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Roles of Peroxisome Proliferator-Activated Receptor-gamma on brain and peripheral inflammation

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Abstract

Peroxisome proliferator-activated receptor-gamma (PPARγ) has been implicated in the pathology of numerous diseases involving diabetes, stroke, cancer or obesity. It is expressed in diverse cell types, including vessels, immune and glial cells, and neurons. PPARγ plays crucial roles in the regulation of cellular differentiation, lipid metabolism, or glucose homeostasis. PPARγ ligands also exert effects on attenuating degenerative processes in the brain, as well as in peripheral systems, and it has been associated with the control of anti-inflammatory mechanisms, oxidative stress, neuronal death, neurogenesis, differentiation, and angiogenesis. This review will highlight key advances in the understanding of the PPARγ-related mechanisms responsible for neuroprotection after brain injuries, both ischemia and traumatic brain injury, and it will also cover the natural and synthetic agonist for PPARγ, angiotensin receptor blockers, and PPARγ antagonists, used in experimental and clinical research. A better understanding of the pleiotropic mechanisms and applications of these drugs to improve the recovery and to repair the acute and chronic induced neuroinflammation after brain injuries will pave the way for more effective therapeutic strategies after brain deficits.

Keywords

brain injury; angiogenesis; agonist; PPAR gamma; inflammation; angiotensin receptor blockers

Introduction

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors that regulate genes essential on various metabolic processes and cell differentiation, but also exert anti-inflammatory properties after brain injury or neurodegenerative diseases (Kapadia et al. 2008; Yonutas and Sullivan 2013). PPARs are members of the nuclear hormone receptor superfamily of ligand-inducible transcription factors that heterodimerize with the retinoid X receptor (RXR), interact with cofactors and act on specific DNA sequences to cause transcriptional activity (Moreno et al. 2004). After interaction with specific ligands, PPARs are translocated to the nucleus, where they change their structure and regulate gene transcription. In addition to transcriptional transactivation, PPARs can

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repress gene transcription by negatively interfering with other transcription factor pathways independent of DNA binding (Abdelrahman et al. 2005). PPARs are transcription factors that belong to the superfamily of nuclear receptors, and the members PPARα (NR1C1), PPAR*β/δ* (NR1C2), and PPARγ (NR1C3) represent the family of PPARs (Ehrmann et al. 2002). They are expressed in different tissues and have central roles in the homeostasis and energy metabolism, regulating energy storage. PPAR-α is expressed highly in the liver, plays a role in fatty acids oxidation, which provides energy for peripheral tissues, lipoprotein metabolism, and has also a potential role in oxidant/antioxidant pathway. PPAR-δ/β promotes fatty acids metabolism and suppresses macrophage-derived inflammation. PPARγ is highly expressed in adipose tissue, where it is a regulator of adipogenesis, lipid metabolism and insulin sensitivity (Tontonoz and Spiegelman 2008). Also, PPARγ activation plays a crucial role in the regulation of proliferation, metabolism, differentiation, development, and inflammatory responses of the central nervous system (CNS) (Gurley et al. 2008), in this way PPARγ agonists have significant therapeutic potential in brain disorders.

The present review mainly discusses the effective neuroprotective role of PPARγ activation in the peripheral and brain inflammation, and the significant role for PPARγ agonist and antagonist in the regulation of neuroinflammatory processes following brain injuries. Also, its role in apoptosis, neurogenesis, differentiation, and angiogenesis that are triggered as consequence of brain damage.

Role of PPARγ in brain inflammation

In the peripheral organs as well as in the CNS, the regulation of inflammatory processes conduces to the reduction of the brain damage and improvement of motor and cognitive outcome. The mediators responsible for this process are the resident microglia and infiltrated inflammatory cells originating from the blood (Morganti-Kossmann et al. 2007; Woodcock and Morganti-Kossmann 2013). Effects on inflammation are regulated through mechanistic signaling pathways where multiples factors interfere and can be modulated by PPARs. The expression of PPARs was analyzed by immunohistochemistry and *in situ* hybridization in several rodent tissues, including the CNS. PPARγ is present in most cell types, vessels, neurons, and astrocytes (Figure 1), where it mediates multimodal function, whereas oligodendrocytes exclusively show PPAR-*β/δ* expression (Giannini et al. 2004; Moreno et al. 2004). PPARγ is also expressed in various immune related cell types, particularly in adipocytes, macrophages, dendritic cells, and microglia (Yuan et al. 2015). PPARγ regulates the alternative activation of immune cells by increasing anti-inflammatory related gene expression (Bouhlel et al. 2007), and down-regulation of pro-inflammatory mediators through their action on activated microglia/macrophages (Kapadia et al. 2008). PPARγ-mediated CD36 upregulation has been involved in the modulation of microglia activation and phenotype, promoting phagocytosis of apoptotic cells and thus contributing to the resolution of inflammation after ischemia (Ballesteros et al. 2014). Also, PPARγ has the ability mainly to inhibit transcription factors, such as the transcription factors activator protein-1, Stat 1 and nuclear factor-kB (NF–κB) (Ricote et al. 1998). PPARγ also mediates down-regulation of pro-inflammatory genes such as cyclooxygenase-2 (COX-2), metalloproteinase-9 (MMP-9), scavenger receptor A, inducible nitric oxide synthase (iNOS),

as well as the production of pro-inflammatory cytokines, chemokines and interleukins (Heneka et al. 2000; Kapadia et al. 2008; Lenglet et al. 2013) (Figure 2). Thus, reducing PPARγ activation may contribute to the chronic inflammation. PPARγ agonists may modulate expression of inflammatory genes through PPARγ-independent mechanisms, as was demonstrated in PPARγ-null embryonic stem cells (Chawla et al. 2001; Moore et al. 2001). The convenience of PPARγ agonists as a tool for down-regulation of brain inflammation that occurs after brain damage is an important area to be developed in the future.

Role of PPARγ in Peripheral Organs

In addition to the CNS, PPARγ activation also occurs in the peripheral organs. PPARγ is predominantly detected in adipose tissue, liver, and intestine, regulating adipocyte differentiation and promotes lipid storage (Akiyama et al. 2005; Berger et al. 2005). Macrophages polarization switch was associated with the interaction between PPARγ and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signal pathway, and it was demonstrated that this disruption of PPARγ impaired alternative M2 macrophage activation/Kupffer cell polarization in a nonalcoholic fatty liver disease (Luo et al. 2017). PPARγ protein increases insulin sensitivity and decreases insulin resistance in adipose tissue, skeletal muscle, and liver (Heald and Cawthorne 2011; Hegarty et al. 2004; Lee et al. 2016; Odegaard et al. 2007; Wang et al. 2009). In the vascular system, PPARγ confers anti-atherosclerotic effects (Blaschke et al. 2006a; Blaschke et al. 2006b). PPARγ antagonizes the metabolic syndrome by downregulating peripheral inflammatory processes, including the suppression of pro-inflammatory cytokines and adhesion molecules (Delerive et al. 2001). Besides, PPARγ activation is considered necessary for inhibiting an intestinal inflammatory response and defending cells oxidative damage (Serra et al. 2016). Recently, it was demonstrated how a novel PPARγ modulator, GED-0507-34, ameliorated intestinal fibrosis in a model of chronic colitis in mice and regulated the major profibrotic cellular and molecular mechanisms (Speca et al. 2016). Recently studies have highlighted the PPARγ signaling association to the microbiota, a low grade of inflammation and host metabolism (Sohn et al. 2015; Wang et al. 2016). However, microbiota-induced PPARγ has also a role beyond the gut (Angelakis et al. 2012; Couvigny et al. 2015; Karrout et al. 2015; Peyrin-Biroulet et al. 2010).

Role of PPARγ on oxidative stress and neuronal survival

The brain damage caused by oxidative stress induces a high rate of oxidative metabolic activity, and relatively low antioxidant capacity and insufficient neuronal cell repair activity. Overproduction of reactive oxygen species (ROS) results in oxidative damage, including lipid peroxidation, and DNA damage, which can lead to cell death (Lozano et al. 2015). Several PPARγ agonists have been shown to exert protective activity against oxidative damage, mitochondrial dysfunction, and apoptosis protecting neurons and glial cells in various animal models. Activation of PPARγ induces expression of antioxidant catalase and copper/zinc superoxide dismutase (SOD), two enzymes capable of alleviating oxidative stress, and inhibiting NADPH oxidase (Dunning et al. 2013; Eslami et al. 2014; Zarzuelo et al. 2013). The PPARγ antagonist GW9662, blocked the increase of PPARγ DNA binding

activity and antioxidant enzymatic activities (SOD and CAT) abolishing the protection of PPARγ activation in OGD-exposed neurons (Zeng et al. 2012). Other mechanisms by which these PPARγ agonists prevent oxidative stress include a decrease in iNOS activity, NFκB blockade, inhibition of TNF-α release, or activation of nuclear factor (erythroid-derived 2)-like 2 (Nrf2) (Heneka and Landreth 2007; Park et al. 2004) (Figure 2).

The role of PPARγ in neurogenesis and differentiation

Neuronal stem cell (NSC) and progenitors following brain injury are thought to proliferate, migrate to and differentiate at injury sites, affecting variable degrees of structural and functional recovery. Endogenous stem cells and stem cell transplant therapy supported by their local vasculature, are promising for new therapeutic strategies in the chronic neuroinflammatory environment that accompany brain damage, stroke or other neurodegenerative diseases (Ormerod et al. 2013; Prakash and Kumar 2014; Qi et al. 2010). PPARγ is essential in regulating the early brain development and post-injury brain repair (Eriksson et al. 1998). PPARγ activation promotes neurite outgrowth in mature neurons significantly contributing to a proper neuronal connectivity in neuronal networks (Miglio et al. 2009). Also, it has been demonstrated that PPARγ-mediated pathways can be involved in the proliferation and differentiation of NSCs (Cimini and Ceru 2008; Wada et al. 2006). PPARγ activation by PPARγ agonists stimulated NSC proliferation and inhibited differentiation into neurons, furthermore abundant activation of PPARγ with higher levels of agonists resulted in cell death (Wada et al. 2006). Oligodendrocytes are required for myelin formation and maintenance (Griggs et al. 2017). PPARγ has a role in the differentiation and function of oligodendrocytes (Roth et al. 2003), being these effects blocked by the PPARγ antagonist GW9662 (Wan Ibrahim et al. 2013). It was demonstrated that GW9662 could also inhibit the differentiation towards neurons and astrocytes induced by pioglitazone and rosiglitazone in neurospheres from adult rat brains (Morales-Garcia et al. 2011). A transient immune response stimulated by lipopolysaccharide (LPS) compromised hippocampal neurogenesis and impaired hippocampus-dependent spatial memory, and PPARγ agonist activity protects neurogenesis and memory from the effects of LPS-produced transient illness (Ormerod et al. 2013). The blockade of PPARγ was able to significantly straight cannabidiol effects on reactive gliosis and subsequently on neuronal damage. Moreover, cannabidiol -mediated activation of PPARγ is associated with a significant neurogenic activity in the granule cell layer of the hippocampus (Esposito et al. 2011).

Role of PPARγ in angiogenesis

Angiogenesis is the formation of new blood vessels around the injured brain restoring the damaged regions and inducing neurovascular repair (Arai et al. 2009). PPARγ activation increases vascular endothelial growth factor (VEGF) expression in human vascular smooth muscle cells (Yamakawa et al. 2000). PPARγ coactivator, (PGC)-1α, is a transcriptional co-activator that powerfully regulates oxidative and mitochondrial metabolism, but also angiogenesis activities in the brain. (PGC)-1α is a known regulator of VEGF gene transcription (Arany et al. 2008), and it was found elevated in the cortex during the chronic hypoxic exposure (Ndubuizu et al. 2010).

Rosiglitazone was found that induce the endothelial cells proliferation, endothelial NOS expression benefiting angiogenesis, preserving the cerebral blood flow and limiting of neurological loss and functional recovery (Chu et al. 2006). By another hand, resveratrol was attributed to its role as an intracellular antioxidant, an anti-inflammatory agent, its ability to induce sirtuin 1 (SIRT1) activity, NOS expression and angiogenesis (Annabi et al. 2012). It was also demonstrated how resveratrol, exerts pharmacological preconditioning by activating (PGC)-1α, reducing the extent of ischemia/reperfusion injury (Tan et al. 2008) (Figure 2). Treatment with PPARγ agonists exerts direct protective action on cerebral glucose and glutamate metabolism, disrupting the regulation of neuronal glucose transporter (GLUT-3) expression and glial glutamate transporter EAAT-2 (Garcia-Bueno et al. 2007).

Natural or physiological PPARγ agonists

Fatty acids are natural modulators of PPARγ; however, their connection with the receptor does not always lead to PPARγ activation and target gene transcription. A physiological PPARγ agonist is the 15-Deoxy-Delta12,14-prostaglandin J_2 ($15dPGJ_2$), a reactive membrane lipid metabolite and anti-inflammatory downstream product of prostaglandin D_2. (Kimura et al. 2008). In basal conditions, physiological PGJ_2 closes a negative feedback loop on COX-2, whereas, in stress conditions, COX-2 is activated by enhanced levels of PGJ_2 (Behl et al. 2016; Liu et al. 2012; Napimoga et al. 2013). Thus, PGJ2's anti-inflammatory effect is more potent in stressful conditions due to induction of endogenous PGJ_2 production, when is combined with exogenous $15dPGJ_2$ (Mouihate et al. 2004).

Pharmacological agonists for PPARγ: Thiazolidinediones

PPARγ agonists have been demonstrated to show a benefit in multiple CNS injury models including spinal cord injury (SCI) (Park et al. 2007), TBI (Yi et al. 2008), and stroke (Collino et al. 2008). PPARγ agonist have been reported to be protective after experimental brain trauma in rodents, reduction mitochondrial dysfunction, cognitive impairment, tissue loss and inflammation (Sauerbeck et al. 2011b; Yi et al. 2008). PPARγ possesses a high number of pharmacological or synthetic high-affinity ligands as thiazolidinediones (TZDs), which include troglitazone, rosiglitazone, pioglitazone, and ciglitazone (White and Murphy 2010). The kinetics of intraperitoneal TZDs are unknown. However, the haft-life of oral TZDs is 4 to 9 hours (Chapelsky et al. 2003) and so it is plausible that they are present during the alteration of PPARγ activation and expression after brain injury. The TZDs have the capacity to reduce the expression of proteins that contribute to the inflammatory damage observed in after brain injuries (Arai et al. 2009; Culman et al. 2007), such as the pro-inflammatory cytokine TNF-α and iNOS, gelatinase B (MMP-9) and COX-2 in LPS-stimulated macrophages, glial cells and neurons (Heneka and Landreth 2007) (Figure 2). It was also found that PPARγ agonist attenuates ischemia-induced activation of microglia and neutrophil infiltration in mice (Tureyen et al. 2007). *Troglitazone* was the first drug approved by the Food and Drug Administration (FDA) for clinical use, followed by *rosiglitazone* and *pioglitazone* (Sood et al. 2000). They were introduced on the market in the early 1990s, and are currently in clinical use to regulate the blood glucose levels in patients with type II diabetes. PPARγ activation enhances the expression of proteins involved in glucose and lipid metabolism, improving insulin resistance by mitigating the effect of TNF-α in

adipocytes (Tyagi et al. 2011). Besides decreasing insulin resistance, TZDs positively affect the vasculature, reducing the high blood pressure and its associated risks, such as atherosclerosis, cardiovascular diseases, and stroke. It was demonstrated that *Pioglitazone* mitigates the severity of radiation-induced cognitive impairment in a well-characterized rat model (Zhao et al. 2007). It also attenuates dopaminergic cell death in a Parkinson's disease model (Breidert et al. 2002), induces upregulation of SOD (Shimazu et al. 2005), COX-2 and TNF-α expression (Zhao et al. 2006) and microglia and macrophage activation (Zhao et al. 2005) in a rat model of stroke, and reduces lesion volume and cerebral inflammation in a murine model of TBI (Thal et al. 2011). A single dose of *Pioglitazone* administered early following lateral fluid percussion injury (LFPI), decreased the cortical lipid and protein oxidative damage, edema, increased the GSH-Px activity, and reduced microglial activation (Pilipovic et al. 2015). *Troglitazone* reduces cell death in cultured cerebellar granule neurons following glutamate exposure, suggesting that it interferes with downstream consequences of glutamate activation (Uryu et al. 2002), and cell death in rat cerebellum exposed to bacterial LPS and interferon-γ (Heneka et al. 2000). Another PPARγ agonist, *rosiglitazone*, has been studied after cerebral ischemia in rats. Rosiglitazone induced brain repair promoting white matter restoration (Han et al. 2015), and found to decrease secondary neuronal damage, gliosis, myelin loss, and neuropathic pain in animal models of SCI while improving motor function recovery (Li et al. 2013; Zhang et al. 2010). It was also found to reduce neuroinflammation, inhibit pro-apoptotic caspase-3, and attenuate both intercellular adhesion molecule 1 (ICAM-1), myeloperoxidase (MPO) activity, and cytokine expression in mouse models of transient cerebral ischemia (Collino et al. 2006; Luo et al. 2006; Sundararajan et al. 2005; Victor et al. 2006a). *Rosiglitazone* has also been shown to interfere with NF-κB activation in an experimental model of autoimmune encephalomyelitis (Iruretagoyena et al. 2006).

Furthermore, two non-thiazolidinedione PPARγ agonists, L-796 and *L-449*, have been shown to decrease middle cerebral artery occlusion (MCAO)-induced infarct size, inhibits NF-κB signaling and improves neurological scores (Pereira et al. 2005). GW1929 treatment ameliorated cognitive deficits, cerebral ischemic-reperfusion, and hippocampal neuronal damage (Kaundal and Sharma 2011a; Kaundal and Sharma 2011b).

PPARγ agonist activity of Angiotensin Receptors blockers

Angiotensin II type 1 (AT1R) receptor blockers (ARBs) have selective PPARγ agonist activity in the stress response to injury (Pang et al. 2012a; Pang et al. 2012b). The net result of the AT1R blockade and PPARγ activation is to improve energy balance and blood flow to the brain with relevant neuroprotective properties after brain injuries (Villapol and Saavedra 2015). ARBs improve stroke outcome, at least in part, through activation PPARγ and blockade of the AT1R in cerebral ischemia models (Jung et al. 2007; Schmerbach et al. 2008). Candesartan and telmisartan are ARBs that induce activation of PPARγ and were studied in ischemic animal models showing neuroprotective features (Schmerbach et al. 2008; Zeng et al. 2013). Telmisartan was demonstrated that suppresses brain injury following ischemia and improves outcome, at least in part, through activation of PPARγ (Kasahara et al. 2010). We have previously demonstrated that candesartan treatment reduced lesion volume, apoptosis and microglia activation, improving performance in the motor and

learning and memory behavior test in a mouse model of traumatic brain injury (TBI) (Villapol et al. 2012), and both drugs, candesartan and telmisartan, decreased lesion volume, apoptosis, gliosis and protected cerebral blood flow after TBI (Villapol et al. 2015). However, we have demonstrated the neurorestorative effects of both ARBs with dual AT1R blocking and PPARγ activation (Figure 3) (Villapol et al. 2015).

PPAR antagonists

PPAR antagonists were used in animal models of brain injury to test whether neuroprotection after damage is mediated by PPARγ activation (Victor et al. 2006b). This widely used pharmacologic antagonist has been shown to bind covalently to the Cys^{313} residue of PPARγ and induce conformational changes that block the recruitment of transcriptional cofactors to the PPARγ/RXR heterodimer (Lee et al. 2002). Contrarily to PPARγ agonist by TZDs, the PPARγ blockage increases lesion size after ischemia. PPARγ antagonist, GW9662, reduces the protective effects of LPS preconditioning against organ damage caused by endotoxemia or ischemia/reperfusion (Collin et al. 2006; Sivarajah et al. 2005). Other studies have shown how a novel PPARγ antagonist, T0070907, blocks and promotes recruitment of nuclear receptor corepressors to PPARγ (Lee et al. 2002). T0070907 is highly specific for PPARγ having an 800-fold preference for PPARγ, over PPARα and PPARδ (Lee et al. 2002). The beneficial neuroprotective effects of telmisartan were reduced by concomitant administration of GW9662, a PPARγ antagonist on ischemia/reperfusion injury (Kasahara et al. 2010), suggesting that PPARγ activation may contribute to part (or all) of the neuroprotective effects of candesartan or telmisartan after TBI (Villapol et al. 2015; Villapol et al. 2012) (Figure 3). In agreement with our studies, PPARγ agonist rosiglitazone reduced infarction volume around 75% in an MCAO rodent model and its protection was completely lost when T0070907 was given along with rosiglitazone (Sobrado et al. 2009).

PPARγ activation after brain injury

Brain damage also induces detrimental secondary damage and neuroinflammatory response (Aronowski and Zhao 2011). There are multiple implicated pathways for inducing central or peripheral inflammation. Neuroprotection merely reduces cell death or lesion volume after brain injury. However, neurorestorative approaches can promote endogenous neurogenesis, axonal sprouting, synaptogenesis, oligodendrogenesis or angiogenesis, which enhance neuroplasticity and improve repair and functional recovery (Xiong et al. 2009). PPARγ agonists confer neuroprotection on the injured brain and PPARγ antagonists reverse the PPARγ activation effects in animal models of ischemia or TBI (Figure 4). PPARγ presents lower levels of expression in the normal adult brain, limited to the hippocampal dentate gyrus, thalamus, basal ganglia, the piriform cortex, and expression in the rat cerebral frontal cortex, mainly in the neurons of layer II (Moreno et al. 2004). Also, PPARγ is expressed in microglia and astrocytes, both important cell types involved in the neuroinflammatory activity in neurological diseases and brain damage (Bernardo and Minghetti 2006; Bernardo and Minghetti 2008). PPARγ activation can simultaneously weaken or reprogram the immune response, death of neurons and glia following CNS injury (Mandrekar-Colucci et al. 2013). Reduction of lesion volume might be associated with anti-inflammatory activities

related to PPARγ agonist activity of TZDs in the ischemic region and improve neurological function (Sundararajan et al. 2005; Zhao et al. 2005). Recent studies indicate that PPARγ agonists attenuate ischemia-induced activation of microglia, expression of ICAM-1 and neutrophil infiltration in C57BL/6mice (Luo et al. 2014; Tureyen et al. 2007). However, PPARγ is also implicated in the differentiation of monocytes to macrophages in the periphery, and PPARγ agonist can inhibit the expression of iNOS, TNF-α, and IL-1β from macrophages (Ricote et al. 1998). The PPARγ antagonist increased infarction size in the absence of exogenous agonist, suggesting that even the low level of PPARγ activation that occurs during ischemia is protective. There are several studies in murine brain ischemia, which showed neuroprotective effects of pioglitazone in transient focal ischemia (Tureyen et al. 2007; Victor et al. 2006a) and brain trauma (Sauerbeck et al. 2011b). However, PPARγ activation and expression increased following brain damage and when the inflammatory response is developing. Mainly, pioglitazone was showing protection of mitochondrial function, reducing inflammation and cortical lesion, and improving cognitive function following TBI (Sauerbeck et al. 2011b). Furthermore, the natural agonist $15dPGJ_2$ decreases the neurological deficits after experimental intracerebral hemorrhage. Both pioglitazone and rosiglitazone share similar protective efficacy after cerebral damage, and both were described that decrease the infarct volume and improve functional recovery from stroke in rats (Sundararajan et al. 2005; Sundararajan and Landreth 2004). However, pioglitazone passes through the blood-brain barrier (BBB), while rosiglitazone is known not to penetrate the BBB (Gemma et al. 2004; Maeshiba et al. 1997). Pioglitazone and troglitazone reduced the release of ROS, disrupting the BBB, microglia activation, damaging endothelial cells, and enhancing leukocyte infiltration (Culman et al. 2007; Ji et al. 2009; Lee et al. 2015; Sauerbeck et al. 2011a; Thal and Neuhaus 2014). Moreover, treatment with PPARγ agonists, either rosiglitazone or pioglitazone significantly reduced oxidative stress, COX-2 protein expression and activation of p38 and p42/44 mitogen-activated protein kinases (MAPKs) and NF-κB, in a rat model of ischemia/reperfusion injury by inhibiting oxidative stress and excessive inflammatory response (Collino et al. 2006).

Conclusion

Brain damage is associated with secondary injury, oxidative stress, and inflammation, generating neurodegeneration and neuropathology (Nizamutdinov and Shapiro 2017). These phenomena could be prevented, mitigated or treated by a combination of therapeutic approaches that involve a neurorestorative process. However, brain injuries have no effective treatment at the present. For this reason, development of effective treatments for brain injuries is a pressing medical necessity. Current therapies, designed to target single pathogenic mechanisms, or on a singular cell type, have not been effective and are likely to fail in clinical trials. PPARγ agonist activity acts as a powerful agent for inducing antioxidant/anti-inflammatory mediated pathways (Mandrekar-Colucci et al. 2013). This beneficial proprieties of PPARγ agonist has the potential for rapid transfer to clinical therapies for brain injuries and peripheral organs damaged. There is a strong rationale to consider novel neuroprotective treatments using pleiotropic drugs that target several neuropathologies. In conclusion, it is essential we continue to search for novel neuroprotective and neurorestorative treatments for brain injuries with high clinical impact;

the pleiotropic effects of PPARγ activation are a promising efficacious candidate. Given the findings presented in this review, the field should continue to focus on elucidating novel targets and therapies that directly, or indirectly, can restore the damaged brain.

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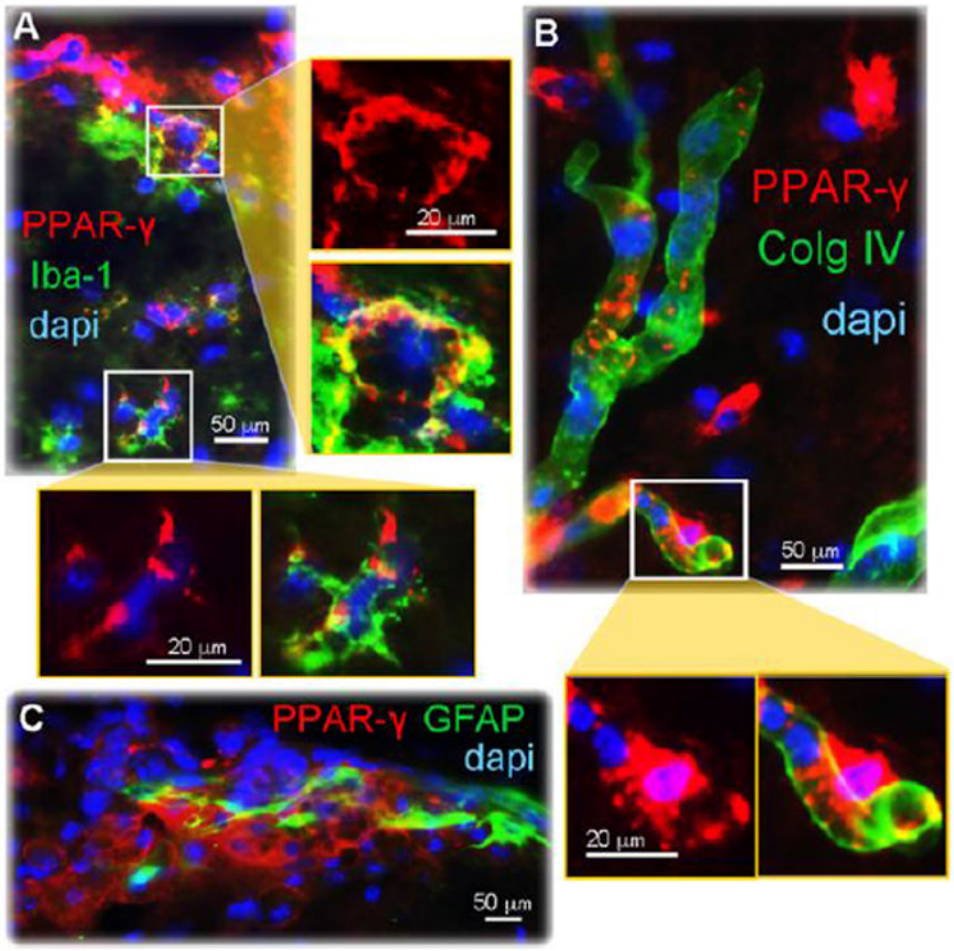

Figure 1. PPARγ expression in different cell types

A. Microglia/macrophages cells (Iba-1, green) express PPARγ (red) at the border of the lesion after brain injury in vacuolated cells with amoeboid morphology (high magnification images in A, right side) or hypertrophy microglia morphology (high magnification images in A, bottom side). B. Blood vessels in the injured brain (Collagen IV (Colg IV), green) express PPARγ (red). A few PPARγ positive cell are extending processes around and along a capillary (green) in the cortex of a mouse (high magnification images in B). C. Astrocytes (GFAP, green) collate around PPARγ positive cells (red) in the injured cortex, with a little co-localization with PPARγ. Nuclei (dapi, blue).

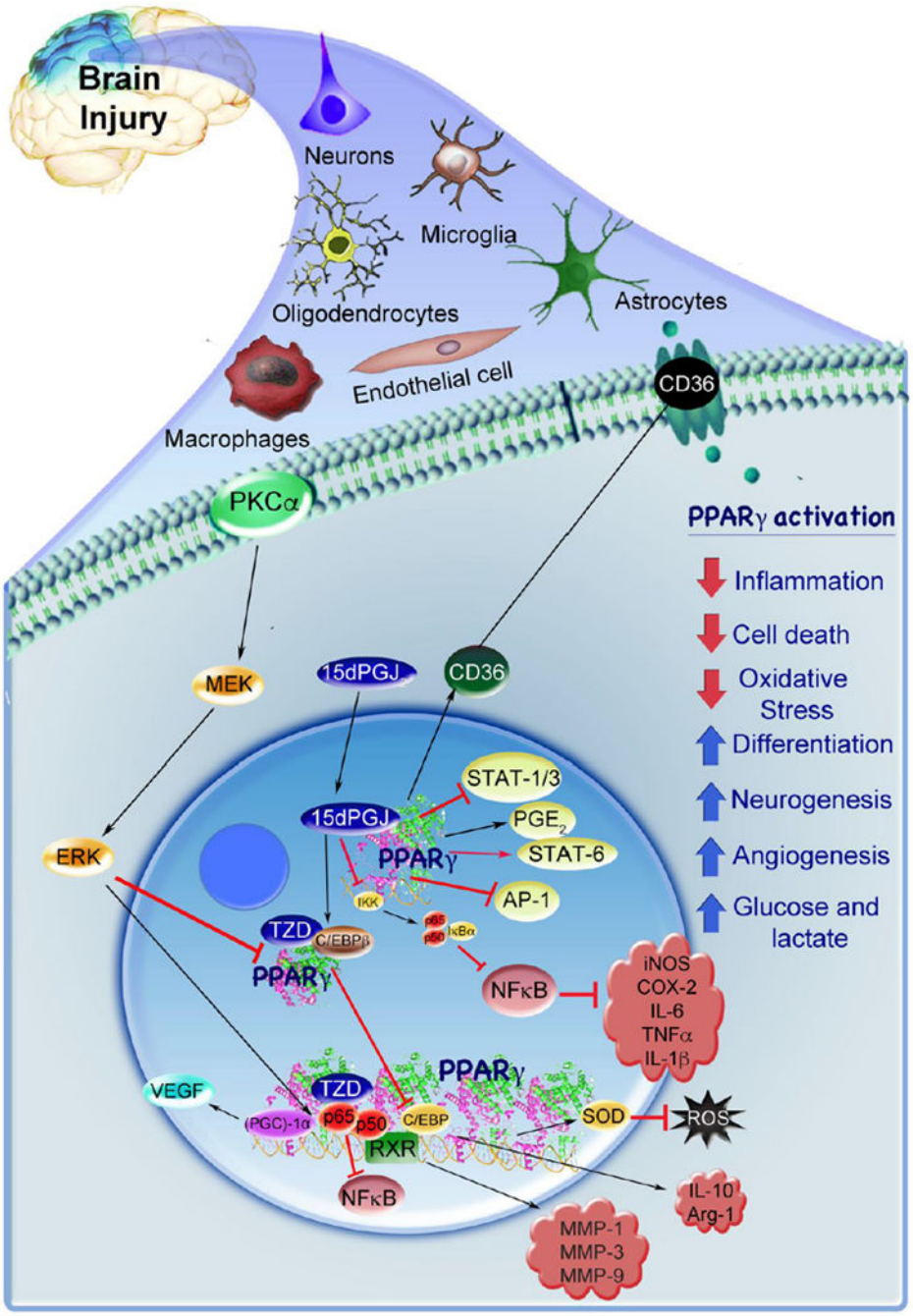

Figure 2. Schematic representation of the PPARγ signaling in nervous cells in the injured brain

PPARγ acts as an anti-inflammatory factor, pro-differentiating transcription factor, and anti-oxidant after brain injury. PPARγ activation also induces angiogenesis and glucose and lactate production in astrocytes. PPARγ ligands are known to inhibit or repress the activity of a number of transcription factors important in neuroinflammation. PPARγ also binds RXR and actives target gene expression through the recruitment of coactivators (PGC)-1a. PPARγ interacts with transcription factors such NF-κB, Stat-1/-3/-6 or C/EBP, and represses their target genes transcription. A variety of endogenous ($15dPGJ_2$) and exogenous

(Thiazolidinediones (TDZs)) compounds, as, have been identified as PPARγ ligands. $15dPGJ_2$ promotes direct binding of PPARγ to Stat-3, and TDZ induces repression of target genes, preventing transactivation of pro-inflammatory cytokines in a PPARγ-dependent manner.

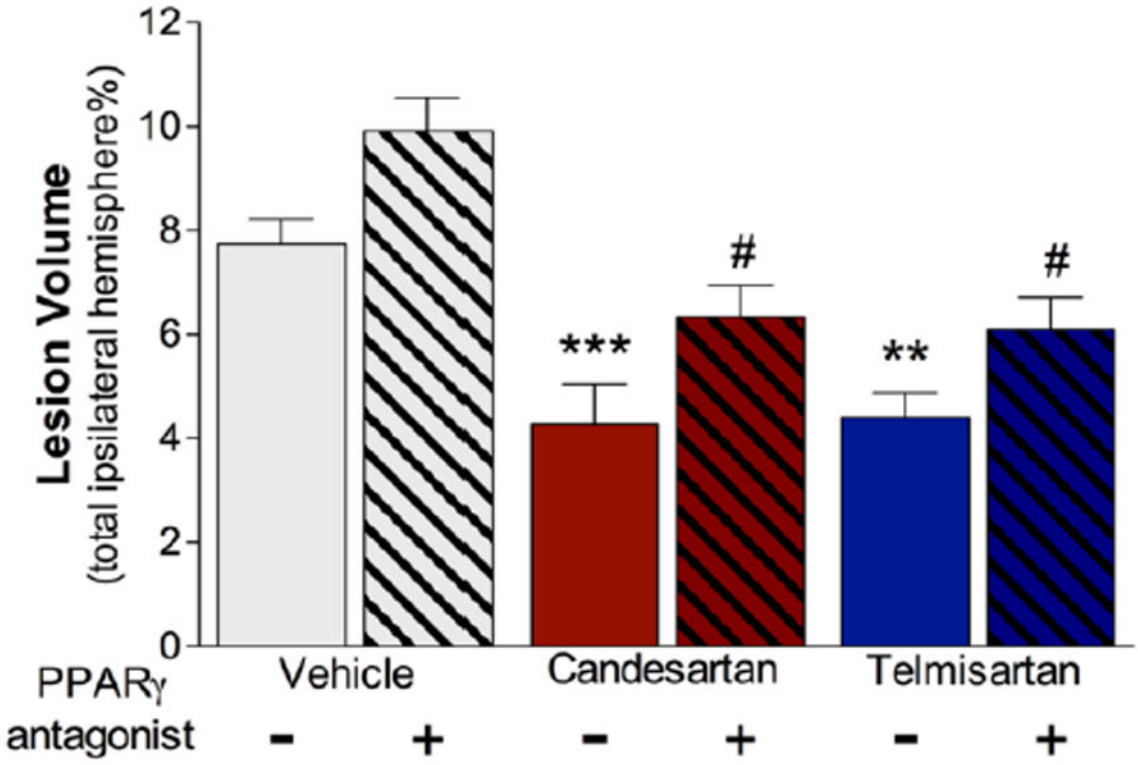

Figure 3. Angiotensin II receptor blockers effectiveness after brain injury is partially dependent on PPARγ activation

Effects on lesion volume at 3-days after traumatic brain injury, candesartan (0.1 mg/Kg) and telmisartan (1 mg/Kg) treatment, significantly reduced the lesion volume, and PPARγ antagonist (T0070907, 2 mg/Kg) administration alone, or combined with candesartan or telmisartan, reverses this effect. Data are mean±SEM, n= 8–15. ***P<0.001, **P<0.01 candesartan or telmisartan versus vehicle; #P<0.05 groups versus PPARγ antagonist. Adapted from (Villapol et al. 2015; Villapol et al. 2012).

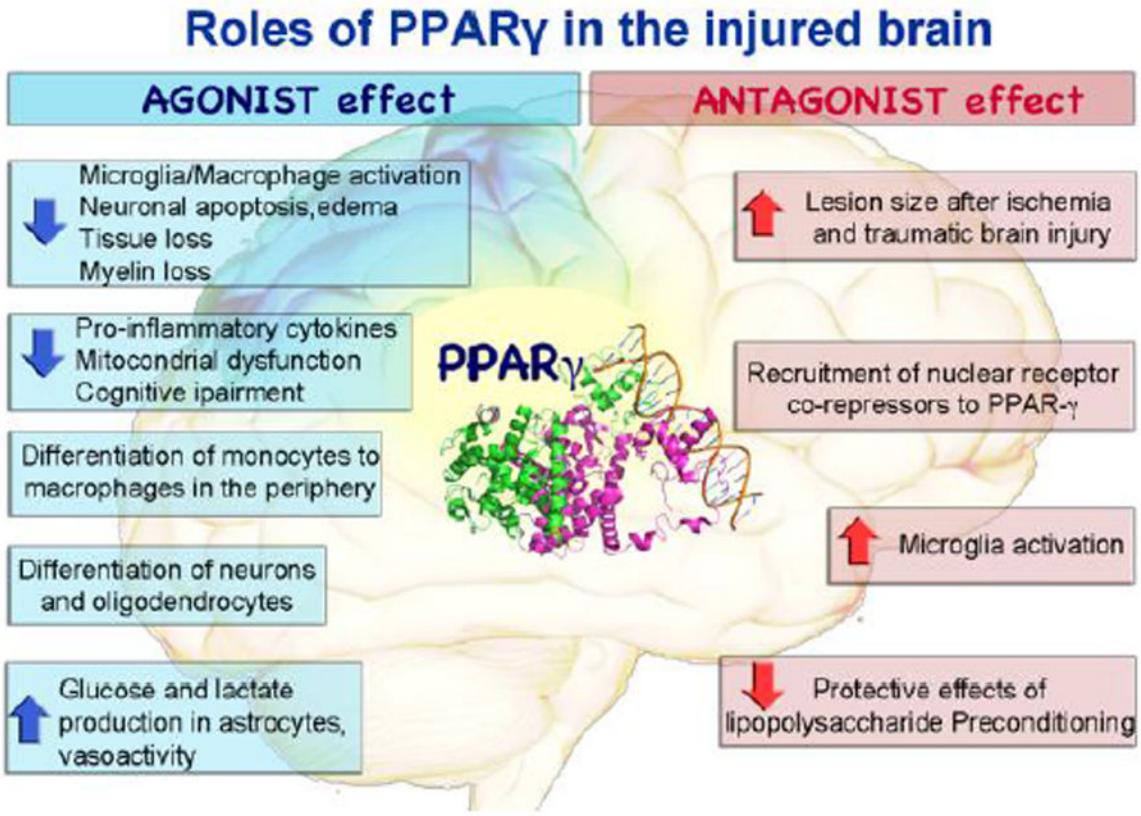

Figure 4. Multiple roles of PPARγ agonist and antagonist effects in the injured brain

PPARγ agonists confer neuroprotection on the injured brain at several operational levels, such as at the anti-inflammatory response, differentiation, or stabilization of vascular processes levels. PPARγ antagonists reverse the PPARγ activation effects such as increasing lesion volume or neuroinflammation in animal models of ischemia or traumatic brain injury.