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REVIEW

Peroxisome Proliferator-Activated Receptor-Gamma (PPAR-ɣ): Molecular Effects and Its Importance as a Novel Therapeutic Target for Cerebral Ischemic Injury

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Abstract
Cerebral ischemic injury is a leading cause of death and long-term disability throughout the world. Peroxisome proliferator-activated receptor gamma (PPAR-ɣ) is a ligand-activated nuclear transcription factor that is a member of the PPAR family. PPAR-ɣ has been shown in several in vitro and in vivo models to prevent post-ischemic inflammation and neuronal damage by negatively controlling the expression of genes modulated by cerebral ischemic injury, indicating a neuroprotective effect during cerebral ischemic injury. A extensive literature review of PubMed, Medline, Bentham, Scopus, and EMBASE (Elsevier) databases was carried out to understand the nature of the extensive work done on the mechanistic role of Peroxisome proliferator activated receptor gamma and its modulation in Cerebral ischemic injury. PPAR-ɣ can interact with specific DNA response elements to control gene transcription and expression when triggered by its ligand. It regulates lipid metabolism, improves insulin sensitivity, modulates antitumor mechanisms, reduces oxidative stress, and inhibits inflammation. This review article provides insights on the current state of research into the neuroprotective effects of PPAR-ɣ in cerebral ischemic injury, as well as the cellular and molecular mechanisms by which these effects are modulated, such as inhibition of inflammation, reduction of oxidative stress, suppression of pro-apoptotic production, modulation of transcription factors, and restoration of injured tissue through neurogenesis and angiogenesis.

Keywords Peroxisome proliferator activated receptor gamma · Cerebral ischemic injury · Neuroinflammation · Insulin · Neurogenesis · Angiogenesis

Introduction

Cerebral Ischemic Injury

Cerebral ischemia, also known as cerebrovascular ischemia or Brain ischemia, is a condition that occurs when the flow of blood to the brain is insufficient to meet its metabolic demands, resulting in limited oxygen supply, causing cell death, cerebral infarction, or ischemic stroke [1]. Cerebral ischemia is divided into few different types like stroke ischemia (when blood vessels are blocked usually by a blood clot/thrombus, a sudden spasm of an artery) [2] or embolic (when thrombus/ embolus that forms in an artery and then lodges in a narrower brain artery) [1]. Stroke also can be an ischemic stroke (interruption of blood supply to the brain via vascular thrombus in middle cerebral artery) [3] or hemorrhagic stroke (when a weakened blood vessel ruptures, causing bleeding in the brain) [4]. About 24% to 46% of acute ischemic stroke is due to large vessel occlusion (LVO) [3]. Untreated hypertension and aging blood vessels have been identified as significant risk factors for hemorrhagic stroke, with hypertensive patients ten times more likely to develop a hemorrhagic stroke than normotensive patients [5]. Another type of ischemia is the Transient Ischemic Attack (TIA), associated with neurological dysfunction, which can be characterized by a temporary interference of cerebral blood flow (CBF), which results from atherosclerotic plaques or thrombus damaging inner walls of brain vasculature [6]. This form of ischemia occurs from minutes to hours which is concluded as the acute nature of the ischemia. Thus, TIA

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does not constitute any permanent brain damage, though it can warn for future stroke. According to the brain regions, we have focal ischemia, which is restricted to a small part of the brain and usually results from a thrombus or embolus occluding a cerebral artery. And global Ischemia, which is a non-stroke ischemia type related to hypoperfusion, results in synaptic and cognitive dysfunction when cardiac arrest, shock, severe hypotension, asphyxia like life-threatening medical condition occurs resulting in insufficient blood supply throughout the entire brain to cause neuronal cell death in the vulnerable CA1 region of the hippocampus and cortex [7].

As the brain is one of the highest energy-consuming organs, and due to stroke initiation, hypoxia-like state and lack of nutrient supply can provoke various neurological disorders. In cerebral ischemic injury, patients suffer from the abrupt onset of hemiparesis or monoparesis, hemisensory and visual deficits, dysarthria, ataxia, nystagmus, and aphasia like neurological deficits [1]. Stroke is one of the foremost causes of death, with a mortality rate of 30% and adult disability in industrialized countries [8]. A lack of effective therapies caused the underestimation of stroke patients. Only a few hospitalized patients will benefit from thrombolytic treatment due to the limited therapeutic window (up to three hours after the onset of symptoms). Furthermore, in the event of an acute ischemic stroke caused by LVO, thrombectomy is the sole treatment available and has benefit effects (therapeutic window up to 6 h from stroke onset and a much later time therapeutic window up to 24 h).

Additionally, several neuroprotective agents that demonstrated promising results in preclinical studies that failed in clinical trials had severe adverse effects or exacerbated stroke outcomes. As a result of the paradox of preclinical success and clinical failure, the quest for new applications for already-approved drugs continues. Recent preclinical and clinical evidence strongly suggests that ligands for the peroxisome proliferator-activated receptor (PPAR-ɣ) confer neuroprotection and enhance neurological function following cerebral ischemic injury.

Peroxisome Proliferator-Activated Receptor-Gamma (PPAR-ɣ)

PPARs are ligand-activated transcription factor proteins belonging to the superfamily of nuclear hormone factors [9]. PPAR exists in three isoforms (α, ɣ, and δ/β), each with its natural agonist. As ligands bind to PPAR, a heterodimeric complex forms, allowing other coactivators, such as PPAR coactivator-1 and -2, PPAR-binding protein, PPAR-interacting protein, CREB binding protein, and steroid receptor coactivator-1 to be recruited. The formed complex then binds to the promoter regions of specific genes that contain a regulatory element called the peroxisome proliferator response element (PPRE; AGG TCA-AGGTCA repeats), activating or transrepressing the target genes [10]. The coactivator binding criterion is met when a specific agonist binds to PPAR. Without a ligand, the PPAR-ɣ: RXR complex can recruit corepressor complexes and PPRE, effectively suppressing target gene transcription. Thus, from this, we can conclude that PPARs have control over the gene expression positively as well as negatively.

Structure of PPAR

PPAR-ɣ, similar to other nuclear receptors is made up of 5 domains named A–E from N to C terminal, which include the ligand-independent activation domain (Activation function 1 (AF1) region and A/B-domain), the DNA-binding domain (DBD) (C-domain), the hinge region (D-domain), and the ligand-dependent ligand-binding domain (LBD) (E/F-domain and AF-2 region) [11]. 13 α-helices and 4 short β-strands make up the ligand-binding domain. It has a T-shaped binding pocket with a volume of 1440 Å3, which is larger than most nuclear receptors and allows it to interact with a wide range of ligands [12]. To provide a binding site for ligands, the PPAR-ɣ LBD is folded into a helical sandwich. The S289, H323, Y473, and H449 residues of the PPAR-ɣ-LBD form hydrogen bonds with polar functional groups on the fully agonist ligand, which are typically carbonyl or carboxyl oxygen atoms, to activate the receptor [13]. Agonist binding causes the LBD AF-2 region to change conformation, which is required for coactivator recruitment. Communication between the N-terminal A/B domain adjacent to the DBD and the carboxyl-terminal LBD regulates PPAR ligand binding [14]. The activity of PPAR-ɣ and its functional states are influenced by post-translational modulations (PTMs) of specific amino acids [15]. Phosphorylation, SUMOylation, and ubiquitination are the three main PTMs that regulate PPAR-ɣ function. If induced by mitogen-activated protein kinases, Ser112 phosphorylation reduces PPAR-ɣ activity [16]. However, it increases its activity when induced by cyclin-dependent kinase (CDK) 7 and CDK9 [16]. CDK5-mediated PPAR-ɣ Ser273 phosphorylation reduces insulin sensitivity [17, 18], and CDK-5-mediated Ser112 down-regulates glial fibrillary acidic protein via the development of PPREs in the brain [19]. SUMOylation at Lys107 decreases activity, whereas SUMOylation at Lys395 is strongly linked to PPAR transrepression of nuclear factor (NF)- κB [20, 21]. PPAR is ubiquitinated, which marks it for proteasomal degradation, a process that is accelerated by interferon (IFN)-γ mediated signaling [22] and tumor necrosis factor (TNF)-α [23], and repressed by sirtuin 1 [24].

Physiology of PPAR-ɣ

PPAR-ɣ controls the storage of fatty acids and the metabolism of glucose. PPAR-ɣ activates genes that promote fat cell lipid uptake and adipogenesis. PPAR-ɣ knockout mice lack adipose tissue, indicating that PPAR-ɣ is a crucial regulator of adipocyte differentiation [25, 26]. The importance of PPARs in lipid and glucose metabolism is well known. Additionally, PPAR agonists have been shown to inhibit the development of inflammatory and neurodegenerative disorders in animal models. Pioglitazone, a PPAR- ɣ agonist, reduced glial activation and the accumulation of Aβ-positive plaques in the hippocampus and cortex of rodents. Reduced electron transport chain enzyme activity and increased mitochondrial-generated oxidative stress are thought to be linked to several neurodegenerative diseases (including Parkinson's disease, Alzheimer's disease, and ischemia) [9, 27]. In recent years, it has been revealed that PPARs modulate inflammation and oxidative stress in ischemic brain injury. Glitazone administration [28] reduces the production of ROS and RNS in ischemic animal models by increasing the expression of antioxidant elements such as SOD, catalase, GSH/GPx, and others, indicating that PPAR-ɣ also modulates oxidative stress. Additionally, PPAR-ɣ has been shown to promote neurogenesis and angiogenesis, suggesting that they could be used to repair damaged brain tissue [29].

Location in Brain

The CNS expresses all three subtypes of PPARs, though at different levels [9, 30]. PPAR- δ/β is widely and robustly expressed in the CNS, whereas PPAR-α and PPAR-ɣ have a more restricted distribution pattern [31, 32]. PPAR-ɣ is easily detectable in certain areas of the brain, such as the basal ganglia, thalamus, piriform cortex, and hippocampus, under physiological conditions [31, 33], and this expression is mainly in neuronal cells [34]. PPAR-ɣ is expressed by a small percentage of astrocytes (20–40%), primarily in processes rather than somata [32]. Although PPAR-ɣ expression has been observed in microglial cultures [35], it is barely detectable in this cell type in vivo under physiological conditions. On the other hand, lipopolysaccharide (LPS) stimulation significantly increases microglial PPAR-ɣ expression in the brain, implying that microglial PPAR-ɣ expression may be influenced by inflammation status [32]. In this review, we focus on recent findings of PPAR-ɣ agonists with neuroprotective activity against ischemic injury, as well as their intracerebral effects and potential application against stroke.

Promoters of Post Ischemic Neuronal Death

According to the literature, there are two major zones of injury in the ischemic brain: the infarct core and the ischemic penumbra. After a stroke, it has been observed that the penumbra, which is a tissue surrounding the ischemic core, can be preserved with some timely therapeutic interventions while the ischemic core undergoes irreversible damage [36]. Generally, in volume, the penumbra is larger than the core, and as the progression of neuronal death, the infarct grows over time by expanding into the penumbra [37]. Therefore, after stroke, many synergistic pathophysiological mechanisms or promoters are involved in triggering the secondary neuronal death, concluding long-term neurological dysfunction. To be specific about promoters, in the post-ischemic state, an immense inflammation starts promptly, which proceeds for days after focal ischemia is considered as a promoter of ischemic neuronal death [38]. During ischemia, a progressive and uncontrollable depolarization of neurons known as anoxic depolarization occurs, promoting calcium (Ca^{2+}) and potassium (K^{+}) release, which results in the release of the neurotransmitter glutamate, and with a wave of spreading depression, more glutamate releases in the penumbra, which promotes excitotoxic secondary neuronal death in core as well as in penumbra by overstimulating the postsynaptic glutamate receptors, primarily NMDA receptors [39]. Abnormally high calcium ions accumulate in the postsynaptic neuron, activating cytotoxic enzymes including proteases, nucleases, and caspases that proceed to neuronal degeneration [40]. Immediately, in ischemic stroke, the ionic gradients across cell membranes collapse, resulting in water influx developing edema. In the brain, due to deprivation of oxygen and glucose, additional mitochondrial dysfunction results in decreased production of ATP and overproduction of reactive oxidative species (ROS), which leads to oxidative stress and endoplasmic reticulum (ER) stress [39, 41]. To accompany this, the expression of inflammatory genes and infiltration of leukocytes into brain parenchyma increases. In the non-ischemic brain, the blood–brain barrier (BBB) is in charge of infiltrating white blood cells into brain parenchyma. However, resultant ischemia leads to the initiation of the adhesion molecules like intercellular adhesion molecule-1 (ICAM-1), E-selectin, and P-selectin on the endothelial cells to promote leukocyte adherence and eruption [42]. The infiltrated macrophages and neutrophils trigger inhabitant microglia and astrocytes. Therefore, resultant stroke leads to trigger leukocytes, neurons, astrocytes, microglia, and oligodendrocytes to generate proinflammatory mediators, cytokines like interleukin (IL)-6 and IL-1β, chemokines like macrophage inflammatory protein-1 α & monocyte chemoattractant protein-1 (MCP1), prostaglandins and free radicals which exacerbate postischemic secondary neuronal

death. All these pathophysiological events are thought to promote post-ischemic neuronal death synergistically.

Role of Transcription Factors in Post Ischemic Inflammation

For therapeutic repair, transcription factors are considered molecular targets since they involve regulating various genes that modulate cellular functions. Transcription factors play a dominant role in modulating inflammation by regulating the expression of cytokines, chemokines, and other inflammatory genes. Cerebral ischemia induces immense variations in gene transcription within minutes of onset [43]. It is known for stimulating numerous transcription factors including hypoxia-inducible factor-1 (HIF1) [44], signal transducer and activator of transcription-3 (STAT3) [45], early growth response1 (Egr1) [46], nuclear factor (erythroid-derived 2)-like 2 (Nrf2) [41], interferon regulatory factor-1 (IRF1) [47], activating transcription factor-3 (ATF3) [48], cAMP response element-binding protein (CREB), cAMP response element modulator (CREM) [49], and nuclear factor-kappa B (NF-κB) [50] that are known to significantly modulate the postischemic inflammatory gene expression [51]. The activation of transcription factors anticipates as a two-edged sword, i.e., it can work both ways as an inducer of neuroprotection or neurotoxic genes. Therefore from various studies, an observation is made that the transcription factors like STAT3, IRF1, C/EBPβ, NF-κB, ATF3, and EGR1 cause several neuronal damages by inducing inflammatory genes [51]. However, transcription factors like HIF1, Nrf2, c-fos, p53, PPARα, PPARγ, and CREB are thought to be advantageous positively as they restrain the expression of genes that promote inflammation or oxidative stress [51–53]. Of these, PPARγ, a ligand-activated transcription factor, was recently shown to prevent inflammatory gene expression in several animal models of CNS disorders [54]. Drugs that target transcription factors could be effective as they act upstream to gene expression, thus preventing inflammation and other destructive pathways.

Numerous Targets for PPAR-ɣ Agonists in Ischemic Injury

In the ischemic core, the neurons confined die immediately due to vascular constriction due to ischemia-induced mitochondrial failure and anoxic depolarization, causing excitotoxicity. In the initial stage of the ischemic phase, the destruction of neurons is considered the result of excitotoxicity due to the stimulation of glutamate receptors, excess calcium ions, and a collapse of ion homeostasis [39]. Furthermore, reactive oxygen species (ROS) overproduction is a remarkable feature of ischemic stroke, and ROS is considered as an essential mediator of ischemic damage. The over-expression of ROS and free radicals in intraneuronal and extraneuronal are a result of stimulating cyclooxygenase (COX)-2 and inducible nitric oxide synthase (iNOS), which directly affects neurons [55]. Although 15-deoxy-D12,14-prostaglandin J2 (15-deoxy-PGJ2) (a natural PPAR-ɣ agonist) is the end product of COX-2 on reaction with arachidonic acid, evidence reveal that 15-deoxy-PGJ2 plays a significant part in the COX-2 enzyme's negative feedback mechanism and suppress IL-1β induced COX-2 expressions in order to reduce inflammation [56]. Secondary neuronal death is prompted by inflammatory reactions that are initiated by the increased assertion and/or release of cytokines such as tumor necrosis factor (TNF)-a and interleukin (Il)-1b, and adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule (VCAM) [57]. These mediators promote the accumulation of leukocytes, macrophages, and activated microglial cells in the ischemic area. Infiltrating inflammatory cells express iNOS and produce large amounts of nitric oxide (NO) with the subsequent production of peroxynitrite. PPAR-ɣ activation can counteract these adverse effects, indicating a promising and neuroprotective role for PPAR-ɣ agonists in stroke (Fig. 1).

Multiple Mechanism Involved in Activation of Intra Cerebral PPAR-ɣ/Protects Against Cerebral Ischemia

PPAR-ɣ agonists evidently and efficiently protect against cerebral ischemia in rodents, and this protection also results in a decrease in apoptosis rates [54]. Moreover, it also has been observed that the PPAR-ɣ antagonist increases the size of ischemia infarct [58], hence concluded that the PPAR-ɣ agonist is a potential protective measure for cerebral ischemic injury. In the event of ischemic injury, the expression of PPAR-ɣ mRNA and protein in neurons and microglia increases [24]. It has been observed that after 24 h, maximal levels are obtained, also the observation has been made that augmented PPAR-ɣ protein levels can still be perceived till 14 days later ischemic injury [58]. Increased PPAR-ɣ expression, however, may not be functionally crucial because cerebral ischemia reduces PPAR-ɣ DNA binding, but it can be fully recovered by the intracerebral application of the PPAR-ɣ agonist 15-deoxy-PGJ2 or systemic treatment with rosiglitazone.

Inhibition of Cyclooxygenase-2 (COX-2) Enzyme

Numerous in vitro and ex vivo experimental studies show an increase of COX-2 expression, especially within ischemic

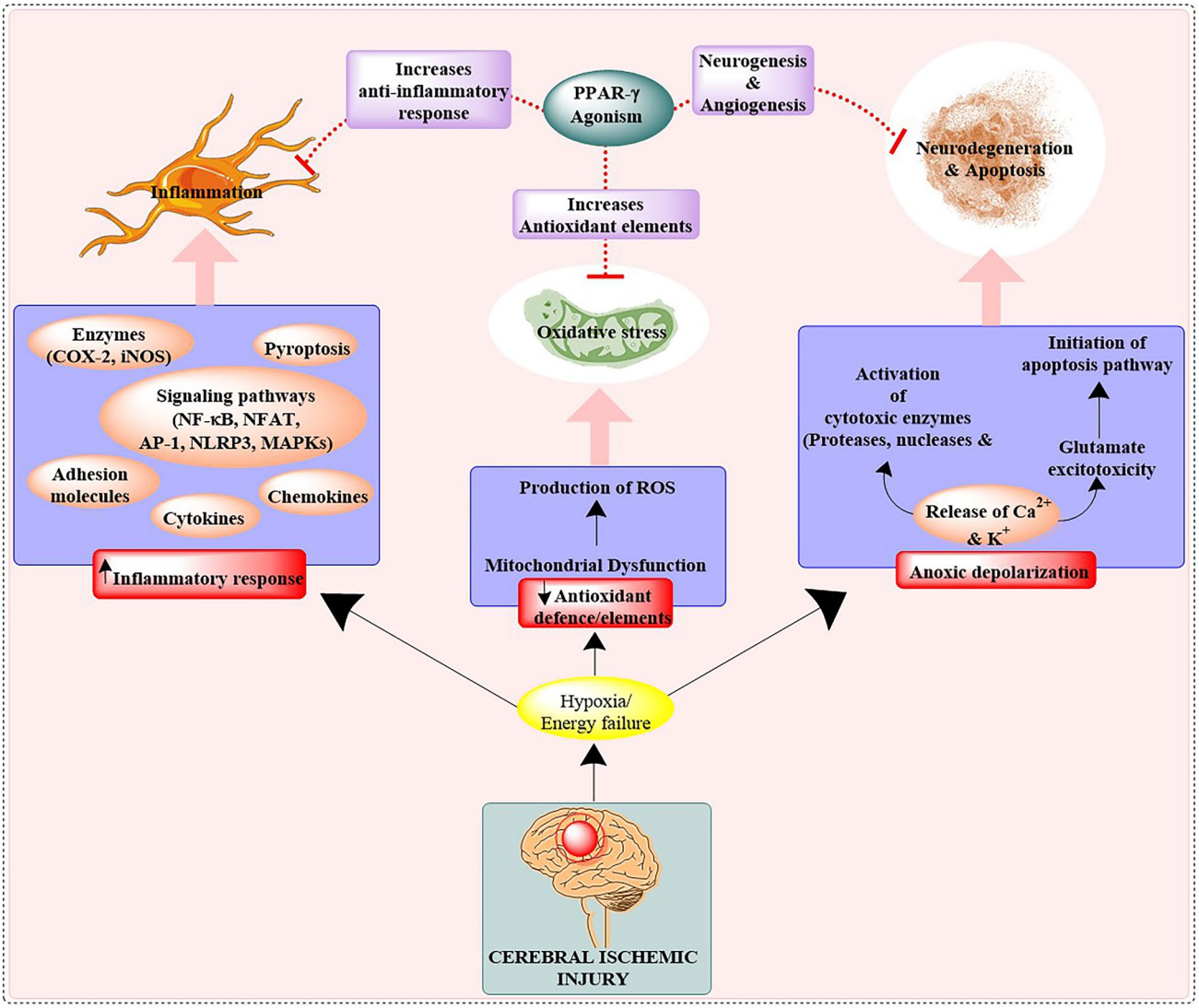


Fig. 1 Role of PPAR-γ in attenuation of cerebral ischemic injury. COX-2: Cyclooxygenase-2 enzyme; iNOS: Inducible nitric oxide synthase; NF-κB: Nuclear factor kappa light chain enhancer of activated B-cells; NFAT: Nuclear factor of activated T-cells; AP-1: Activator protein-1; NLRP3: NLR family pyrin domain containing 3; MAPKs: Mitogen-activated protein kinases; ROS: Reactive oxygen species; Ca^{2+}: Calcium; K^{+}: Potassium

neurons worsening the ischemic injury and promoting neuronal death. Therefore, it has been established that in ischemic neurons, expression of COX-2 increases vividly, and by generating superoxide oxidative stress as well as the synthesis of prostaglandin increases which promotes inflammation that worsens the ischemic induced injury. COX-2 is known to have an association with excitotoxicity mediated by N-methyl-D-aspartate (NMDA) receptors, due to which free radical-mediated lipid peroxidation gets initiated [59], and also its association with the synthesis of prostaglandins as well as with neuronal cell death. In primary neuronal cell cultures, it was discovered that increasing PPAR-ɣ activity inhibits COX-2 expression, lowers Ca2+ concentrations [60], and protects neurons from NMDA-induced excitatory neurotoxicity [61] also shows a defense mechanism against the inflammation initiated in lipopolysaccharide-induced neuronal death [62]. As a result, activation of the PPAR-ɣ receptor raises the possibility of suppressing neurodegenerative target genes like COX-2, which is actively involved in the ROS generation, increasing oxidative stress and mitochondrial dysfunction. It ultimately results in the activation of apoptosis caspase cascades, worsening the ischemic injury. Systemic and intracerebroventricular administration of thiazolidinedione (TZD), a PPAR-ɣ agonist, significantly reduces COX-2 expression in peri-infarct cortical zones following transient middle cerebral artery occlusion (MCAO) or common carotid artery occlusion [9]. Hence, inhibition of COX-2 enzyme via activation of cerebral PPAR-ɣ facilitates

the protection of neurons against ischemic injury initiated by excitotoxicity and anoxia. Intracerebroventricular infusion of pioglitazone five days before and two days after MCAO reduces infarct size, tumor necrosis factor (TNF-α), COX-2 expression, and the number of cells positively stained for COX-1 and COX-2 in the peri-infarct cortical regions [63]. A potent natural PPAR-ɣ agonist, curcumin provides neuroprotection against ischemic injury by suppressing the COX-2 enzyme [64] (Table 1).

The Antioxidant Action of PPAR-ɣ

Antioxidant Activity of PPAR-ɣ Through Antioxidant Elements

Agonists of PPAR-ɣ affect ROS production on various cellular levels. A major antioxidant enzyme, catalase, is regulated by PPAR-ɣ via PPREs containing canonical direct repeat-1(DR-1) domain [65]. Also, PPAR-ɣ activation results in NrF2/KAEP pathway [66] that enhances antioxidant elements like MnSOD [67], GPx3 [68], and HO-1 [69]. By far, the most well-studied transcription factor is Nrf2, which has oxidant/electrophile sensing capability. Several studies have strongly supported the existence of mutual regulation of the pathways Nrf2 and PPAR-ɣ to strengthen each other's expression [65, 70]. In this regard, the Nrf2 and PPAR-ɣ pathways are frequently connected via a positive feedback loop that simultaneously regulates the expression of both transcription factors and their target antioxidant genes. The concept of PPAR-ɣ as a direct target gene induced by transcriptional Nrf2 activation reveals the molecular mechanisms governing the Nrf2 mediated regulation of PPAR-ɣ [71]. Per this observation, numerous other researchers have documented the Nrf2's direct binding to newly identified antioxidant response elements (AREs) in the PPAR-ɣ promoter regions using gel shift and coimmunoprecipitation assays [12, 65, 70]. ARE sequences found in the 784/764 and 916 regions of the PPAR-ɣpromoter were required for Nrf2-mediated regulation of PPAR-ɣ expression in their research. In vivo studies shows that PPAR-ɣ expression is significantly lower in Nrf2 knockout mice, providing further evidence for Nrf2's direct control on PPAR-ɣ [12]. 5-Hydroxy-4-phenyl-butenolide (5H4PB), a PPAR-ɣ agonist, activated the signaling pathway of Nrf2/ARE, which is essential in cellular defense against oxidative stress, resulting in the upregulation of ARE-dependent cytoprotective genes such as HO-1, catalase, as well as SOD without cytotoxicity [72]. Furthermore, in mouse fibroblast cells, 5H4PB significantly reduced the production of intracellular ROS, glutathione oxidation, and DNA damage caused by H_2O_2 exposure. Mangiferin (MF) has antisecretory and antioxidant gastroprotective effects in ischemia/ reperfused rats. Through the Nrf2/HO-1, PPAR-ɣ/NF-κB signaling pathways, MF provides gastroprotective mechanisms by partially modulating oxidative stress, inflammation, and apoptosis [73]. It has been demonstrated that glitazones stimulate CuZN-superoxide dismutase, an antioxidant enzyme that scavenges free oxygen radicals in ischemic tissue. Before occlusion of the common carotid artery, rats were given pioglitazone or rosiglitazone, which reduced nitrite and ROS production, lipid peroxidation, and reversed glutathione depletion in the hippocampus [28]. Rosiglitazone, along with the activation of antioxidant enzymes like SOD, catalase, etc., also regulates the expression of B-cell lymphoma 2 (Bcl-2), Bcl-2-associated X protein (Bax); thus, attributing to the protection of neurons [66]. Thiazolidinediones-mediated PPAR-ɣ activation induces GPx3 gene expression, decreasing extracellular H_2O_2 [74]. HO-1 is a critical antioxidant enzyme and an Nrf2 regulated gene contributing a vital function in preventing inflammation. The inducible isoform of HO is in charge of the oxidative cleavage of the heme groups that results in the release of biliverdin, carbon monoxide, and ferrous iron [69]. HO-1 can be strongly induced in many tissues in response to cellular stress caused by various stimuli, such as ROS and prostaglandins. The activity of the HO-1 enzyme reduces oxidative stress, the inflammatory response, and the rate of apoptosis. By interacting with two PPRE DR-1 located between 1740 and 1826 kb from the initial transcription site, PPAR-ɣ induces HO-1 expression in human vascular cells [75] (Fig. 2).

Additionally, PPAR-ɣ induces the expression of HO-1 during oxidative stress caused by elevated glucose levels and age-related macular degeneration. Though, after status epilepticus, rosiglitazone has been found to increases the anti-oxidative activity of SOD and GSH while decreasing the expression of HO-1 in the hippocampus [67]. To make matters even more complicated, the PPAR-ɣ agonist 15d-PGJ2 can increase the expressions of HO-1 independently of PPAR-ɣ via NRF2 or GSH-dependent mechanisms [76] (Table 1).

Antioxidant Activity of PPAR-ɣ Through NOS

It has been proposed that PPAR-ɣ activation modulates the expression of eNOS and iNOS. When produced in large quantities, these enzymes generate NO from arginine and form highly reactive peroxynitrite when reacting with oxygen (O_2). Aortic segments in endothelial-specific knockout PPAR-ɣ mice produce less NO compared to controls. In addition, decreased expression correlates with an increase in oxidative stress parameters, indicating that PPAR-ɣ protects from oxidative stress by controlling the expression of eNOS [77]. High NO output by iNOS, on the other hand, is typically associated with complex immunomodulatory and antitumor pathways, and defective iNOS expression induction appears to be involved in the pathophysiology

Table 1 Ligands of PPAR-ɣused in Cerebral Ischemic Injury

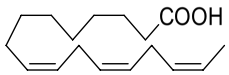
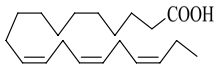
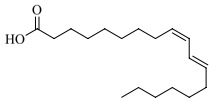
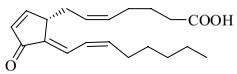
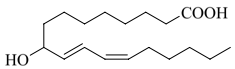
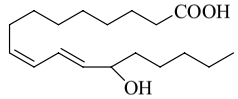
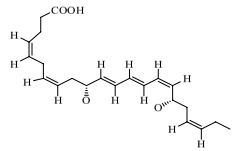
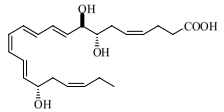
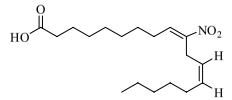
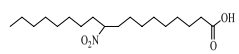
S. No	Ligands		Activity	Chemical structures	Mechanism	References
Natural ligands						
1	Unsaturated fatty acid	Linoleic acid	Agonist		It increases the mRNA expression of PPAR-ɣ and anti-inflammatory action by suppressing the activation of TNF-α and NF-κB pathway	[213, 214]
2		Eicosapentaenoic acid	Agonist		↑ mRNA expression of PPAR-ɣ. Anti-inflammatory by ↓IL-1, ↓IL-6, and ↓TNF-α, inhibits NF-κB signaling pathway	[215, 216]
3		Docosahexaenoic acid	Agonist		Anti-inflammatory by ↓IL-1, ↓IL-6, and ↓TNF-α, inhibits NF-κB signaling pathway	[216]
4		Conjugated linoleic acid	Agonist		Anti-inflammatory by ↓IL-1, ↓IL-6, and ↓TNF-α, inhibits NF-κB signaling pathway	[216]
5	Oxidized polyun-saturated fatty acids (PUFA) derivatives	$15dPGJ_2$	Agonist		Activation of the PPAR-ɣ receptor leads to the inhibition of overexpression of IL-1β, IL-6, and TNF-α. Thus, shows the anti-inflammatory property, neuroprotective in cerebral ischemia	[38]
6		9-HODE	Agonist		Anti-inflammation activity by supressing proinflammatory cytokine, chemokines and adhesion molecules	[217, 218]
7		13-HODE	Agonist		Anti-inflammation activity by supressing pro-inflammatory cytokine, chemokines and adhesion molecules	[217, 218]
8		Neuroprotectin D_1 (NPD_1)	Agonist		Inhibits COX-2, ↓TNF-α induced pro-inflammatory elements, ↓IL-1β, inhibits NF-κB signaling pathway, upregulates antiapoptotic Bcl-2 proteins and Bcl-xL and ↓proapoptotic Bax and Bad	[219–222]
9		Resolvin D_1 (RvD_1)	Agonist		Inhibits neutrophil activation, ↓TNF-α, IL-6, suppresses IκBα degradation and p65 nuclear translocation and inhibits NF-κB signalling pathway	[223, 224]
10	Nitrated Fatty acids	Nitrolinoleic acids	Agonist		Anti-oxidant activity by activation of Kaep1/Nrf2 signaling pathway	[225]
11		Nitrooleic acid	Agonist		↓TNF-α, ↓IL-1β, inhibits Bax activation	[226, 227]

Table 1 (continued)

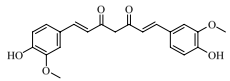
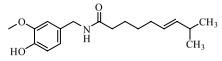
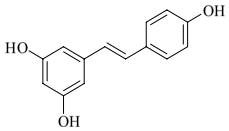
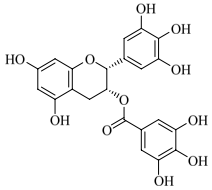
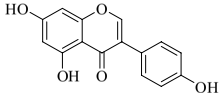
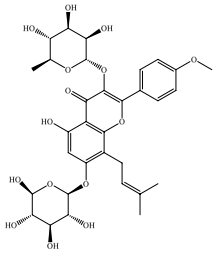
S. No	Ligands		Activity	Chemical structures	Mechanism	References
12	Flavonoids	Curcumin	Agonist		It upregulates PPAR-γ and thus binding of PPARγ-PPRE binding activity, hence suppressing neuroinflammatory mediators like IL-1β, TNF-α, PGE_2, NO, COX-2 and iNOS.Also, supressed IκBα degradation and thus, inhibits NF-κB-p65 signaling pathway	[64, 228]
13		Capsaicin	Agonist		Inhibits NF-κB, TNF-α, MMP-2 expression	[229]
14		Resveratrol	Antagonist		Blocks PPAR-γ activity via sirtuin 1 pathway	[230–232]
15		Epigallocatechin gallate (EGCG)	Agonist		Inhibits up-regulation of MMP9 activity	[233]
16		Genistein	Agonist		Inhibits NLRP3 inflammasome and MMP9 and reduce oxidative stress	[139, 197, 234]
17		Icariin	Agonist		Anti-inflammatory activity by ↓IL-1β, inhibits NF-κB signaling pathway	[235]

Table 1 (continued)

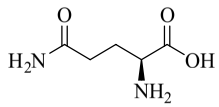
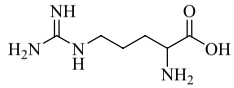
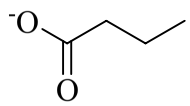
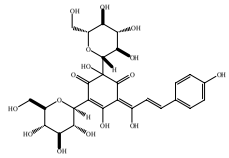
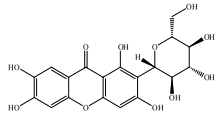
S. No	Ligands		Activity	Chemical structures	Mechanism	References
18	Other Nutrients	Glutamine	Agonist		Via 15-S-HETE & 13-OXO-ODE activates PPAR-γ receptor. And inhibits the Nrf2/Are signaling pathway	[236, 237]
19		Arginine	Antagonist		Arginine blocks PPAR-γ's activity via phosphorylation of c-Jun and increases inflammation by AP-1 pathway	[236]
20		Butyrate	Agonist		It inhibits the expression of pro-inflammatory cytokines (IL-1β, IL-6) chemokines, adhesion molecules (I-CAM, V-CAM) and apoptosis to provide neuroprotection	[238]
21	Miscellenaeous	Hydroxysafflor yellow-A	Agonist		Anti-inflammatory activity by inhibiting p38 MAPK phosphorylation	[106]
22		Mangiferin	Agonist		Anti-oxidant and anti-inflammatory activity by activating Nrf2 pathway which ↑HO-1 and inhibits NF-κB signaling pathway	[73]

Table 1 (continued)

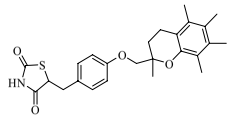
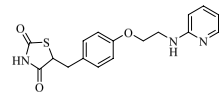
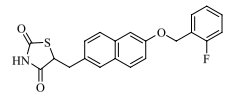
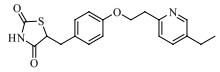
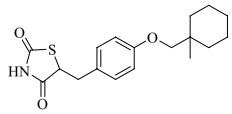
S. No	Ligands		Activity	Chemical structures	Mechanism	References
Synthetic ligands						
23	Glitazones	Troglitazone	Agonist		Anti-inflammatory activity via inhibition of overexpression of IL-1β, IL-6, and TNF-α, as well as reduction of adhesion molecules like MAdCAM-1, VACM-1, I-CAM-1 & E-selectin. It also reduces the expression of α4β7integrin dependent lymphocyte adhesion. It attenuates glutamate toxicity	[38, 110, 111]
24		Rosiglitazone	Agonist		Antioxidant activity by increasing the expression of SOD, Catalase, GSH, as well as UCP-2 expression. Anti-inflammatory activity by increasing the production of pro-inflammatory cytokines like LIX, MCP-1, MIP-2, G-CSF & KC as well as by supressing the expressions of IL-1β, TNF-α, NF-κB, p38 & P42/44 MAPK activation. Also, increases the expression of Bcl-2 and Bax. Promotes angiogenesis	[34,66,84,90, 103,116,189]
25		Netoglitazone	Agonist		Anti-inflammatory activity by inhibiting IL-1, IL-6, TNF-α as well as inhibiting the activation of NF-KB and JAK-STAR signaling pathways	[239, 240]
26		Pioglitazone	Agonist		Promotes Angiogenesis. Anti-inflammatory activity by ↓COX-2, ↓TNF-α, ↓NLRP3-inflammosome, ↓iNOS expression, ↑TGF-β, and ↑ IL-10 as well as inhibiting NF-κB and p38 stress kinase pathway. Antioxidant activity by ↑ SOD expressions and ↓ production of ROS	[63, 88, 115, 189]
27		Ciglitazone	Agonist		↓MPO activity, ↓cytokine production, ↓NF-κB, ↓JNK/AP-1	[241]

Table 1 (continued)

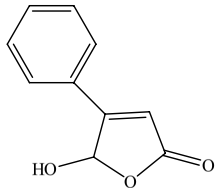
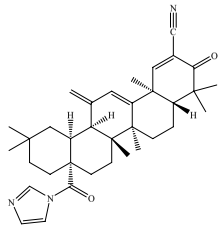
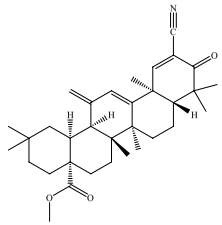
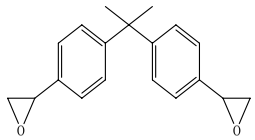
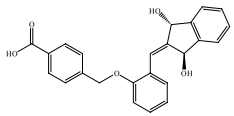
S. No	Ligands		Activity	Chemical structures	Mechanism	References
28	Novel drugs	5-Hydroxy-4-phenyl-butanolide	Agonist		Antioxidant activity through activation of Nrf2/ARE signaling pathway	[72]
29		CDDO	Partial agonist		Anti-proliferative and Pro-apoptotic activity through PPAR-γ activation. But when combine with TNF compound it inhibits NF-κB pathway. It also reported to induce Antioxidant Response by the Transcription Factor NRF2	[242, 243]
30		CDDO-Me	Agonist		Through Keap1/Nrf2 and surpression of NF-κB exerts anti-inflammatory action	[242, 244]
31		BADGE	Antagonist		Blocks TZDs antagonist	[245]
32		AM 879	Non-agonist		Blocks Cdk5-mediated phosphorylation of PPAR-γ	[246]

Table 1 (continued)

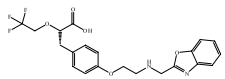
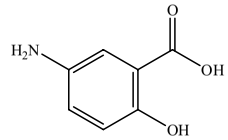
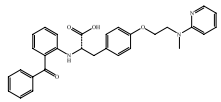
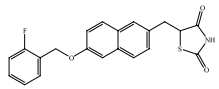
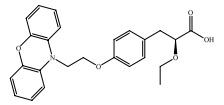
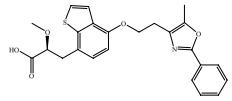
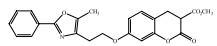
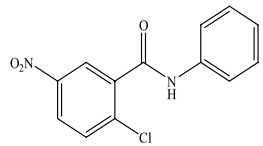
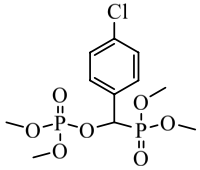
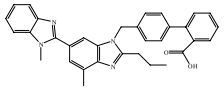
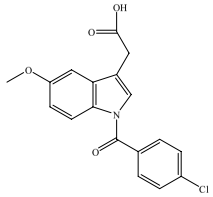
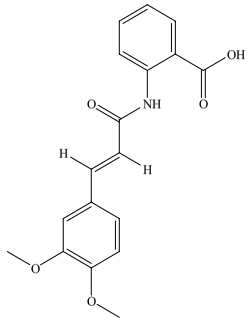
S. No	Ligands	Activity	Chemical structures	Mechanism	References
33	SB 219994	Agonist		Inhibits NF-κB signaling pathway by supressing the degradation of IκBα	[247]
34	5- ASA/mesalamine	Agonist		↓IL-1β, ↓iNOS, ↓TNF-α, ↓IL-6, ↓NF-κB, COX-2 inhibition	[248]
35	GW 1929	Agonist		↑expression of PPAR-γ and CD36, ↓NF-κB, inhibits COX-2,	[249]
36	MCC 555	Agonist		↓TNF-α induced VCAM-1	[250]
37	Ragaglitazar	Dual Agonist		By reducing ↓IL-6, ↓ TNF-α shows anti-inflammatory activity	[251]
38	Aleglitazar	Dual agonist		Inhibits TNF-α mediated inflammation. ↑ pro-inflammatory mediators	[252]
39	T33	Dual agonist		Anti-inflammatory activity by ↓TNF-α, ↓IL-1β and inhibiting COX-2. It also upregulates the expression of IκBα thereby, inhibits NF-κB signaling pathway	[253]
40	GW 9662	Antagonist		Blocks PPAR-γ receptor and ↑TNF-α induced inflammation	[254]
41	Mifobate	Antagonist		Selectively inhibits TZD-induced PPAR-γ transcriptional activity	[255]

Table 1 (continued)

S. No	Ligands		Activity	Chemical structures	Mechanism	References
42	Miscellaneous	Telmisartan	Partial agonist		Antioxidant activity by ↑eNOS. Anti-inflammatory by inhibiting p38 MAPK activation, ↓pyroptosis by inhibiting the HMGB-1 expression	[80, 104, 149]
43		Indomethacin	Agonist		Inhibits COX-2 and iNOS. ↓ Microglia activation	[138, 256]
44		Tranilast	Agonist		Anti-inflammatory activity by ↓IL-6, IL-8, ↓ chemokines (CCL20, CXCL2, CXCL3 & CXCL1) and ↓ TNF-α stimulated macrophages	[98]

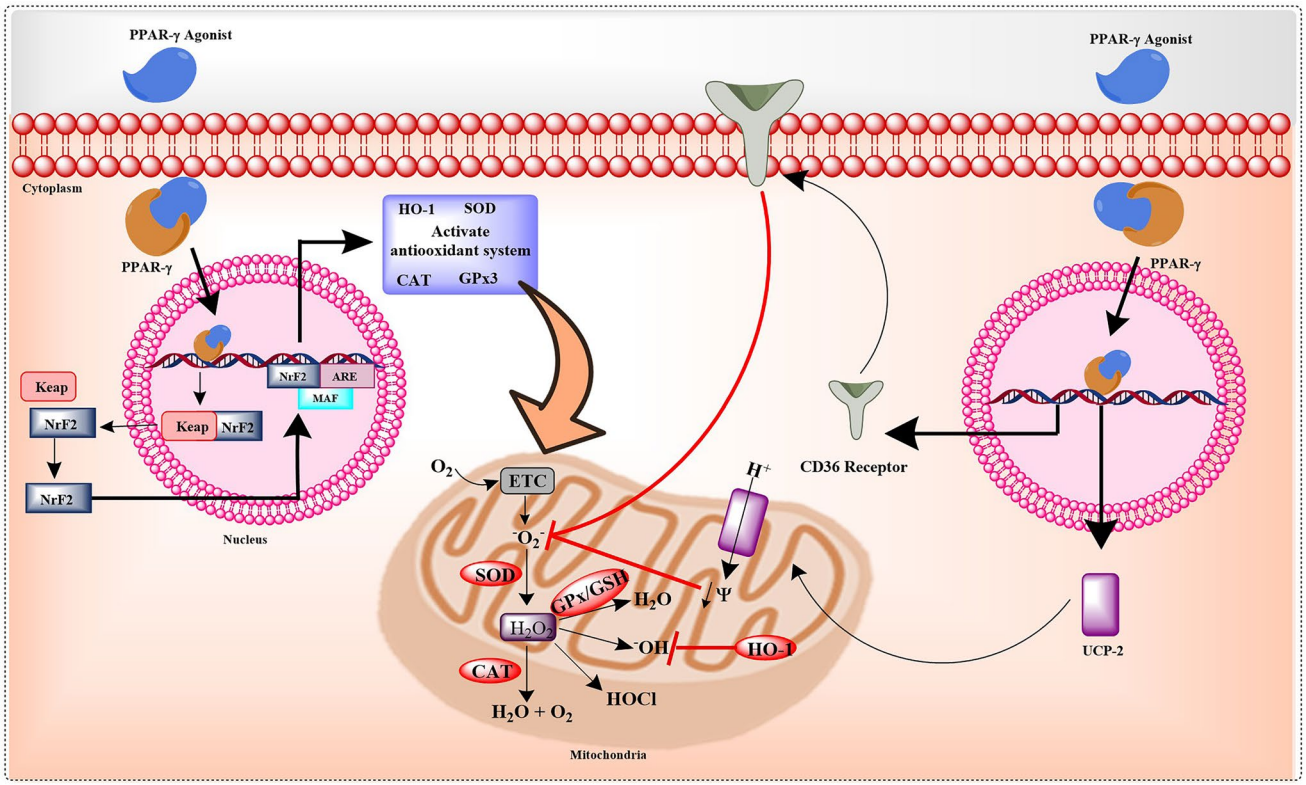


Fig. 2 Antioxidant activity of PPAR-ɣ. Nrf2: Nuclear factor erythroid 2-related factor 2; Kaep: Kelch-like ECH-associated protein; ARE: Antioxidant response element; HO-1: Heme oxygenase-1; SOD: Superoxide dismutase; CAT: Catalase; GPx3: Glutathione peroxidase 3; ETC: Electron transport chain; O_2: Oxygen; H_2O_2: Hydrogen peroxide; UCP-2: Uncoupling protein-2; CD36: Cluster of differentiation 36 receptor

of many human diseases [78]. PPAR-ɣ agonists suppress iNOS expression in various cells, including activated macrophages, lipotoxic pancreatic islets, and LPS-activated Schwann cells, implying a protective role of PPAR-ɣ against reactive peroxynitrite [66]. PPAR-ɣ ligand 15d-PGJ2 and ciglitazone increase the release of cultured endothelial NO without increasing the eNOS expression [79]. Telmisartan, an AT_1 receptor blocker with PPAR-ɣ agonistic property, inhibited vasoconstriction in mice resistance arteries, which was mediated by a PPAR-ɣ dependent increase in eNOS expression and activation, regardless of its ability to block the classical AT1 receptor [80]. Therefore, through the eNOS pathway, PPAR-ɣ shows antioxidant action in ischemia–reperfusion injury, providing neuroprotection. Both TZD and non-TZD PPAR agonists, on the other hand, minimize iNOS expression in inflammatory cells, which is thought to be a significant source of the detrimental radical peroxynitrite [24] (Table 1).

Antioxidant Activity of PPAR-ɣ via CD36 Receptor

CD36 receptor, a scavenger receptor that mediates the recognition and internalization of oxidized lipids, can also be regulated by PPAR-ɣ [81]. Indeed, it has been demonstrated that treatment with PPAR-ɣ ligands increases CD36 expression in murine macrophages [82], possibly due to the binding of PPAR-ɣ to the functional, active PPRE located in the gene promoter (Table 1).

Antioxidant Activity of PPAR-ɣ via UCPs

Uncoupling proteins (UCPs) are mitochondrial carrier proteins required to reduce mitochondrial membrane potential and metabolic energy dissipation like heat, respiration maintenance, glucose disposal rate, insulin secretion, and preventing the accumulation of ROS [83]. In hypertensive rat models, oral administration of rosiglitazone increases UCP-2 expression. It exerts an antihypertensive effect by inhibiting sympathetic vasomotor activity via a PPAR-ɣ dependent protective effect against oxidative stress [84].

Anti-inflammatory Activity of PPAR-ɣ

Since PPAR-ɣ's agonists demonstrated a wide range of protective effects in many animal models of neurological and cardiovascular diseases, the anti-inflammatory roles

of PPAR-ɣ have received a great deal of attention. The majority of research has focused on the effects of PPAR-ɣ on monocyte/macrophage and endothelial cells, as these cells can modulate the development of inflammatory cytokines and regulate immune cell differentiation and function. PPAR-ɣ activation has been shown to reduce immune reactions outside of the nervous system and act as a potential anti-inflammatory agent in ischemic brains. Its activation decreases the expression of intracellular adhesion molecule-1 (ICAM-1), matrix metalloproteinase (MMP)-9, and a few other inflammatory cytokines in the ischemic brain [29] (Fig. 4) (Table 1).

Neuroprotection Against Neuroinflammation via Reduction of Cytokines

It has been demonstrated that agonists of the PPAR-ɣ receptor inhibit the proliferation of human monocytes and monocyte-derived cell lines, thereby inhibiting the development of proinflammatory cytokines such as TNF-α, IL-1β, and IL-6 (Fig. 4) [85, 86]. Rosiglitazone inhibits microglia and macrophage penetration into the peri-infarct area of the brain and the development of IL-1β [87]. In stroke models, PPAR-ɣ agonists have been reported to inhibit the entire spectrum of proinflammatory mediators. Various studies have shown that pioglitazone inhibits the proinflammatory cytokine IL-1β [88] and expression of TNF-α in the MCAO model of secondary intracerebral hemorrhage ischemia (sICH) [89]. Additionally, three days after ischemia, pioglitazone increases the expression of the anti-inflammatory cytokines TGFβ- and IL-10 in infarcted tissue [89]. Rosiglitazone shows neuroprotective activity after traumatic spinal cord injury by reducing TNF-α and IL-1β [90]. Apart from rosiglitazone and pioglitazone, also telmisartan [91, 92], darglitazone [93], 15-deoxy-Δ-12, 14-prostaglandin J2 (15d-PGJ2) [94, 95], L-796,449 [95], and 12-hydroxyeicosatetraenoic acid [96] have reported to lower inflammation in ischemic stroke models.A PPAR-ɣ agonist, 2-hydroxyethyl 5-chloro-4,5-didehydrojasmonate (J11-C1), reduces the synthesis of proinflammatory cytokines like IL-6 and IL-8, as well as chemokines such as CCL20, CXCL2, CXCL3, and CXCL1 in colon tissues and LPS or TNF-α stimulated macrophages and epithelial cells [97]. Significantly, anti-inflammatory activity, like TNF-α inhibition, can be achieved solely by stimulating intracerebral PPAR-ɣ with pioglitazone administered intracerebroventricularly. At last, rosiglitazone and pioglitazone suppress NF-κB signaling and activate the p38 stress kinase [54]. Recently, Tranilast, an anti-allergic drug, decreases the mRNA and proteins levels of multiple proinflammatory cytokines and affect NF-κβ, and inhibits the kappa β protein expression via upregulation of PPAR-ɣ [98].

Neuroprotection Against Neuroinflammation Through MAPK Signaling Pathway

It is believed that p38 MAPKs are the essential MAPKs that generate proinflammatory mediators like IL-1β, IL-6, TNF-α, and COX-2. Also, activation of the pathway increases the expression of VCAM-1, iNOS, and differentiation of immune cells like GM-CSF, EPO, CSF, and CD-40 [99]. Several studies [100–102] found that Glitazones inhibit activation of p38 MAPK, reduce inflammation, and be used in rescuing the penumbra in cerebral ischemia. Along with inhibiting the phosphorylation of p38 MAPK, Rosiglitazone also inhibits p42/44 MAPK's phosphorylation, thus reducing neuroinflammation [103]. Other than glitazones, telmisartan [104], which acts as an agonist of PPAR-ɣ, also decreases neuroinflammation by inhibiting p38 MAPK activation. Natural products such as curcumin [105], Hydroxysafflor yellow A [106] either activate PPAR- ɣ or, by increasing PPAR-ɣ expression, protect the neurons from inflammatory injury by inhibiting p38 MAPK phosphorylation (Table 1).

Neuroprotection Against Neuroinflammation Through Suppression of Adhesion Molecules

Adhesion molecules are cell-surface proteins that mediate interactions between cells or between cells and the extracellular matrix (ECM) [107]. They play an essential role in the inflammatory response. The various migration steps of leucocytes from the bloodstream to the inflammatory foci are mediated by selectins, integrins, and immunoglobulin (Ig) gene superfamily adhesion receptors. Endothelial cell (EC) activation increases the expression of several CAM, causing EC cells to come into contact with leucocytes [108]. Selectins mediate leukocytes' initial interactions (tethering/rolling) with activated endothelial cells, while integrins and Ig superfamily CAM mediate the cells' firm adherence and subsequent extravasation. Leukocytes are activated during rolling by intracellular signals generated by CAM and chemokine receptors. Blocking CAM's role or expression has emerged as a new therapeutic target for reducing inflammation in various diseases [108]. As a result, PPAR-ɣ activation suppresses pro-inflammatory adhesion molecule expression as well as leukocyte recruitment (Fig. 4) [109]. TNF-α induced MAdCAM-1, VCAM-1, ICAM-1, and E-selectin expression has been shown to be reduced by troglitazone. Furthermore, it reduces the expression of α4β7 integrin-dependent lymphocyte adhesion to TNF-α cultured endothelial cells [110, 111]. $15dPGJ_2$ is a naturally occurring (PUFA derivative) PPAR-ɣ agonist, which markedly attenuated the VCAM-1 and ICAM-1 expression

induced by TNF-α. Bezafibrate, a selective PPAR-ɣ agonist, reduces TNF-α induced expression of ICAM-1, VCAM-1, and MCP-1 in human retinal microvascular endothelial cells [112]. Therefore, this indicates that PPAR-ɣ agonists have beneficial effects in modulating inflammatory response in cerebral ischemic injury.

Neuroprotection Against Neuroinflammation via Inhibition of NF-κB Signaling Pathway

NF-κB is an inducible transcription factor that controls various innate and adaptive immune functions and is a crucial mediator of inflammatory responses. Many pro-inflammatory genes, such as cytokines and chemokines, are influenced by NF-κB. It also helps regulate the inflammasome [113]. Innate immune cells and inflammatory T cells are regulated by the transcription factor NF-κB, regulating their survival, activation, and differentiation [114]. Because of this, to limit/prevent inflammation, the pathway of NF-κB must be halted, and many studies provide evidence of halting the NF-**κ**B pathway by PPAR-ɣ agonists to prevent inflammation (Fig. 3). The suppression of IL-1 and TNF-α by PPAR-ɣ is thought to be mediated by the inhibition of NF-κB [52]. Pioglitazone and rosiglitazone upregulate PPAR-ɣ dependent genes while inhibiting NF-κB activation and proinflammatory cytokine secretion (LIX, MCP-1, MIP-2, G-CSF, KC) in response to LPS in Cftr-KO mice. By the Iκβα (an NF-κB negative regulator) production, PPAR-ɣ agonists attenuate NF-B-dependent inflammation [115].

Additionally, 15dPGJ2 has been shown to inhibit the production of proinflammatory cytokines in the porcine endometrium by suppressing the NF-B pathway

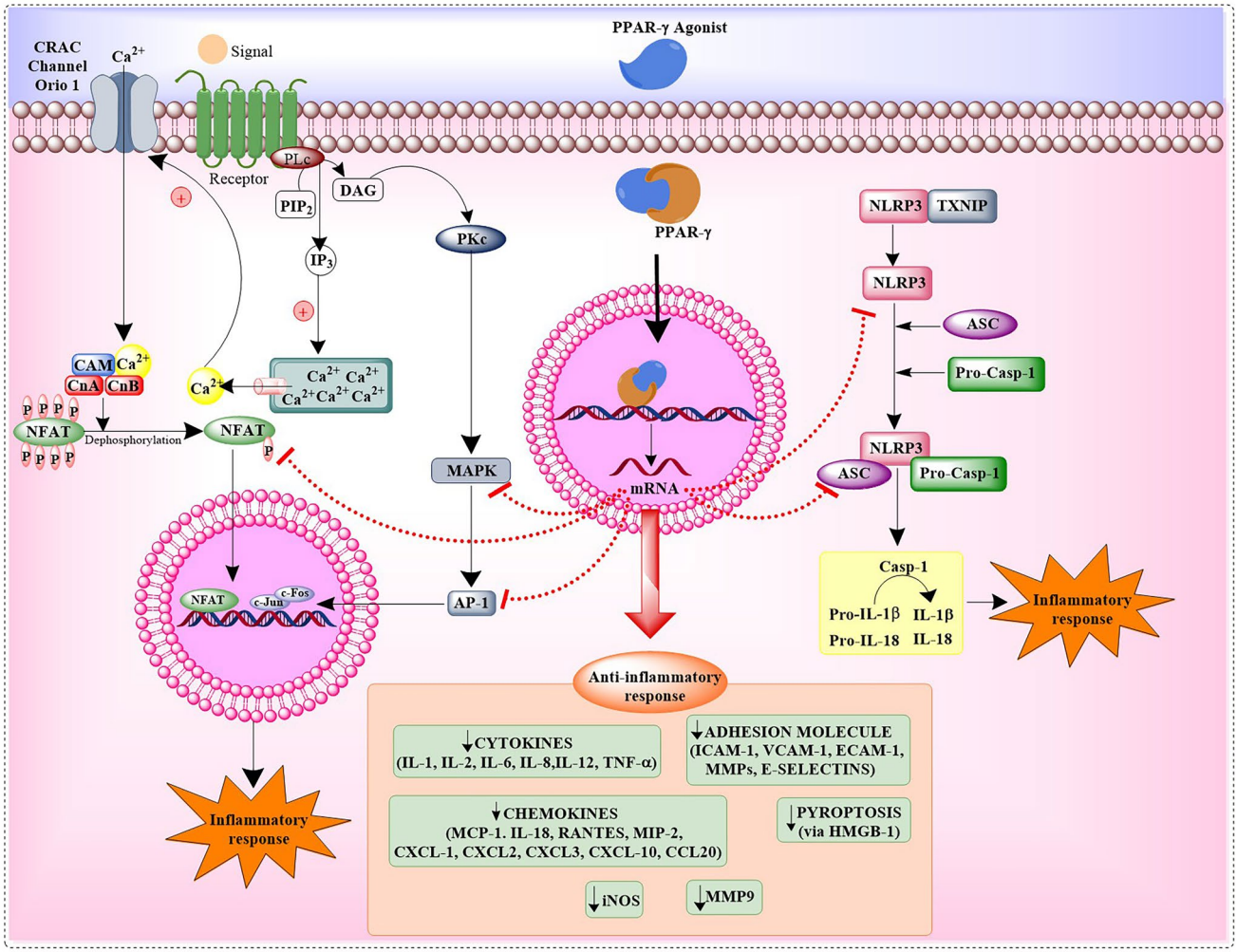


Fig. 3 Anti-inflammatory activity of PPAR-ɣ by suppressing NF-κB signaling pathway. NF-κB: Nuclear factor kappa light chain enhancer of activated B-cells; IL: Interleukins; TNF-α: Tumour necrosis factor-alpha; MCPs: Membrane cofactor proteins; RANTES: Regulated on activation, normal T-cell expressed and secreted; ICAM- Intracellular adhesion molecule; VCAM: Vascular adhesion molecule; ECAM: Endothelial cell adhesion molecule; MMPs: Matrix metalloproteinases; MAPK: Mitogen-activated protein kinase; COX: Cyclooxygenase; iNOS: Inducible nitric oxide synthase; ERK: Extracellular regulated kinase; JNK: c-Jun N-terminal kinase

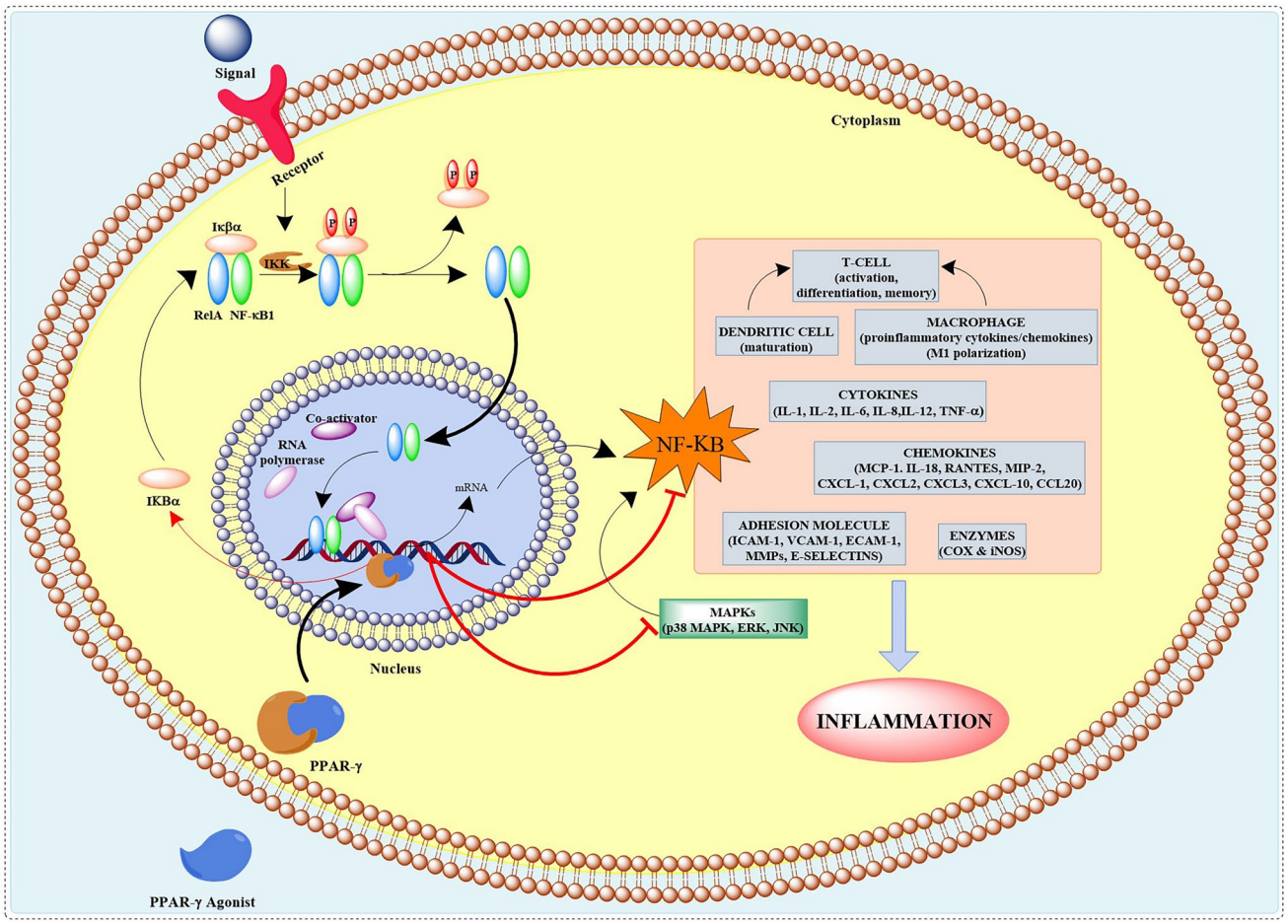


Fig. 4 Anti-inflammatory activity of PPAR-γ through inhibition of NFAT, MAPK, AP-1, NLRP3 signaling pathway. CAM: Calmodulin; CnA & B: Calcineurin A & B; NFAT: Nuclear factor of activated T-cells; PKc: Protein kinase C; MAPK: Mitogen-activated protein kinase; AP-1: Activator protein-1; NLRP3: NLR family pyrin domain containing 3; TXNIP: Thioredoxin-interacting protein; ASC: Apoptosis-associated speck-like protein containing a CARD; Pro-casp-1: Procaspase-1; IL: Interleukins; TNF-α: Tumour necrosis factor-alpha; ICAM- Intracellular adhesion molecule; VCAM: Vescular adhesion molecule; ECAM: Endothelial cell adhesion molecule; MMPs: Matrix metalloproteinases; MCPs: Membrane cofactor proteins; RANTES: Regulated on activation, normal T-cell expressed and secreted; MIP: Macrophage inflammatory protein-2; CXCLs: Chemokine (C-X-C motif) ligands; CCL20: Chemokine (C–C motif) ligand 20; iNOS: Inducible nitric oxide synthase; HMGB-1: High mobility group box protein-1

[116]. Also, in ischemia, PPAR-γ found to reduce inflammation through the inhibition of the NF-**κ**B pathway. Luteoloside exerted a neuroprotective effect on cerebral ischemic injury induced by MCAO in rats. It upregulates PPAR-γ expression and acts as an anti-inflammatory agent by suppressing the NF-**κ**B pathway [117]. In cerebral ischemia, PPAR-γ's activity upregulates Nrf2 signaling, which suppresses NF-κB signaling, inhibiting the production of inflammatory cytokines and chemokines. Chrysin, an agonist of PPAR-γ receptor, rescues a rat myocardium from ischemia–reperfusion injury via PPAR-γ/Nrf2 activation. It significantly inhibited inflammatory response by activating the Nrf2 signaling pathway, which inhibits the production of inflammatory cytokines and chemokines by suppressing the NF-**κ**B pathway [118]. Huo et al. studies reveal that PPAR-γ is an E3 ubiquitin ligase that induces the ubiquitination and degradation of NF-κB when interacting with it.

Additionally, the PPARligand-binding domain delivered Lys48-linked polyubiquitin, which resulted in NF-κB ubiquitination and degradation.Lys28 was considered necessary for ubiquitination and degradation of p65 mediated by PPAR-γ, as it inhibited proinflammatory responses mediated by NF-κB/p65 [119]. These results demonstrate that PPAR-γ E3 ubiquitin ligase activity promotes ubiquitination and degradation of p65 through Lys48-linked ubiquitination. This function is required to stop NF-κB signaling pathway-induced inflammation (Table 1).

Downregulation of NLRP3 Expression by PPAR-γ

NLRP3 (NLR Family Pyrin Domain-Containing 3) inflammasome contributes to producing proinflammatory cytokines, such as IL-1β and IL-18, during infection and tissue injury. Multiple molecular and cellular events, including ion flux, mitochondrial dysfunction, and ROS, can cause the NLRP3 inflammasome to be expressed [120, 121]. The NLRP3 inflammasome is comprised of NLRP3, an apoptosis-associated speck-like protein with a caspase recruitment domain (ASC) at its C-terminal and procaspase-1 [122]. Recently, it was discovered that thioredoxin-interacting protein (TXNIP) activation is crucial in the relationship between oxidative stress, inflammation, and apoptosis in neurons [123]. Since IR (ionizing radiation) and ROS trigger mitochondrial oxidative stress, TXNIP dissociates from the complex and binds to NLRP3 inflammasomes, causing them to activate [123], causing caspase-1 to activate and the cleavage of pro-IL-1 and pro-IL-18, resulting in cell death and the release of multiple intracellular proinflammatory molecules.

Furthermore, after an ischemic stroke, NF-κB and MAPK signaling pathways promote activation of the NLRP3 inflammasome in neurons [124]. PPAR-γ binding sites were discovered in the promoter regions of a member of the NLRP3 family of proteins in a recent study, suggesting a correlation between PPAR-γ activity and the NLRP3 family of proteins [125]. PPAR-γ inhibited the formation of the NLRP3 inflammasome by decreasing NLRP3-ASC and NLRP3-NLRP3 interactions and NLRP3-dependent ASC oligomerization, which was mediated by an interaction between the PPAR-DNA-binding domain and NLRP3's nucleotide-binding and leucine-rich repeat domains. Umbelliferone (UMB) is a coumarin derivative when administered in a rat model of MCAO-induced focal cerebral ischemia, upregulated the expression of PPAR-γ, which reduces the levels of IL-1β and IL-18, thus exerting an anti-inflammatory effect through suppression of TXNIP/NLRP3 inflammasome [125]. Additionally, administration of Pioglitazone in an animal model of retinal ischemia/reperfusion injury also shows suppression of NLRP3 inflammasome via inhibiting NF-**κ**B and p38 phosphorylation [126].

Additionally, it has been documented recently that activating the Nrf2 signaling pathway through PPAR-γ inhibits the NLRP3 inflammasome, resulting in a decrease in proinflammatory cytokines IL-1β and IL-18, as well as proinflammatory chemokines, resulting in anti-inflammatory activity [127]. This inflammation-reducing mechanism may be used to save the penumbra during cerebral ischemic injury. Ferulic acid in the methotrexate-induced nephrotoxicity animal model upregulates the expression of PPAR-γ, which strongly facilitates the expression of Nrf2/ARE/HO-1 signaling pathway that reduces the ROS overproduction and suppression of NF-**κ**B/NLRP3 inflammasome, thus protecting the cells from further injury [127]. In a recent study, PPAR-γ acts as an endogenous modulator that attenuates the inflammatory activation of NLRP3 in macrophages [128]. As a result, by blocking the NLRP3 inflammatory pathway, PPAR-γ may potentially rescue the penumbra in cerebral ischaemic injury from further inflammatory injury (Table 1).

Inhibition of NFAT Pathway by PPAR-γ

NFAT (Nuclear Factor of Activated T Cell) proteins were initially identified in T cells as transcriptional interleukin-2 activators, the primary T cell immune response regulator. They are found in an inactive phosphorylation state in the cytoplasm [129]. Calcineurin (CaN) is calmodulin (CaM)-dependent serine/threonine protein phosphatase. It mainly dephosphorylates phosphatidylserine and phosphatidylthreonine, with NFAT family proteins serving as the key in vivo substrates [130]. NMDA receptors and other Ca^{2+} channels are activated during cerebral ischemia, causing calcium levels to rise abnormally. This excess of intracellular calcium activates the calcium sensor protein STIM1, which forms oligomers and migrates to the junction between the endoplasmic reticulum and the plasma membrane. It binds to the calcium release-activated calcium (CRAC) channel Orai1. Orai1 activates Ca^{2+}-dependent CaN, which dephosphorylates the cytoplasmic NFAT protein, causing it to move quickly into the nucleus and increase the downstream activity of proinflammatory factor IL-2 [131]. PPAR-γ inhibits the NFAT pathway by preventing NFAT from binding to its DNA target region or inhibiting its nuclear translocation. PPAR-γ inhibits IL-2 expression in T-cell-mediated inflammation by binding to ligands that prevent binding of NFAT to its DNA target region and subsequent transcription or by blocking the protein–protein interactions [132].

Additionally, 15dPGJ2, a PPAR-γ agonist, inhibits NFAT nuclear translocation, thus reducing its activity, which results in a decrease in expressions of IL-2. To prove this finding, the PPAR-γ antagonist reversed the effect of 15dPGJ2 in NFAT transcription. Recently, in rats, n-PUFA has been shown to mitigate Crohn's disease by increasing the PPAR-γ expression, inhibiting the NFAT pathway, and reducing inflammation [133]. In addition, IL-4 is an anti-inflammatory cytokine that promotes its anti-inflammatory activity by increasing the expression of PPAR-γ, which further inhibits NFAT transactivation to reduce inflammation [134].

Anti-inflammatory Activity of PPAR-γ Through Inhibition of MMP9

MMPs (matrix metalloproteinases) are enzymes involved in bone development and repair and the interaction of inflammatory cells and skeletal progenitors [135]. MMP9

is found in inflammatory cells that play a role in regulating inflammation in several tissues and diseases. Current insights from both animal and human models have shown that increased expression of MMPs exists in almost all inflammatory diseases and defense, as well as in general tissue repair and recovery. Cytokines, chemokines, and accessory proteins that bind, retain, or concentrate chemokines are MMP substrates that are important in activating or amplifying inflammatory responses [136]. Glitazones significantly decreased the gelatinolytic activity of MMP-9 induced by TNF-α and PMA in bronchial epithelial cell lines in a concentration-dependent manner [137]. PPAR-ɣ can therefore be used in cerebral ischemia to reduce neuroinflammation by inhibiting the activity of MMP9. Mifepristone reduces neuroinflammation caused by cerebral ischemia–reperfusion injury by increasing the expression of PPAR-ɣ, which significantly reduces the activity of MMP9 [138]. Through the activation of PPAR-ɣ, Genistein inhibits MMP-9 along with inhibition of p38 MAPK phosphorylation, reduces neuroinflammation, and can therefore be used in treating cerebral ischemia [139].

Modulation of iNOS System by PPAR-ɣ

NO is a biological mediator produced by the reaction of L-arginine with NADPH and molecular oxygen in living organisms. However, excessive NO production, catalyzed by iNOS, a soluble enzyme that is active in its dimeric form, is cytotoxic [140]. Through sirt1's iNOS-dependent S-nitrosylation (SNO), the acetylation (Ac) and activation of p65 NF-**κ**B and p53 increases, thereby inducing and/or enhancing inflammatory response and apoptotic change [141]. Therefore, inflammation is modulated by PPAR-ɣ, which blocks iNOS and the production of NO. In macrophages, mesangial cells, and other inflammatory cells, PPAR-ɣ agonists reduce the expression of iNOS as well as the production of NO in a dose-dependent manner. However, the mechanisms underlying PPAR-ɣ and its agonists' inhibition of iNOS expression remain unknown. Pioglitazone attenuates ovarian ischemia–reperfusion injury in female rats by downregulation of iNOS expression and OH-1 [142]. This reflects PPAR-ɣ's ability to suppress the expression of iNOS, thereby limiting inflammation in cerebral ischemia. Phillyrin (Phi) is an anti-inflammatory compound extracted from the fruits of the medicinal plant Forsythia suspensa (Thunb.). Phi, through the activation of PPAR-ɣ, suppresses the expression of NF-κB along with pro-inflammatory factors like IL-1β, IL-6, TNF-α, and iNOS limits the inflammation in the traumatic brain injury model in mice [143] (Table 1).

Pyroptosis Inhibition via HMGB-1

Activation of PPAR-ɣ has been shown to effectively inhibit neuronal pyroptosis, a form of programmed inflammatory cell death, in MCAO and in vitro cultured astrocytes [144]. Along with inhibiting the release of cytokines such as IL-1 and IL-18, pioglitazone has been shown to inhibit pyroptosis-related proteins such as caspase-1, NLRP3, and Apoptosis-associated speck-like protein containing a CARD (ASC) [145]. High-mobility group protein-1 (HMGB-1) was one of the primary mechanisms responsible for the inhibition of pyroptosis. HMGB-1 is a significant DAMP (damage-associated molecular pattern) released into the extracellular environment by damaged or necrotic tissues in the ischemic brain. It acts as an endogenous danger signal, inducing neuroinflammation and microglial activation [146]. It has proinflammatory activity due to its translocation from the nucleus to the cytoplasm and releases into the extracellular space. It tends to bind with advanced glycation end products (RAGE), a transmembrane innate immune receptor that regulates proinflammatory responses, as well as the MAPK and NF-κB signaling pathways, after being released into the extracellular space [147]. Pyroptosis-related cell death can thus be reduced by blocking the cytoplasmic translocation of HMGB-1 and RAGE, which the PPAR-ɣ agonist pioglitazone can accomplish, which not only blocks the cytoplasmic translocation of both HMGB-1 and RAGE but also reduces the levels of pyroptosis-related protein Rac1-GTP, the active form of Ras-related C3 botulinum toxin substrate 1 (Rac1), in both MCAO and OGD models [144]. The oral administration of EPA inhibits the HMGB-1/TLR9 pathway and reduces HMGB-1 expression in an ovariectomized rat model of cerebral ischemia [148]. Telmisartan reduces the neuroinflammation after cerebral ischemia through activation of PPAR-ɣ, targeting the HMGB-1 expression and secretion [149]. This finding supports the use of PPAR-ɣ in post-ischemic injury. Various studies show pyroptosis inhibitory activity, targeting the HMGB-1 expression by TZDs [84, 150, 151], confirming neuroprotection. Another study found that pretreatment with umbelliferone activated PPAR-ɣ and inhibited TXNIP/NLRP3 signaling in the rat MCAO model, implying that PPAR-ɣ is involved in pyroptosis reduction [125].

Inhibition of AP-1 Pathway by PPAR-ɣ

The transcription factor activator protein 1 (AP-1) controls gene expression in response to various stimuli such as cytokines, growth factors, stress, and bacterial and viral infections [152]. The various Jun (c-Jun, junB, junD) and Fos [c-fos, fosB, fos-related antigen-1(fra-1)] family protein combinations determine the composition of active hetero/homodimers within the cell as well as the function of the

genes they regulate [153]. External signals, such as those caused by cerebral ischemia, can trigger the transcription of early genes such as c-Fos and c-Jun, followed by their translation into nuclear proteins of the Fos and Jun families [154]. After re-translocation to the nucleus, it binds to the target gene's DNA regulatory region, controlling its transcriptional efficiency and expression and acting as a messenger in signal cascades. AP-1 can cause apoptosis and the production of adhesion and inflammatory factors during inflammatory reactions [155]. By competing with AP-1 for binding to the p300 and CBP coactivators, PPAR-ɣ inhibits the AP-1 signaling pathway [156]. This reduces the expression of inflammatory cytokines. As a result, it plays a neuroprotective role in cerebral ischemia by preventing inflammatory cell infiltration as well as cytotoxicity. Oleic acid is an endogenous PPAR-ɣ agonist that may reduce inflammatory factor expression in cerebral ischemia, possibly due to PPAR-ɣ's antagonistic effect on AP-1 signaling, which the PPAR-ɣ antagonist GW9662 may suppress. Isoniazid, an antibiotic for tuberculosis, through PPAR-ɣ activation, suppresses inflammation in zebrafish by inhibiting the transcriptional regulatory activity of AP-1 and NF-**κ**B [157]. In summary, PPAR-ɣ inhibits various inflammatory pathways and cytokines, thus acting as a neuroprotective factor in cerebral ischemic injury (Table 1; Fig. 4.

PPAR-ɣ Mediated Inhibition of Apoptosis

PPAR- has a complex multi-mechanistic neuroprotective function in cerebral ischemic injury, involving the regulation of numerous processes, including inflammation inhibition, oxidative stress reduction, pro-apoptotic factor production suppression, and pro-apoptotic factor expression promotion [24]. After an ischemic injury, ROS synthesis increases, resulting in damage to intracellular biofilm lipids (for example, MDA), proteins, and nucleic acids, as well as mitochondrial damage and elicited release of apoptosis-inducing factor (AIF) and cytochrome C (Cyt-C) from mitochondria [158]. The activation of cleaved caspase-3 and cleaved caspase-9, which control the levels of anti-apoptotic proteins, is part of a downstream cascade caused by increased AIF and Cyt-C levels. During ischemic injury, PPAR-ɣ activation can suppress the signaling pathway of NF-κB, also known as the PPAR-ɣ-ERK-NF-κB signaling pathway, and reduces the expression of iNOS, gelatinase B, and scavenger receptor A secretion, thus inhibits the pro-apoptotic protein caspase-3 expression and promoting the anti-apoptotic protein Bcl-2 expression, which can protect cells from death [159]. By suppressing the pathway of JAK-STAT, PPAR-ɣ decreases the production of IFN-ɣ and iNOS, thereby regulating apoptosis [160]. PPAR-ɣ inhibits the JAK-STAT pathway, inhibiting the development of IFN- and iNOS and thus controlling apoptosis.

Additionally, by upregulating the cytoprotective response factor HO-1, PPAR-ɣ can protect neurons from ischemic injury-induced apoptosis [161]. Its anti-apoptotic properties may be a result of its anti-inflammatory and antioxidant properties. By blocking pyroptosis-related proteins such as caspase-1, the NLRP3 inflammasome, and ASC, and decreasing the cytokines (IL-1β and IL-18) release, the PPAR-ɣ agonist pioglitazone was able to effectively reverse neuronal pyroptosis induced by ischemia and hypoxia in in-vivo MCAO and OGD models [144]. On the ischemic side of the middle cerebral artery, PPAR-ɣ positive cells were detected, and treatment with the natural agonist 15d-PGJ2 decreased infarct size, caspase-3 expression, the necrotic cascade response, and apoptosis [162]. Through activation of PPAR-ɣ, Bergenin increases the expression of anti-apoptotic protein Bcl-2 as well as inhibited the expression of Bax. Along with this, Bergenin decreases ROS production by regulating the p38 MAPK pathway [163]. Furthermore, the PPAR-ɣ agonist rosiglitazone induces p38 and JNK MAPK phosphorylation in neurons. It prevents neuronal apoptosis in an animal model of cerebral ischemia, primarily by promoting DUSP8 and Bcl-xl upregulation [60]. In the MCAO stroke model, PPAR-ɣ-deficient mice had an extended infarct region. The neuronal deficiency was more severe in PPAR-ɣ—deficient models. Furthermore, in PPAR-ɣ—deficient mice, cell death-promoting Bcl-2 associated X and active caspase-3 expression was increased, while cell death-resisting Bcl-2 expression was suppressed. In cerebral ischemic injury, this was characterized by reinforced endoplasmic reticulum (ER) stress reactions in in-vivo brain specimens as well as in vitro neurons [164]. As a result, this demonstrated that PPAR-ɣ protected the brain from cerebral ischemic injury by suppressing ER stress, implying that PPAR-ɣ is a potential target in treating ischemia. PARP-1 (poly ADP-ribose polymerase-1) is a protease that is widely expressed in eukaryotic cells and plays an essential role in sensing and regulating cellular stress as well as repairing the damage. When DNA damage occurs, activation of PARP-1 promotes DNA repair and maintains genomic stability, whereas failure to repair DNA damage may result in apoptosis and caspase signaling activation [165]. As a result, inhibiting PARP-1 activation has neuroprotective properties. The analysis of proapoptotic markers in the OGD model revealed significantly increased caspase-3 and PARP1 protein levels, which were relieved by the PPAR-ɣ agonist 15d-PGJ2 and could be reversed by administration of the PPAR-ɣreceptor inhibitor GW9662 [166]. *Clinacanthus nutans* (*C. nutans*) is a traditional herbal medicine that is widely used in Asian countries to treat various ailments such as snake and insect bites, skin rashes, viral infections, and cancer. It mitigates neuronal apoptosis and cerebral ischemic injury by selectively increasing the CCAAT enhancer-binding protein (C/EBP) β binding to specific C/EBP binding

site (− 332 ~ − 325) on the PPAR-γ promoter to augment its transcription. C/EBPβ upregulation of PPAR-γ expression is a novel transcriptional activation that suppresses ischemic neuronal apoptosis and brain infarction [167]. Therefore, C. nutans can improve the C/EBPβ- PPAR-γ neuroprotective signaling pathway, opens the door to future drug development to prevent and treat ischemic stroke (Table 1).

Role of PPAR-γ in Neurogenesis and Differentiation

After a brain injury, neuronal stem cells (NSC) and progenitors are thought to proliferate, migrate to, and differentiate at injury sites, affecting structural and functional recovery to varying degrees. Endogenous stem cells and stem cell transplantation therapy, which are supported by their local vasculature, are promising new therapeutic strategies in the chronic neuroinflammatory environment that occurs with brain damage, stroke, and other neurodegenerative diseases [168–170]. PPAR-γ is essential for the regulation of early brain development and post-injury brain repair [24]. PPAR-γ activation promotes neurite growth in mature neurons, vital for maintaining proper neuronal connectivity in neuronal networks [171]. PPARγ-mediated pathways have also been shown to play a role in the proliferation and differentiation of NSCs [172, 173]. PPAR-γ activation by PPAR-γ agonists stimulated NSC proliferation and inhibited neuron differentiation, while abundant PPAR activation with higher agonist levels resulted in cell death [174]. Oligodendrocytes are required to form and maintain myelin [175], and PPAR-γ plays a role in the differentiation and function of oligodendrocytes [176]. It has been seen that M2 microglia promotes neurogenesis and oligodendrogenesis from neural stem/progenitor cells by increasing the level of 15dPGJ2, an endogenous PPAR-γ ligand that activates PPAR-γ receptor, and these effects are blocked by the PPAR-γ antagonist GW9662 [177, 178]. It has been shown that GW9662 may also inhibit the differentiation of neurons and astrocytes induced by pioglitazone and rosiglitazone in adult rat brains [179].

A transient immune response induced by lipopolysaccharide (LPS) impaired hippocampal neurogenesis and hippocampus-dependent spatial memory. PPAR agonist activity protects neurogenesis and memory from the effects of LPS-induced transient illness [168]. The blockade of PPAR-γ was able to significantly correct the effects of cannabidiol on reactive gliosis and, subsequently, neuronal damage. Besides, cannabidiol-mediated activation of PPAR-γ is associated with significant neurogenic activity in the granule cell layer of the hippocampus [180]. Promoting microglia/macrophage polarisation from proinflammatory M1 to anti-inflammatory M2 phenotype was considered a potential treatment for ischemic stroke. Following cerebral ischaemic injury, Astragaloside IV, the PPAR-γ agonist, has been found to promote microglia M2 polarisation and enhances neurogenesis and angiogenesis [181]. Also, glitazone treatment in the early pot-ischaemic phase and inhibiting pro-inflammatory cytokines promote neurogenesis by activating the innate and bone marrow-derived stem cells in rats [182]. These results together, therefore, suggest that PPAR-γmediated activation may enhance neurogenesis, angiogenesis, and neurological functional recovery, which may be partially achieved by transforming microglia/macrophage from M1 to M2 phenotype in a PPAR-γ dependent manner after cerebral ischemia, thereby contributing to the improvement in ischaemic brain tissue repair. Propane-2-sulfonic acid octadec-9-enyl-amide (N15), a novel PPAR-α/γdual agonist, protected rats from ischemia-induced acute brain damage and improved cognitive ability during the chronic phase of ischaemic stroke. Oral administration of N15 in the MCAO rat model improves survival post-MCAO and increases the newly mature neurons, and enhanced the expression levels of growth-associated protein-43, synaptophysin, and brain-derived neurotrophic factor and neurotrophin-3 in the hippocampus [183] hence, promoting neurogenesis and neuroplasticity in mCAO rats by PPAR-α/γ signaling pathway. These data indicate that PPAR-γ ligands might support the structural and functional recovery of the brain following ischemic insults (Table 1).

Repairing of Damaged Tissue Through Angiogenesis by PPAR-γ

Angiogenesis is the formation of new blood vessels around an injured brain that help to restore damaged areas and trigger neurovascular repair [184]. PPAR-γ's activation increases the vascular endothelial growth factor (VEGF) in human vascular smooth muscle cells [185]. PPAR-γ coactivator (PGC)-1α is a transcriptional coactivator regulating oxidative and mitochondrial metabolism and angiogenesis activity in the brain. (PGC)-1a is a known VEGF gene transcription regulator elevated in the cortex during chronic hypoxic exposure [186, 187]. Rosiglitazone has been shown to increase endothelial cell proliferation, NOS expression in endothelial cells, promote angiogenesis, maintain CBF, and reduce neurological loss and functional recovery [188]. In the ischemic model of KKAy mice, pioglitazone administration reduced VEGF protein levels and increased eNOS phosphorylation at Ser-1177 and Akt phosphorylation at Ser-473 in the ischemic muscle [189]. As a result, it appears that eNOS activation is required for pioglitazone to promote angiogenesis in ischaemic tissue. Nevertheless, in another study, it was found that the Akt-VEGF pathway is necessary for pioglitazone's ischemia-induced angiogenic effect and that pioglitazone does so in a PPAR-γ-independent manner [190]. In addition, 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 [191]. Resveratrol has also been shown to perform pharmacological pre-conditioning by activation (PGC)-1α, reducing the extent of ischemia/reperfusion injury [192]. Cilostazol has also been shown to increase the collateral blood flow in the ischemic hind limbs of STZ-induced diabetic mice through a PPAR-ɣ-dependent mechanism [193].

Alleviation of Neurological Deficits

A reduced infarcted area, primarily a morphological feature, is not always associated with improved neurological outcome, which is the most clinically relevant endpoint of any stroke treatment. Is it possible for PPAR-ɣ agonists to improve neurological functions? Indeed, both TZD and non-TZD PPAR-ɣ agonists improve ischemic stroke recovery; this improvement could be attributed to the stimulation of exclusively cerebral PPAR-ɣ, as demonstrated by intracerebral pioglitazone application**.** Pioglitazone and rosiglitazone have been shown to enhance learning and memory [194]. Curcumin has also been shown to improve STZ-induced dementia in mice by activating the PPAR-ɣ receptor [195]. Pioglitazone has also been shown to promote locomotive recovery following spinal cord injury [196]. Thus, based on the data presented above, we can infer that PPAR-ɣ can mitigate the neurological deficits caused by cerebral ischemic injury.

Preconditioning Neuroprotection

The ischemic preconditioning (IPC) can induce brain ischemic tolerance (BIT) in accordance with previous studies [197]. Although several molecular regulatory pathways have been linked to IPC, the protective mechanisms underlying it are not fully understood [198]. After brain ischemia, extracellular glutamate accumulation, also known as excitatory glutamate neurotoxicity, causes neuronal death [40]. Excitatory amino acid transporters (EAATs) maintain the glutamate level in the extracellular space under normal conditions [199]. There have been five types of EAATs discovered so far. The most abundant EAAT in the brain is EAAT2, also known as glial glutamate transporter-1 (GLT-1); it is primarily responsible for glutamate uptake (up to 90%) and keeps extracellular glutamate levels below neurotoxic levels [199]. It has been found that cerebral IPC increases GLT-1 function and expression in the hippocampal CA1 region in rats and that the GLT-1 selective antagonist dihydrokainate and GLT1 antisense oligodeoxynucleotides reduce BIT induced by IPC [200, 201].

Furthermore, other studies back up the idea that GLT-1 is involved in the induction of BIT induced by IPC [202, 203]. However, the mechanism by which GLT-1 is regulated during this process is unclear. PPAR-ɣ plays a neuroprotective role in a variety of neurological disorders, including cerebral ischemia [29, 201]. When mice with PPAR-ɣknockouts have their middle cerebral arteries occluded (MCAO), they have more brain damage [201]. Furthermore, a human study found that a higher plasma concentration of 15-dPGJ2, an endogenous PPAR-ɣ agonist, is linked to better neurological outcomes in acute ischemic stroke [204]. Neuroprotective mechanisms of PPAR-ɣ include anti-inflammatory effects, prevention of apoptosis, reduction of oxidative stress, and inhibition of glutamate excitotoxicity [24, 38].

Interestingly, it has been found that GLT-1 may be the target protein for PPAR-ɣ [205]. Activation of the PPAR-ɣ results in increasing the promoter activity of GLT1/EAAT2 by fourfold, thus providing neuroprotection [205]. Several studies [206–208] have shown that pre-conditioning with pioglitazone protects from apoptosis and mitochondrial ultrastructure injuries during ischemia by inhibiting PI3K and p42/44 MAPK pathways. An extracellular signal-regulated kinase (ERK), discovered 30 years ago as part of the mitogen-activated protein kinase (MAPK) family, exerts cellular effects by controlling multiple nuclear transcription factors and cytosolic proteins. The ERK pathway is thought to be linked to inflammatory responses, apoptosis, and autophagy. During hepatic ischaemic reperfusion injury, inhibiting the ERK pathway was found to be protective. PPAR has been linked to cell proliferation, differentiation, and apoptosis in studies. Simultaneously, there is a large body of evidence that phosphorylated ERK (p-ERK) can activate PPAR. For inflammatory response and apoptosis, the ERK/PPAR signaling pathway has been widely used. Cafestol is a natural diterpene extract from coffee beans that are primarily found in unfiltered coffee. According to the findings, Cafestol has various potential pharmacological effects, including anti-inflammation, antioxidant, liver protection, antitumor, and anti-diabetes. The anti-inflammatory effect of cafestol is thought to be due to the inhibition of the ERK pathway [209]. Cafestol also affects the metabolic pathways that are linked to PPAR [210]. By inhibiting the ERK/PPAR pathway, Cafestol pre-conditioning reduces inflammation, apoptosis, and autophagy during HIRI [211]. Also, preconditioning with hyperbaric oxygen (HBO) gives neuroprotection against cerebral ischemic injury. Preconditioning with HBO increases the levels of PPAR-ɣ mRNA and protein, PPAR-ɣ DNA binding activity, 15d-PGJ_2, and antioxidant enzymatic activities. So, on preconditioning with HBO, it has been observed that it triggers the activation of the PPAR-ɣ receptor, which further leads to the production of 15d-PGJ_2, and subsequently increases the downstream antioxidant enzymatic activities [212], hence, provides neuroprotection in cerebral ischaemic injury.

Clinical Studies on PPAR-ɣ Agonists Against Diseases Involving Injury

There are very few clinical trials that have been conducted related to PPAR-ɣ in ischemic injury. Diabetes mellitus increases the risk of coronary heart disease, stroke, and peripheral vascular disease. It has been identified as an independent risk factor for the progression of coronary artery disease. Diabetes has been linked to an increased risk of cardiovascular death in both men and women. The introduction of stents in diabetic patients showed increased restenosis (a section of an artery that had previously been treated for blockage narrows again) rates and late loss index compared to nondiabetic patients. Therefore, combining the thin-strut MULTI-LINK stent and pharmacologic therapy with the oral PPAR-ɣ agonist rosiglitazone has been hypothesized to reduce restenosis after intracoronary stenting in type 2 diabetic patients; however, the results of this study are not known yet [257]. Although the same problem of restenosis occurs even with drug-eluting stents (DESs), and to reduce restenosis, a comparative study of telmisartan which is well-known for its selective PPAR-ɣ activity with valsartan, which is an angiotensin receptor blocker with negligible PPAR-ɣ activity, has been conducted.

In comparison, Telmisartan showed a significant reduction in neointima volume and pulse wave velocity than valsartan. Furthermore, a reduction in IL-6 and TNF-α levels was significantly greater in the telmisartan group than in the valsartan group [258]. In another clinical study, pioglitazone's effect on insulin resistance, the clinical course of atherosclerosis, and coronary heart disease have been evaluated. Pioglitazone administration in diabetic patients has been shown to normalize systolic blood pressure. It reduces the chances of ischemic cell death in atherosclerosis and coronary heart disease [258]. This data demonstrates the importance of PPAR-ɣ in preventing ischemic cell death. Thus this mechanism can be used in cerebral ischemic injury to provide neuroprotection.

Future Perspective

Selective activation of different PPAR isoforms may account for differences in molecular pathways underlying neuroprotection, and these differences are still poorly understood. Finally, using PPAR-ɣ agonists to target harmful processes associated with ischemic injury will enhance current treatment procedures for patients with cerebral ischemic injury. Critical issues, however, remain unresolved. Until firm conclusions about the therapeutic efficacy of PPAR-ɣ ligands can be drawn, well-structured clinical trials testing their effect on ischemic injury recovery are needed.

Concluding Remarks

Despite the lack of clinical evidence, animal models indicate that PPAR-ɣ activation could be a rational and successful technique for preventing cerebral ischemic injury. As most would expect, given their pleiotropic pharmacological profile, the beneficial effects of PPAR-ɣ agonists in experimental ischemic models are mediated by various mechanisms. The neuroprotective properties tend to be specifically linked to oxidative damage reduction, as well as anti-inflammatory and anti-apoptotic properties. In animal models, PPAR-ɣ not only decreases inflammation and oxidative stress, but it also tends to play a role in tissue regeneration by facilitating angiogenesis and neurogenesis. Neuroprotection can also be achieved by preconditioning with PPAR-ɣ agonists by attenuating inflammation and oxidative stress-mediated by glutamate excitotoxicity. As a result, PPAR-ɣ, via multiple mechanistic pathways, can be considered a potential therapeutic candidate for the treatment of cerebral ischemic injury.

Author's Perspective

The mechanism of cerebral ischemic injury is still not well known. Studies reveal that cerebral ischemic injury increases the expression of PPAR-ɣ. Our review demonstrates that PPAR-ɣ, by its interactions with various downstream pathways and multi-targeted effects, may play a potentially protective role against cerebral ischemic injury. PPAR-ɣ has been shown to protect against neuroinflammation, oxidative stress complimented with neurogenesis and angiogenesis, which helps restore the damaged tissue. Various preclinical studies have been shown that PPAR-ɣ agonistic ligands such as 15d-PGJ2, pioglitazone, troglitazone, and rosiglitazone exert neuroprotective effects by promoting PPAR-ɣ activation and expression. Furthermore, it exerts anti-inflammatory activity by reducing inflammation via inhibition of proinflammatory cytokines (TNF-α, IL-1β, IL-6, etc.), modulation of MAPK signaling pathway, Adhesion molecules, NF-κβ, NFAT, NLRP-3 inflammasome, AP-1 signaling pathway and modulates iNOS expression. It also regulates the expression of antioxidant elements, which aids in the reduction of oxidative stress in ischemic injury. Preconditioning with a PPAR-ɣ agonist protects neurons and prevents them from suffering from cerebral ischemia injury. However, animal and cell models are frequently used in the related investigation of PPAR-ɣ's neuroprotective function in cerebral ischemic injury, and there is a lack of large-scale clinical research at present. As a result, we can investigate related topics more extensively and precisely with the advancement of molecular biology, bioinformatics,

and other technologies. This can lead us to develop more effective, targeted, potent PPAR-γ agonists as a therapeutic intervention in treating cerebral ischemia.

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Declarations

Competing interests There are no conflicts of interest.

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