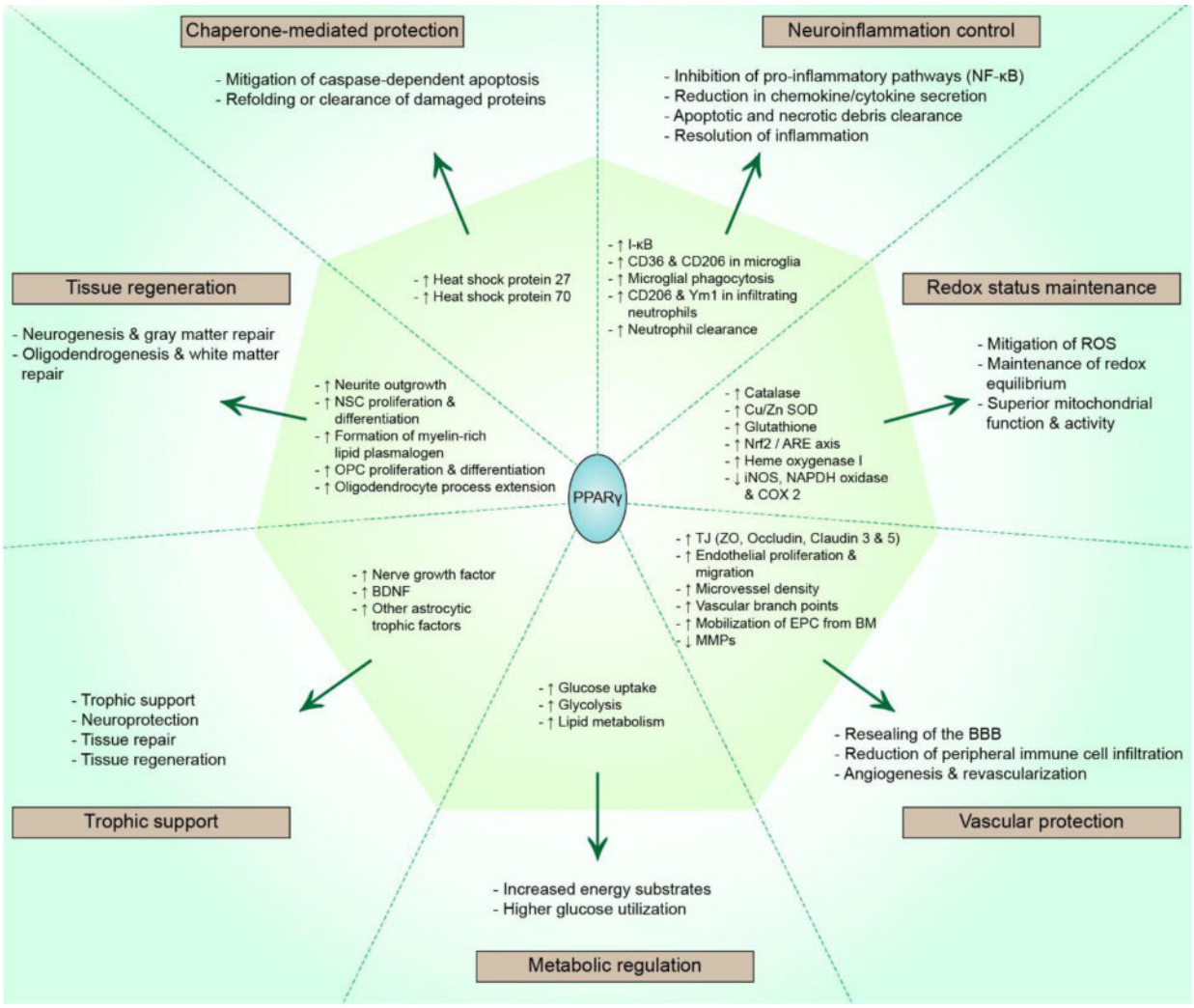

Figure 6.

Potential mechanisms underlying the CNS protective effects of PPARγ. Abbreviations: antioxidant response element (ARE), blood-brain barrier (BBB), bone marrow (BM), brain-derived neurotrophic factor (BDNF), Cu/Zn superoxide dismutase (Cu/Zn SOD), cyclooxygenase 2 (COX-2), endothelial precursor cells (EPCs), inducible nitric oxide synthase (iNOS), inhibitor of kappa B (IκB), insulin-like growth factor (IGF), matrix metalloproteinases (MMPs), neural stem cell (NSC), nicotinamide adenine dinucleotide phosphate (NADPH), nuclear factor (erythroid-derived 2)-like 2 (Nrf2), oligodendrocyte precursor cell (OPC), reactive oxygen species (ROS), tight junction (TJ), zona occludens (ZO).

Table 1

Clinical studies of PPARγ agonists safety and therapeutic effects in ischemic stroke.

Study ID	Reagent	Indication	Patient	Adverse events	Effects	Center	Ref.
	PGZ or RGZ	Functional Independence Measure (FIM) of ischemic stroke	Stroke with T2DM	Not mentioned	PGZ and RGZ significantly improved FIM.	US	(Lee and Reding, 2007)
	PGZ or RGZ	Incidence of stroke	T2DM	Heart failure	RGZ imposed a higher risk of developing stroke or heart failure, PGZ did not influence risk of stroke	China	(Lu *et al.*, 2013)
	PGZ or RGZ	Incidence of stroke	T2DM aged 65 or older	Not mentioned	RGZ increased incidence of stroke.	US	(Graham *et al.*, 2010)
	PGZ or RGZ	Incidence of stroke	T2DM with high risk of cardiovascular diseases	Not mentioned	RGZ increased incidence of stroke.	US	(Shaya *et al.*, 2009)
	PGZ or RGZ	Incidence of stroke	T2DM	Not mentioned	No significant effects	UK	(Azoulay *et al.*, 2010)
	PGZ or RGZ	Incidence of TIA	T2DM	Not mentioned	RGZ increased incidence of TIA	Taiwan	(Hsiao *et al.*, 2009)
	PGZ or RGZ	Incidence of stroke and TIA	DM	Not mentioned	No significant effects	US	(Habib *et al.*, 2009)
	PGZ or RGZ	Incidence of stroke	DM patients aged 65 or older	Congestive heart failure	No significant effects	US	(Winkelmayer *et al.*, 2008)
ISRCTNNCT00174993 (PROactive)	PGZ	Incidenc e of stroke	T2DM	Edema, heart failure, hypoglycemia, bladder tumors, prostate cancer, weight gain	PGZ reduced risk of stroke and recurrent stroke	Multicenter	(Charbonnel *et al.*, 2004; Dormandy *et al.*, 2005; Katzan, 2007; Wilcox *et al.*, 2007; Erdmann *et al.*, 2010; Scheen, 2012; Erdmann *et al.*, 2014; Erdmann *et al.*, 2016)
NCT00091949 (IRIS)	PGZ	Incidence of secondary stroke or TIA	Insulin-resistant, nondiabetic patients with recent ischemic stroke or TIA	Edema, shortness of breath, bone fractures and weight gain	PGZ prevented secondary ischemic stroke and myocardial infarction	Multicenter	(Viscoli *et al.*, 2014; Bath *et al.*, 2016; Inzucchi and Furie, 2016; Kernan *et al.*, 2016)
UMIN000013499	PGZ	Incidence of secondary stroke	Insulin-resistant, nondiabetic patients	Edema, rashes, bladder cancer, cytopenia, heart failure	PGZ reduced incidence of recurrence of stroke	Japan	(Tanaka *et al.*, 2015)

Study ID	Reagent	Indication	Patient	Adverse events	Effects	Center	Ref.
			with recent ischemic stroke or TIA				
	PGZ	Incidence of stroke	T2DM with high risk of cardiovascular diseases	Edema, cancer	No significant effects	Japan	(Yoshii *et al.*, 2014)
	PGZ	Incidence of stroke	T2DM	Bladder cancer and bone fracture	PGZ reduced risk of stroke compared with insulin in T2DM patients	US	(Vallarino *et al.*, 2013)
	RGZ	Incidence of stroke	Metabolic syndrome undergoing percutaneous coronary intervention (PCI)	Not mentioned	RGZ displayed a statistical trend to decrease stroke incidence	Multicenter	(Bhatt *et al.*, 2007)
NCT00379769 (RECORD)	RGZ	Incidence of stroke	T2DM	Heart failure, myocardial infarction, bone fracture	RGZ reduced incidence of stroke	Multicenter	(Home *et al.*, 2009; Nissen and Wolski, 2010; Mahaffey *et al.*, 2013)
NCT00006305 (BARI2D)	RGZ	Incidence of stroke	T2DM and coronary artery disease	Bone fracture	RGZ reduced incidence of stroke	Multicenter	(Bach *et al.*, 2013)
	RGZ	Incidence of stroke	DM patients aged 65 or older	Not mentioned	No significant effects	Quebec	(Vanasse *et al.*, 2009)