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# Broad-spectrum neuroprotection against traumatic brain injury by agonism of peroxisome proliferator-activated receptors☆

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## Abstract

In a recent issue of *Experimental Neurology*, Sauerbeck and colleagues demonstrated that treatment with the peroxisome proliferator-activated receptor (PPAR) agonist Pioglitazone after experimental traumatic brain injury (TBI) in rats was protective against mitochondrial dysfunction, cognitive impairment, cortical tissue loss and microglial activation. In this commentary, we review the key findings of this work and their relevance to previous and future neurotrauma research. More broadly, we speculate about their significance in the context of developing therapeutic strategies for a wide range of neuroinflammatory conditions.

### Keywords

Peroxisome proliferator-activated receptors; Neuroprotection; Pioglitazone; Traumatic brain injury

Despite an abundance of laboratory and clinical research over the last three decades, an effective neuroprotective agent for the treatment of traumatic brain injury (TBI) remains elusive (Narayan et al., 2002; Maas et al., 2010). The multi-factorial nature of the pathophysiology of TBI likely contributes to this situation, such that any potential benefit gained by targeting a single molecule or pathway may be masked by the plethora of simultaneously activated cascades. Neurotrauma research has more recently focused on widening the therapeutic approach, for example, by the application of broad-spectrum drugs including minocycline and erythropoietin. The prevailing view is that targeting a wider range of pathological mechanisms in concert may provide greater clinical benefit (Vink and Nimmo, 2009). Consistent with this view, a 2009 workshop sponsored by the National Institute of Neurological Disorders and Stroke, recommended a combinatorial approach for the treatment of TBI, focusing on therapeutics with complementary targets and effects (Margulies and Hicks, 2009).

☆Commentary on Sauerbeck et al. (2011) Experimental Neurology 227:128–135.



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An alternative approach is to target specific factors which themselves are inherently multi-functional by nature. Peroxisome proliferator-activated receptors (PPARs) are ligand-activated, nuclear membrane-associated transcription factors, which target several downstream genes involved in inflammation and oxidative stress. Sauerbeck and colleagues from the University of Kentucky have recently published work in *Experimental Neurology*, which describes the neuroprotection afforded by the PPAR agonist Pioglitazone in an animal model of TBI (Sauerbeck et al., 2011). This commentary aims to discuss their key results and the significance of their findings, in the broader context of potential therapies for both acute and chronic CNS neurodegeneration.

There are three known isoforms of PPAR, designated PPARα, PPARβ/ δ and PPARγ, which exhibit distinct physiological and pharmacological functions based on differences in tissue distribution and target genes (Kliewer et al., 2001). PPARs form heterodimers with the retinoid X receptors upon activation, enabling them to bind specific response elements contained within the enhancer sites of downstream genes (Cabrero et al., 2002). In this manner, PPARs function to regulate gene transcription. PPARα and PPARγ in particular are mainly expressed in tissues with a high level of fatty acid catabolism, and have long been known for their central roles in the control of lipid metabolism and glucose absorption. The PPARγ agonists Rosiglitazone and Pioglitazone have been approved by the Food and Drug Administration (FDA) for use in Type 2 diabetes, based on their insulin-sensitizing properties (Sood et al., 2000).

More recently, PPAR agonists have been of particular interest to the neuroscience community. PPARα and PPARγ are widely distributed in the CNS, with reported expression in both cerebral and spinal vasculature, as well as in neurons and astrocytes (Bordet et al., 2006). One well-known target of PPARα and PPARγ is nuclear factor kappa B (NF-κB), whose activity is suppressed by PPAR agonism (Cabrero et al., 2002; Xu et al., 2010). Thus PPAR activation results in the reduced expression of several key downstream inflammatory genes, including interleukin (IL)-6, IL-1β, tumor necrosis factor (TNF)-α and cyclooxygenase (COX)-2, as well as a number of adhesion molecules, chemokines and metalloproteinases (Bordet et al., 2006). This mechanism of action is likely to underlie the reported anti-inflammatory effects of PPAR agonism in the injured CNS, which responds to TBI with a robust and multi-factorial immune response (Morganti-Kossmann et al., 2007). TBI remains an elusive therapeutic target, and the possibility that PPAR ligands may ameliorate pathophysiology following injury is an alluring one.

In the current study, Sauerbeck and colleagues subjected rats to a well-characterized controlled cortical impact model of moderate focal TBI. Pioglitazone (10 mg/kg) or vehicle was administered i.p. at 15 min after injury and then daily for 4 consecutive days (Sauerbeck et al., 2011). A third cohort received the PPARγ antagonist T0070907 in addition to Pioglitazone, a paradigm intended to demonstrate whether or not an observed effect was receptor-specific. As hypothesized, Pioglitazone was capable of protecting mitochondrial function, reducing inflammation, minimizing cortical tissue loss and improving cognitive function following TBI.

The paper focuses initially on Pioglitazone in relation to mitochondrial activity, no doubt due to the authors' extensive background investigating mitochondrial dysfunction in post-traumatic neuronal cell death (Sullivan et al., 2004). At 25 h after injury, Pioglitazone altered mitochondrial oxygen consumption, indicating the preservation of mitochondrial function compared to vehicle-treated animals (Sauerbeck et al., 2011). This improvement was significant only in animals that received two doses of Pioglitazone (15 min and 24 h post-injury), compared to those that only received a single initial administration, suggesting that sustained agonism of PPARs may be required to elicit an effect. Furthermore, the authors' surmise that an even greater improvement of mitochondrial function may be evident beyond the acute post-injury period. These findings confirm earlier data from another group, who demonstrated that PPARγ agonism with Rosiglitazone ameliorates mitochondrial dysfunction in several different neuronal cell populations (Fuenzalida et al., 2007; Quintanilla et al., 2008). Furthermore, a recent *in vitro* study provided evidence that the degree of neuronal cell survival is dependent upon the extent of PPAR agonism-induced mitochondrial biogenesis, highlighting the importance of maintaining or restoring adequate mitochondrial function in the CNS (Miglio et al., 2009). The current study by Sauerbeck and colleagues is the first to report a similar protection of mitochondrial function afforded by PPAR agonism in the context of TBI.

Following on from this, Sauerbeck and colleagues quantified the extent of cortical loss in traumatized animals, on brain sections collected 16 days after injury. In this experiment, rats received an initial dose of Pioglitazone at 15 min post-injury, then every 24 h thereafter for 4 consecutive days (Sauerbeck et al., 2011). Compared to vehicle-treated animals, Pioglitazone significantly reduced the average lesion volume by approximately 50%, effectively halving the degree of tissue loss. This protective effect was abolished in animals who received co-administration of the PPARγ antagonist T0070907, suggesting that PPARγ activation is necessary for tissue sparing in this context. The clarification of this distinction adds strength to this study, as it has been proposed that pharmacological agonism of PPAR's may also induce neuroprotection by mechanisms which are independent of binding to PPAR receptors (Kapadia et al., 2008).

To determine whether tissue sparing following Pioglitazone treatment resulted in a subsequent improvement in neurological function, cognitive impairment was assessed in each animal, across 4 trial days, using the standardized Morris Water Maze. In brief, the authors found that treatment with Pioglitazone improved cognitive function compared to vehicle-treated animals, measured as a reduction in both the latency and distance traveled to reach the platform (Sauerbeck et al., 2011). One perceived weakness of this study is the small sample size used for functional testing ($n$=4–6 per group), such that the presented results are collapsed to represent data from all testing days combined, in order to gain sufficient statistical power for a meaningful analysis. Given the importance of improving neurological outcomes in patients with TBI, it is disappointing that the drug effect seen in these experiments was not more robust. Perhaps an additional measure of cognitive or even motor function may have also been appropriate, in order to provide a better understanding of the neurological consequences of Pioglitazone treatment in this study.

Lastly, Sauerbeck and colleagues sought to evaluate the effect of Pioglitazone on the post-traumatic neuroinflammatory response, by stereologically quantifying OX-42 immunolabeled reactive microglia within the pericontusional cortex at 16 days after injury. As hypothesized, given the known mechanisms of inflammatory gene suppression by PPAR agonism, Pioglitazone treatment significantly reduced the extent of microglial activation compared to vehicle treatment (Sauerbeck et al., 2011). In comparison to its effect on tissue loss and cognitive function, co-administration of the PPARγ antagonist did not prevent Pioglitazone from reducing post-traumatic inflammation, indicating that the suppression of microglial activation by Pioglitazone was a PPARγ-independent process.

Overall, these findings corroborate a number of previous studies which have explored the use of different PPARα and PPARγ ligands in CNS injury models, including TBI (Besson et al., 2005; Chen et al., 2007; Yi et al., 2008), spinal cord injury (SCI) (McTigue et al., 2007; Park et al., 2007) and stroke (Collino et al., 2006; Allahtavakoli et al., 2009) (also reviewed by Stahel et al. 2008). A recent systematic review of pharmacological PPAR agonism in 22 pre-clinical studies of cerebral ischemia found that Pioglitazone was consistently effective at reducing infarct volume and improving neurological outcome, regardless of the study quality, timing of drug administration or dose (White and Murphy, 2010). Of the two FDA-approved PPARγ agonists, Rosiglitazone has been shown to have a 10-fold higher binding affinity for the PPARγ receptor (Kapadia et al., 2008). However, studies in focal ischemia and SCI have suggested that comparable doses of Rosiglitazone and Pioglitazone are needed to induce the same degree of neuroprotection (Park et al., 2007; Tureyen et al., 2007). This phenomenon may result from Pioglitazone's increased ability to cross the blood–brain barrier (BBB), which renders it the more attractive drug for CNS conditions such as TBI, and highlights the relevance of the current study. In addition, there is evidence that Pioglitazone can partially activated the PPARα receptor (Sakamoto et al., 2000), thereby having a potentially broader pharmacological effect. Importantly, Sauerbeck's study is novel as the first to investigate Pioglitazone following TBI, based on the rationale that activation of either PPARα (Chen et al., 2007) or PPARγ (Yi et al., 2008) alone is protective in experimental TBI, and that targeting both isoforms simultaneously is likely to result in greater protection.

The breadth of the therapeutic window during which PPARα and PPARγ agonismis efficacious following TBI remains to be characterized. An initial dose of Pioglitazone at 15 min post-injury as administered in the current study is unlikely to be clinically applicable, and further studies are needed to determine whether delayed treatment initiation is equally beneficial. There is currently conflicting evidence in this regard, with one study demonstrating that PPARγ agonism was able to reduce neurological deficits in rats only if administered as early as 2 h after SCI (Park et al., 2007), whilst another found that postponing Rosiglitazone treatment until 24 h post-ischemic injury was still significantly neuroprotective (Allahtavakoli et al., 2009).

In addition, this paper highlights the importance of identifying both PPARγ receptor-dependent and independent mechanisms of Pioglitazone, in order to better understand the likely outcomes and potential side effects resulting from therapeutic treatment. The authors determine that Pioglitazone's actions on tissue loss and cognitive function are mediated by

activation of the PPARγ receptor, whilst attenuation of microglial activation does not rely on receptor binding. The findings of studies designed such as this one are difficult to interpret in terms of relating the results to one another – for example, it is unclear whether Pioglitazone treatment directly alters cognitive function, or whether the improvement in cognition results indirectly from reduced cortical damage in treated mice, and a consequential reduction in cognitive impairment. Given our current understanding of the mechanisms underlying PPAR activation and subsequent transcription or suppression of numerous genes involved in inflammation and oxidative stress (Bordet et al., 2006; Stahel et al., 2008), it is possible that the neuroprotective effects seen in this study result from a multitude of different processes. Recently, a potential role for PPAR's has been identified in the regulation of neural stem cell proliferation and differentiation, with evidence that Pioglitazone can stimulate a PPARγ-dependent increase in proliferating progenitor cells *in vivo*, and an expansion of neurospheres *in vitro* (Morales-Garcia et al., 2011). Elucidating these precise mechanisms of action should be addressed in future studies.

The pleiotropic nature of PPAR agonists such as Pioglitazone has also ensured attention as potential neuroprotective agents in other CNS conditions, not only in acute injuries but also in chronic disease states which have a neuroinflammatory component. Oral treatment of Pioglitazone has been shown to reduce glial activation and plaque aggregation in the hippocampus and cortex of a murine transgenic model of Alzheimer's disease (Heneka et al., 2005). Similarly, inflammation and dopaminergic cell loss in the substantia nigra *pars compacta* were significantly attenuated following oral Pioglitazone administration in a Parkinson's disease model (Breidert et al., 2002). Pioglitazone has also been shown to have potential benefit in autoimmune disease, as treatment in a well-characterized mouse model of multiple sclerosis was effective at reducing the severity of motor symptoms and overall mortality (Feinstein et al., 2002).Whether the neuroprotective function of Pioglitazone differs depending on the route of administration (i.e. oral versus injection) still needs to be established. However, moving into clinical trials to evaluate this PPARγ and partial PPARα receptor agonist in the wide range of CNS conditions for which it may be of benefit should be facilitated by its established FDA approval status and current use in humans. In fact, the PPAR agonist NP03112 is currently the focus of a Phase II clinical trial for the treatment of Alzheimer's disease (Morales-Garcia et al., 2011).

In conclusion, characterizing the therapeutic potential of new pharmacological agents in the preclinical setting is an essential component of neurotrauma research. The robust neuroprotective effect of Pioglitazone in this model of TBI highlights the importance of interfering with inflammatory and oxidative stress processes in the injured brain, and corresponds well with previous research using other PPAR ligands in TBI and SCI. Furthermore, this study supports future investigation into the precise mechanisms by which PPAR ligands such as Pioglitazone exert their neuroprotective effects. The challenge now is to define the optimal time-frame during which treatment is most efficacious, and to answer the fundamental question of whether PPAR agonism will be similarly neuroprotective in brain-injured patients.

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