

# Protective Effects of Pioglitazone on Cognitive Impairment and the Underlying Mechanisms: A Review of Literature

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**Abstract:** Pioglitazone, a peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) agonist, is known to have anti-inflammatory and anti-oxidant effects on the brain, and its clinical potential in the treatment of cognitive impairment in diseases such as Alzheimer's disease (AD) and Parkinson disease (PD) is currently being explored. This review focused on the reported beneficial effects of pioglitazone on cognitive dysfunction and summarized the associated mechanisms associated with pioglitazone-induced improvement in cognitive dysfunction. Our review of the relevant literature indicated that there is conclusive evidence of the effect of pioglitazone on improving cognitive impairment via its agonistic effect on PPAR- $\gamma$ . Further, several mechanisms of action have been reported, and these include enhanced NF-kB and p38 activity; regulation of the pro-inflammatory cytokines IL-1, IL-6, and TNF- $\alpha$ ; inhibition of A $\beta$  production; alterations in the levels of mitochondrial proteins such as mitoNEET; regulation of protein kinases such as CDK5 and JNK; regulation of ROS and MDA levels and the levels of the antioxidant proteins TRX1 and PON2; and increased expression of thyroid hormone receptors. Despite these promising findings, pioglitazone treatment is also associated with cardiovascular risks, such as weight gain and edema, which subsequently increase the risk of mortality. Further, it has been documented that pioglitazone may be unable to cross the blood–brain barrier when administered in certain forms, and it can also cause cell death when administered at high concentrations. Therefore, further research is required to explore the effects of acute and chronic pioglitazone treatment on memory function and the associated risks, in order to determine its clinical applicability in the treatment of cognitive disorders. Nonetheless, the current literature does demonstrate that pioglitazone promotes the function of PPAR receptors in ameliorating inflammation, oxidative stress, amyloidogenesis, and hypothyroidism, and enhancing neurogenesis, synaptic plasticity, and mitochondrial function. Therefore, these mechanisms of PPAR receptors warrant further investigation in order to establish the clinical applicability of pioglitazone in the treatment of cognitive disorders, such as PD and AD, and neuronal impairment in conditions such as diabetes.

**Keywords:** peroxisome proliferator-activated receptor gamma agonist, cognitive impairment, neuroinflammation, mitochondria

## Introduction

Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear receptor superfamily and are comprised of three isoforms: PPAR- $\alpha$ , PPAR- $\beta$ , and PPAR- $\gamma$ . PPAR- $\gamma$  is considered to be a regulator of glucose metabolism and fatty acid synthesis via the activation of factors that promote adipocyte differentiation.<sup>1</sup> PPAR- $\gamma$  is also known to be involved in the regulation of several physiological processes, such as the increased response of insulin receptors to insulin, lipid metabolism, and cellular proliferation.<sup>2</sup> Therefore, PPAR- $\gamma$  is an interesting therapeutic target for the treatment of metabolic disorders.

Pioglitazone is a thiazolidinedione that acts as an activator of PPAR- $\gamma$  and is commonly used to treat hypoglycemia. Recent studies have shown that certain pioglitazone formulations can cross the blood–brain barrier and improve the response of insulin receptors to insulin, regulate glucose metabolism in the brain, and reduce neuroinflammation.<sup>3,4</sup> Attenuation of neuroinflammation can improve cognitive impairment. Accordingly, pioglitazone administration has been shown to lead to improvement in cognitive impairment caused by Alzheimer's disease (AD) and Parkinson disease (PD),

**Table 1** Effect of Pioglitazone on Different Organ System

Sl.No.	Organ	Effect of Pioglitazone
1	Liver	↑ Insulin sensitivity
		↓ Liver steatosis
		↓ VLDL secretion/↑ HDL-C
		↑ Hepatic glucose production
2	Bone	↑ Osteoclastogenesis
		↓ Osteoblastogenesis
		↑ Adipogenesis
		↑ Osteocyte apoptosis
3	Heart	↑ Exacerbation of diastolic dysfunction
		↓ Coronary atherosclerosis
4	Kidneys	↑ Increase plasma volume
		↑ Plasma renin activity
		↑ Sodium reabsorption
5	Muscle	↓ Muscle lipotoxicity
		↑ Insulin sensitivity
6	Ovaries	↓ Systemic hyperinsulinemia
7	Adipose tissue	↑ Adiponectin
		↑ Insulin sensitivity
		↑ TG synthesis
		↓ Adipokine release
8	Arterial wall	↓ Inflammation
		↓ Macrophage recruitment
		↑ Cholesterol efflux

**Abbreviations:** VLDL, Very low density lipoproteins; HDL-C, High density lipoprotein cholesterol; TG, Triglycerides.

as well as improvement in dopaminergic neuronal survival in the brain.<sup>5–11</sup> However, although the results of preclinical studies on model animals and cells lines have been promising, there is not enough evidence to conclusively support the application of pioglitazone for the treatment of cognitive disorders in the clinical setting. In order to understand its clinical potential, it is important to further explore its mechanisms of action that affect cognitive function.

With regard to its mechanism of action in improving cognitive impairment, pioglitazone has been shown to ameliorate inflammation, oxidative stress, amyloidogenesis, and hypothyroidism, as well as enhance neurogenesis, synaptic plasticity, and mitochondrial function via its effects on the relevant PPAR-mediated pathways. Some of these effects of pioglitazone include promoting the anti-inflammatory NF- $\kappa$ B and p38 pathways; inhibiting the expression of beta-secretase 1, which is important for A $\beta$  production; enhancing the expression of proteins that are important for mitochondrial function, such as PGC-1 $\alpha$  and mitoNEET; inhibiting the increase in the production of the pro-inflammatory cytokines IL-1, IL-6, and TNF- $\alpha$  induced by bacterial lipopolysaccharides; regulation of the expression of protein kinases such as AKT and JNK; modulation of the antioxidant proteins TRX1, BDNF, and calcium-calmodulin-dependent protein kinase II (CaMKII); inhibition of ROS

**Table 2** Subtypes of PPAR Receptors and Their Distribution

Sl. No.	Organ/Tissue	PPAR- $\alpha$	PPAR- $\beta/\delta$	PPAR- $\gamma$	
1	Adipose tissue	–	↑ FFA oxidation	↑ Adipogenesis	
				↑ fatty acid storage	
			↓ Body weight	↑ adiponectin	
				↓ TNF-alpha	
2	Muscle	↑ FFA oxidation	↑ FFA oxidation	↑ Insulin mediated glucose uptake	
				↑ Reverse cholesterol transport	
				↓ Inflammation	
3	Liver	↑ FFA oxidation	↑ FFA oxidation	↑ Fatty acid storage	
		↑ HDL			
		↓ Triglycerides			
		↓ LDL			↓ Body weight
		↓ VLDL			
4	Vessel wall	↑ Reverse cholesterol transport	↓ Inflammation	↑ Reverse cholesterol transport	
		↓ Inflammation		↓ Inflammation	

**Abbreviations:** FFA, Free fatty acid; TNF, Tumor necrosis factor; HDL, High density lipoprotein; LDL, Low density lipoprotein; VLDL, Very low density lipoprotein.

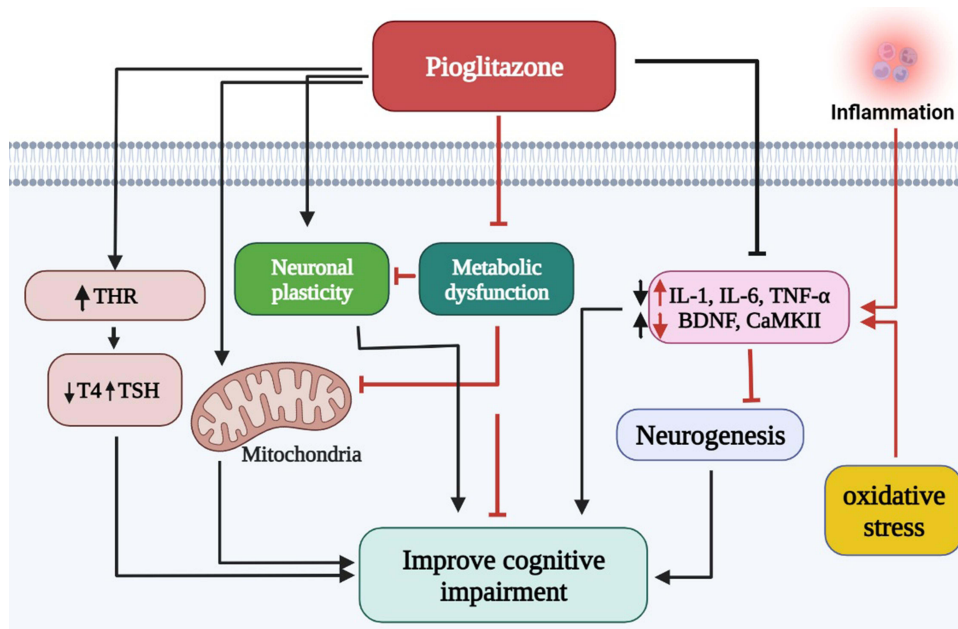
and MDA production; promotion of thyroid function via increased activation of thyroid hormone receptors; and modulation of the LRP1, GSK-3 $\beta$ , and Nrf2/ARE pathways, which are involved in synaptic transmission (Table 1). Despite these promising findings, PPAR- $\gamma$  activation has been reported to increase cardiovascular risks. Therefore, it is important to be cautious about cardiovascular complications in patients receiving drugs that target PPAR- $\gamma$ .

This review focused on studies that report the beneficial effects of pioglitazone on cognitive impairment and the associated mechanisms, such as changes in the expression or activity of proteins, mitochondrial function, neuroinflammation, oxidative stress, synaptic transmission, and thyroid function (Figure 1) (Table 2). We hope that our review will guide researchers to investigate these mechanisms in depth in the future and shed light on the potential clinical applications of pioglitazone for the treatment of cognitive disorders.

## Pioglitazone and Neuroinflammation

Neuroinflammation plays a key role in the pathogenesis of brain diseases<sup>12</sup> and has been implicated in the development of neurodegenerative diseases and cognitive decline.<sup>13</sup> In the central nervous system, inflammatory effectors derived from immune systems, as well as glial cells, specifically, microglia, act as sensors of disturbed brain tissue homeostasis and accumulate locally in response to neuronal cell injury.<sup>14</sup> The production of inflammatory and neurotoxic mediators, such as cytokines, has been commonly linked to intracellular mechanisms, such as protein degradation, mitochondrial dysfunction, axonal transport defects, and apoptosis, which contribute to the progression of neurodegenerative diseases.<sup>12</sup>

The activation of PPAR $\gamma$  has been demonstrated to reduce neuroinflammation.<sup>15,16</sup> PPAR $\gamma$  upregulates cluster of differentiation 36 or CD36, which is involved in the modulation of microglial activation and phenotypic differentiation, and this promotes the phagocytosis of apoptotic cells and contributes to the resolution of inflammation.<sup>15,17</sup> Moreover, PPAR $\gamma$  mediates the downregulation of proinflammatory genes and reduces the production of proinflammatory chemokines, cytokines, and interleukins.<sup>15,18,19</sup> Accordingly, PPAR $\gamma$  agonists have been found to exert anti-inflammatory effects by inducing an increase in the expression of anti-inflammatory-related genes in activated microglia and macrophages.<sup>20</sup> In particular, the beneficial effects of the PPAR $\gamma$  agonist pioglitazone in the reduction of brain



**Figure 1** Mechanisms of pioglitazone in the improvement of memory impairment. The diagram depicts the factors that cause memory impairment (red lines) and the potential protective effects of pioglitazone (black lines).

inflammatory responses have been detected in different *in vivo* and *in vitro* models of neurological conditions, such as AD, PD, Huntington's disease, schizophrenia, and autism spectrum disorders.<sup>21–23</sup> With regard to the mechanisms of pioglitazone, through its effect on PPAR $\gamma$ , it has been found to induce an antioxidant effect and reduce the levels of inflammatory molecules by inhibiting common inflammatory signaling pathways. For instance, pioglitazone reduced the inhibition of both nuclear factor kinase B (NF- $\kappa$ B) and p38 mitogen-activated protein kinase activity,<sup>24,25</sup> which are known to ameliorate the neuroinflammatory response and oxidative stress.<sup>26,27</sup>

Apart from neuroinflammation, increased amyloid- $\beta$  (A $\beta$ ) levels, oxidative stress, and mitochondrial dysfunction are other mechanisms associated with cognitive impairment in neurodegenerative diseases such as AD.<sup>21,28–30</sup> The combination of pioglitazone with fenofibrate was found to be effective in ameliorating the behavioral, neurochemical, and histopathological changes associated with amyloidogenesis induced by increased A $\beta$  levels in model AD mice, and the data indicate that this is a promising therapeutic approach in the management of AD complicated by diabetes and hypercholesterolemia.<sup>29</sup> In another study, administration of pioglitazone was found to provide protection from lipopolysaccharide (LPS)-induced neuroinflammation and amyloidogenesis via targeting the glutamatergic and inflammatory pathways.<sup>30</sup> Based on similar reports by several studies, it is speculated that pioglitazone causes a reduction in A $\beta$  levels by decreasing A $\beta$  formation or increasing its clearance.<sup>26,27,31</sup>

The literature so far indicates that downregulation of the levels of PPAR $\gamma$  and activation of microglia, brain inflammation, and amyloidogenesis are involved in the onset of cognitive deterioration in PD.<sup>32,33</sup> Pioglitazone has an ameliorative effect on PD by decreasing microglial activation, downregulating PPAR $\gamma$  phosphorylation, increasing PPAR $\gamma$  expression, inhibiting beta-secretase 1 expression, and inhibiting A $\beta$  production.<sup>34</sup> There is considerable literature on the mechanisms of pioglitazone in improving cognitive dysfunction associated with PD, and discussing all of these is beyond the scope of the current review. Nonetheless, these mechanisms of cognitive impairment and its improvement by pioglitazone are likely to be true for other cognitive diseases too. Therefore, these findings warrant careful consideration for the treatment of cognitive decline associated with neurological diseases.

## Pioglitazone and Mitochondria

Mitochondrial respiration is the main source of energy in cells.<sup>35</sup> Mitochondria also regulate Ca<sup>2+</sup> signaling, the generation of reactive oxygen species, synaptic function and plasticity, and the arbitration of cell survival,<sup>36</sup> and mitochondrial dysfunction contributes to ageing and neurodegenerative diseases.<sup>37,38</sup> Mitochondria are also involved

in the long-term potentiation of synaptic transmission, a significant process in memory and learning.<sup>39–41</sup> Cognitive impairment has been associated with increased brain mitochondrial oxidative stress, cellular energy depletion, impairment of mitochondrial electron transport and systems, and decreased mitochondrial integrity.<sup>42–44</sup>

Alterations in mitochondrial  $\text{Ca}^{2+}$  efflux, A $\beta$  plaque accumulation, and intracellular deposition of hyperphosphorylated tau are known to accelerate memory deficits in AD.<sup>45</sup> In addition, reduced levels of peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC1- $\alpha$ ), along with decreased ATP levels in the AD brain, trigger a decrease in mitochondrial density in different brain regions, but earlier data contradict this finding.<sup>46</sup> Further, the level of PPAR $\gamma$  protein was found to be increased in the temporal cortex of AD patients.<sup>47,48</sup> Therefore, this line of research requires further research in the future.

The activation of PPAR $\gamma$  stimulates the PGC1 signaling pathway, thus increasing mitochondrial function and mass and counteracting cognitive dysfunction.<sup>49</sup> Through its agonistic effect on PPAR $\gamma$ , pioglitazone has been shown to improve mitochondrial bioenergetics and maintain mitochondrial function, thus promoting cognitive recovery.<sup>50,51</sup> In particular, pioglitazone improves learning and memory by improving synaptic activity and reducing amyloid and tau pathologies.<sup>23</sup> With regard to the underlying molecular mechanisms, pioglitazone was found to increase the expression of PGC-1 $\alpha$  and the production of uncoupling protein 2, a mitochondrial protein that reduces reactive oxygen species, as well as COX-1, and prevents tumor necrosis factor- $\alpha$  (TNF $\alpha$ )-mediated effects.<sup>21,52</sup>

According to small-scale pilot studies on type 2 diabetes mellitus (DM2), pioglitazone increases cerebral blood flow and delays the onset of dementia; the findings indicate that its effects on cognition interacted with its insulin-lowering effects, even in cases without DM2.<sup>23</sup> Several clinical trials conducted along this line have indicated that pioglitazone administration improved cognitive function.<sup>26</sup> Further, combining pioglitazone with other antidiabetic drugs, as well as lowering its dose, had beneficial effects in terms of enhancing memory parameters.<sup>41,42</sup> However, a recent study conducted on randomly selected participants of all age groups suggested that pioglitazone did not slow down the memory impairment and, in fact, was associated with deaths in test populations.<sup>23,53</sup> This study indicated that cardiovascular risks, such as weight gain and edema, which increased the load on the system, were the major causes of mortality.<sup>23</sup> Further, the lack of any effect of pioglitazone on dementia parameters was attributed to its unavailability in the brain cells due to its inability to cross the blood–brain barrier.<sup>15,23,53</sup>

MitoNEET is a protein in the mitochondrial outer membrane that plays a central role in the regulation of mitochondrial function and metabolism.<sup>54</sup> Overexpression of mitoNEET has been found to lead to a significant reduction in inflammation and provide protection against oxidative stress.<sup>55</sup> A recent study demonstrated that pioglitazone exerts neuroprotective and functional benefits following traumatic brain injury by targeting mitoNEET.<sup>56</sup> Further, delayed pioglitazone treatment was found to be more effective in improving mitochondrial bioenergetics and attenuating brain atrophy, thus improving cognitive and motor performance.<sup>55</sup> These findings could mean that the ameliorative effect of pioglitazone on cognitive impairment might involve its effect on mitoNEET. Therefore, it would be interesting to explore the mitoNEET-targeting mechanisms of pioglitazone in the treatment of cognitive disorders.

## Role of Pioglitazone in Neurogenesis

Adult neurogenesis is defined as the formation of mature functional neurons from neural stem cells in the brain.<sup>57</sup> It involves several events that begin with the division of a precursor cell and end with the presence of new mature functional neurons.<sup>57,58</sup> Triggers, such as stress,<sup>59</sup> bacterial LPS,<sup>60</sup> and ischemia,<sup>17</sup> cause neuroinflammatory processes in different brain regions such as the hippocampus and cortex.<sup>61</sup> Microglia are immune cells located within the central nervous system that play a crucial role in the neuroinflammatory response.<sup>62</sup> The activation of microglia and neuroinflammation can seriously affect the regeneration of neurons in different brain regions.<sup>63</sup> Microglial activation caused by LPS administration or elevated levels of proinflammatory cytokines, such as interleukin-6 (IL-6) and TNF $\alpha$ , can disrupt hippocampal neurogenesis and thus affect cognitive and olfactory function, contributing to many neurodegenerative diseases.<sup>64</sup>

PPAR $\gamma$  is involved in the proliferation and differentiation of neural stem cells, controls the production of inflammatory mediators, and is essential in the regulation of brain development and repair following injury. PPAR $\gamma$  exists in most cell types, neurons, vessels, and astrocytes, where it performs multiple functions.<sup>65</sup> In one study performed on experimental mice subjected to diesel exhaust, which causes microglial activation and neuroinflammation, it was found that diesel exhaust reduced adult hippocampal neurogenesis, with male mice showing fewer new neurons in the hippocampal subgranular zone,

the olfactory bulb, and the subventricular zone, and female mice showing fewer new neurons in the olfactory bulb.<sup>66</sup> However, administration of the PPAR $\alpha$  agonist pioglitazone suppressed the effects of diesel exhaust on microglia and neuroinflammation.<sup>67</sup> In another study, rats were administered LPS, which is known to cause inflammation by promoting the synthesis of the cytokines IL-1, IL-6, and TNF- $\alpha$ , leading to cognitive impairment in rats.<sup>64,68</sup> Administration of pioglitazone prior to LPS exposure protected rats from LPS-induced learning and memory impairment through the regulation of secreted cytokines and the improvement of oxidative stress and brain-derived neurotrophic factor (BDNF) levels.<sup>69</sup> However, despite the well-documented anti-inflammatory effects of pioglitazone, it can cause cell death when administered at high concentrations.<sup>70</sup> Therefore, its application in the treatment of PD, AD, DM2, and other diseases associated with cognitive impairment should be assessed with caution.

## Effect of Pioglitazone on Protein Kinases

Protein kinases and phosphatases are phosphotransferase enzymes that catalyze the transfer of phosphates between substrates. A protein kinase catalyzes the transfer of  $\gamma$ -phosphate from ATP (or GTP) to its protein substrates, thus regulating the reactions that modulate the structures and functions of many cellular proteins within cells.<sup>71</sup> An imbalance between kinase and/or phosphatase functions has been considered to be the primary cause of deregulated protein phosphorylation. AD is a progressive neurodegenerative disorder characterized by severe impairment of memory and cognitive function<sup>72</sup> that results from the accumulation of misfolded A $\beta$  and phosphorylated tau proteins in the aging brain.<sup>73</sup> These misfolded proteins form intraneuronal neurofibrillary tangles<sup>74</sup> that lead to oxidative and inflammatory damage, resulting in energy failure and synaptic dysfunction.<sup>75</sup>

In the AD brain, the expression or activity of kinases, such as Akt, extracellular signal-regulated kinase 1 and 2 (ERK1/2), cAMP-dependent protein kinase (PKA), glycogen synthase kinase-3 $\beta$  (GSK-3 $\beta$ ), p70S6 kinase, and cyclin-dependent protein kinases 5 (Cdk5), was found to be increased, whereas that of several protein phosphatases, such as PP1, PP2A, and PP5, was found to be decreased.<sup>76,77</sup> One study demonstrated that pioglitazone could inhibit the *in vitro* phosphorylation of PPAR $\gamma$  by inhibiting the expression of cyclin-dependent kinase 5 (CDK5), which increases the expression of the insulin-degrading enzyme and inhibits  $\beta$ -amyloid cleavage enzyme 1 through PPAR $\gamma$  target genes, leading to A $\beta$  degradation and reduced A $\beta$  production.<sup>78</sup> In accordance with these findings, reduction of A $\beta$  levels in the brain exerted neuroprotective effects in an AD model.<sup>33</sup> Importantly, the use of pioglitazone improved spatial learning, enhanced AKT signaling, and attenuated tau hyperphosphorylation and neuroinflammation<sup>79</sup> through enhanced microglial uptake of A $\beta$ .<sup>80,81</sup>

PD is a neurodegenerative disorder characterized by non-motor and motor symptoms caused by a depletion of striatal dopamine owing to the degradation of dopaminergic neurons in the substantia nigra.<sup>82,83</sup> The available data from several previous studies strongly implicate the dysfunction of kinase activities and phosphorylation pathways in the pathogenesis of PD.<sup>6,32</sup> Some of the important protein kinases associated with increased risk of PD are PTEN (phosphatase and tensin homolog)-induced putative kinase 1 (PINK1), and leucine-rich repeat kinase 2 (LRRK2).<sup>29,32</sup> In particular, PINK1 and LRRK2—along with their associated protein kinase B (AKT) and c-Jun N-terminal kinase (JNK) signaling pathways—are being intensively studied with respect to their relationship to PD.<sup>31,77</sup>

Some studies have demonstrated that treatment with the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine activates caspase-3, leading to neuronal death by apoptosis; however, treatment with neuroprotective drugs such as pioglitazone inhibits the activity of caspase-3 and reduces neuronal damage.<sup>84,85</sup> Previous studies have also indicated that pioglitazone protects dopaminergic neurons by inhibiting abnormal microglia activation, interfering with the phosphorylation of JNK and NF- $\kappa$ B, and suppressing cyclooxygenase 2 expression and subsequent prostaglandin E(2) synthesis.<sup>86</sup>

Thus, the beneficial effects of pioglitazone in PD and AD seem to be linked to its effects on the regulation of protein kinases, and therefore, its protein kinase-related mechanisms should be explored further in the treatment of cognitive disorders.

## Pioglitazone and Oxidative Stress

Chronic exposure to stress increases the levels of stress hormones, such as cortisol, and leads to several health complications, including alterations in brain functions.<sup>87,88</sup> In addition, severe and long-term elevation in the levels of stress hormones can induce changes in normal brain structure and function,<sup>89</sup> ultimately affecting cognitive function and leading to memory impairment.<sup>90,91</sup> Several studies conducted in experimental rats have revealed that stress alters the expression and function of



proteins, such as BDNF and CaMKII, which affect cognitive function.<sup>92–94</sup> Earlier studies indicated that activation of the NMDA receptor in glutamatergic excitatory pathways following a behavioral experience is essential for long-term memory (LTM) storage.<sup>95</sup> When this receptor is activated, calcium enters into the neurons and binds to calmodulin to form the Ca<sub>2</sub>C/CaM complex, which is recognized by multiple enzymes and induces a molecular signaling cascade whose main function is to reshape synaptic structure and physiology, as well as regulate the expression of genes necessary for the formation of LTM.<sup>100</sup> It is considered that CaMKII is one of the main targets of Ca<sup>2</sup>C/CaM, and accordingly, CaMKII activity is increased in response to learning and its inhibition causes LTM impairment.

Interestingly, pioglitazone has been reported to exert antioxidant activity,<sup>96</sup> and treatment with pioglitazone was found to rescue the cardiovascular system and cognitive impairment caused by elevated levels of oxidative stress.<sup>97</sup> The underlying mechanisms of the cardioprotective effects and improvement in memory impairment induced by pioglitazone were found to be mediated via modulation of the antioxidant protein TRX1<sup>98</sup> and increased expression of BDNF and CaMKII. In particular, CaMKII binding and pioglitazone-induced phosphorylation has been found to regulate autonomous activity and the location and/or transport of proteins in the post-synaptic density, including the NMDA receptor, synapsin 1, F-actin, and calcium channels, to regions of interest.<sup>99</sup> In addition, the expression of p47phox and gp91phox, which is increased under conditions of oxidative stress, was reduced following treatment with pioglitazone.<sup>96</sup> Further, several studies have pointed to the effect of pioglitazone on increased expression of the antioxidant protein PON2.<sup>100,101</sup>

Malondialdehyde (MDA) is one of the products generated from the peroxidation of fatty acids, and an increase in the levels of reactive oxygen species has been positively correlated with overexpression of MDA.<sup>102,103</sup> Pioglitazone has also been found to reduce oxidative stress through a reduction in the levels of MDA and inhibition of ROS production and inflammatory pathways; this further verifies its potent antioxidant activity.<sup>104</sup> All these findings indicate the role of pioglitazone against stress in the brain via regulation of TRX1, p47phox, and gp91phox activity, and the levels of MDA and ROS.

## Pioglitazone and Thyroid Function

Thyroid hormones, such as thyroxine (T4) and triiodothyronine (T3), regulate many physiological functions.<sup>105</sup> These hormones play essential roles in brain development, particularly in neurogenesis and synaptogenesis.<sup>106,107</sup> More specifically, T3 and T4 are produced by thyroid follicular cells in the thyroid gland and then released into the bloodstream, from where they are capable of crossing the blood–brain barrier<sup>108,109</sup> and ultimately binding to thyroid hormone receptor (THR). THRs are nuclear receptors that can be classified into two isoforms, THR $\alpha$  and THR $\beta$ ,<sup>110</sup> the distribution of which differs among tissues. The THR $\alpha$ 1 receptor is predominantly expressed in the heart and skeletal muscle,<sup>111</sup> whereas THR $\beta$ 1 is primarily expressed in the liver, kidney, and brain.<sup>112</sup> Of note, THRs are abundantly expressed in the hippocampus, the structure within which memory is formed in the brain.<sup>107</sup> THR $\alpha$ -knockout mice exhibited memory impairment; this confirms the role of THR $\alpha$  in memory processes.<sup>113,114</sup> Hence, in hyperthyroidism, hypothyroidism, and cretinism, which are characterized by abnormal levels of thyroid hormones,<sup>115</sup> hippocampal functionality might be altered and potentially result in cognitive dysfunction.<sup>116</sup> Indeed, neuroimaging studies have reported that in patients with hypothyroidism, the structure and function of the hippocampus were altered.<sup>117–119</sup>

Treatment with pioglitazone has been shown to enhance the activation of THRs and, thus, learning and memory processes.<sup>112</sup> Memory impairment caused by hypothyroidism was improved by pioglitazone via a reduction in oxidative stress that was attributed to the increased expression of superoxide dismutase and catalase.<sup>120</sup> In addition, pioglitazone treatment in patients with DM2 was associated with reduced levels of T4 and increased levels of TSH; this indicates the possible activation of THRs through the activation of PPAR $\gamma$ . Thus, one of the mechanisms by which pioglitazone improves memory impairment caused by diabetes and hypothyroidism may involve the activation of THRs. However, the details of these mechanisms underlying improvement in cognitive impairment by treatment with pioglitazone in patients with hypothyroidism require further investigation.

## Pioglitazone and Synaptic Transmission

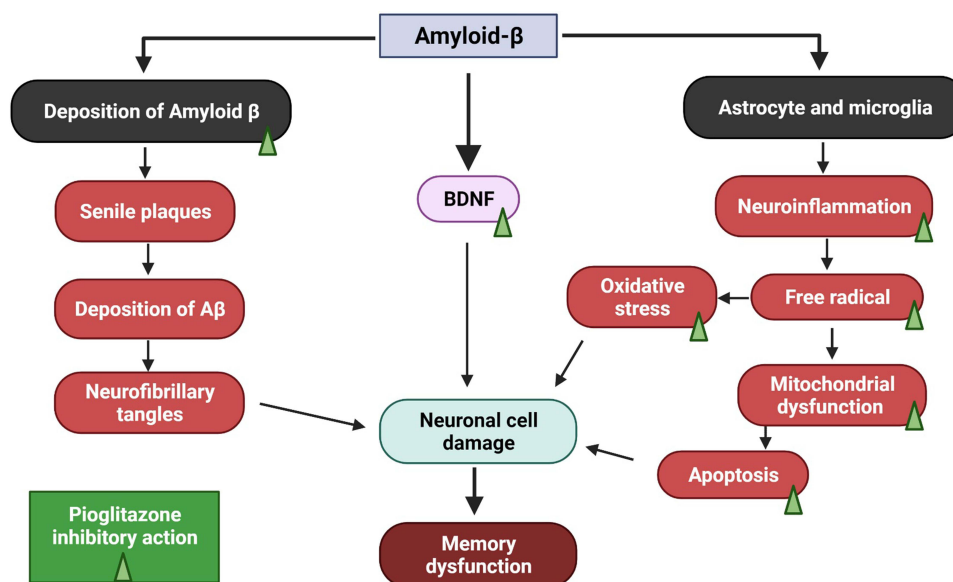
Synaptic transmission is a physiological process via which neurons communicate with other cells through synapses.<sup>121</sup> This communication occurs via chemical and electrical synaptic transmission.<sup>122</sup> Chemical synaptic transmission occurs when a neurotransmitter is released into the synapse and binds to specific postsynaptic receptors, whereas electrical

synaptic transmission occurs when electrical signals transferred through neurons are involved in neurotransmitter release.<sup>122,123</sup> In learning and memory processes, neurons are stimulated and lead to the firing of other neurons with action potential, thus enhancing the release of neurotransmitters through the activation of calcium channels in presynaptic neurons.<sup>124,125</sup> Alterations in these processes, whether they occur in pre- or postsynaptic neurons, can impair memory function.<sup>126</sup> For instance, changes in the expression and function of proteins have been observed in both pre- and postsynaptic neurons in AD and PD.<sup>127</sup>

Synaptic transmission in ischemic neurons is impaired as a result of the reduction in the activity of PI3K/Akt and Nrf2/ARE pathways, and pioglitazone treatment has been found to increase the pro-survival PI3K/Akt pathway by increasing the phosphorylation of Akt in Ser<sup>473</sup> and GSK-3 $\beta$  in Ser<sup>9</sup> residues. This further improved the activity of the Nrf2/ARE antioxidant pathway.<sup>128</sup> It has also been shown that lipoprotein receptor-related protein 1 (LRP1) and nuclear factor kappa B (NF- $\kappa$ B) p65 were downregulated in AD, but they were upregulated by pioglitazone treatment.<sup>6,129</sup> All together, these findings demonstrate that pioglitazone can improve synaptic transmission by increasing the expression and phosphorylation of LRP1, NF- $\kappa$ B p65, Akt in Ser<sup>473</sup>, and GSK-3 $\beta$  in Ser<sup>9</sup> residues, and increasing the activity of the Nrf2/ARE pathways. Thus, the mechanisms via which pioglitazone improves memory impairment in AD and PD, and perhaps metabolic diseases such as DM2, might involve its effects on the LRP1, NF- $\kappa$ B p65, Akt, GSK-3 $\beta$ , and Nrf2/ARE pathways, so these pathways warrant further research in the future with regard to the identification of potential treatment targets.

## Conclusion

The findings reported in the studies included in the current review demonstrate that pioglitazone can improve memory function via the activation of PPAR receptors. The included studies have indicated that PPAR receptors play a role in ameliorating inflammation, oxidative stress, amyloidogenesis, and hypothyroidism, and enhancing neurogenesis, synaptic plasticity, and mitochondrial function; further, the effects of pioglitazone on these processes are also evident. Based on these findings, we believe that further in-depth investigations into these mechanisms will help establish the potential of pioglitazone in terms of its clinical applicability in the management of cognitive disorders (Figure 2).



**Figure 2** Mechanism of protective effect of pioglitazone on memory impairment.



## Disclosure

The authors report no conflicts of interest related to this work.

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