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Commentary

In search of the neuroprotective mechanism of thiazolidinediones in Parkinson's disease

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ABSTRACT

The oral antidiabetic thiazolidinediones exert protective effects in models of Parkinson's disease and other neurological diseases. While the antidiabetic effect is due to activation of PPARγ, the mechanisms underlying the neuroprotection are more controversial. It may involve activation of PPARγ blocking inflammation and apoptosis. However, new evidence suggests an antioxidative PPARγ-independent action. Here we discuss recent data on the mode of action of TZDs in models of PD and their implication for the translation into the clinic.

Parkinson's disease (PD) is a chronic neurodegenerative disease characterized by progressive loss of dopaminergic neurons in the substantia nigra. Although the specific pathomechanism of PD is still unclear, there is evidence that points to the involvement of mitochondrial dysfunction, oxidative stress, and inflammation (Gupta et al., 2008). Currently available treatment options do not prevent disease progression, but rather provide only symptomatic relief illustrating the need for a causative therapy.

In recent years, the insulin-sensitizing thiazolidinediones (TZDs), activators of the peroxisome proliferator-activated receptor γ (PPARγ), including rosiglitazone and pioglitazone, have been found to exert neuroprotective effects in preclinical models of several neurodegenerative conditions including Alzheimer's disease (Landreth et al., 2008; Nicolakakis et al., 2008), cerebral ischemia (Collino et al., 2008), amyotrophic lateral sclerosis (Kiaei et al., 2005), as well as PD (Carta et al., 2011; Chaturvedi and Beal, 2008). The primary target of TZDs, PPARγ, is a ligand-activated transcription factor that belongs to the nuclear hormone receptor family. PPARγ has originally been characterized as a regulator of glucose and lipid metabolism in adipocytes, but more recent work also revealed PPARγ expression in various other cell types including cells of the immune system and also in the central nervous system (Giannini et al., 2004; Lu et al., 2011).

TZDs in PD models. Several studies have shown that TZDs have neuroprotective properties in different models of PD (for two excellent reviews see Carta et al., 2011; Chaturvedi and Beal, 2008). Administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridin (MPTP) causes clinical symptoms of PD as well as dopaminergic neurodegeneration. Therefore, MPTP application has served as a model for PD and has been widely used to develop novel therapeutic strategies. Conversion of MPTP to 1-methyl-4-phenyl-pyridium (MPP^+) by monoamine oxidase B (MAO-B) in non-neuronal cells is necessary to elicit degeneration of the dopaminergic neurons of the substantia nigra (Vila and Przedborski, 2003).

In the acute MPTP model of PD, Breidert et al. (2002) found the TZD pioglitazone to completely block dopaminergic neurodegeneration and to diminish astrocytic and microglial activation upon MPTP administration. However, pioglitazone treatment did not alleviate MPTP-induced loss of tyrosine hydroxylase-positive fibers in the striatum and had only partially protective effects on MPTP-induced decline in striatal tissue levels of dopamine, and on decline in the dopamine degradation products 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid. Another study confirmed the neuroprotective properties of pioglitazone in a subacute MPTP model of PD (Dehmer et al., 2004). MPTP-induced neuronal loss and nitrotyrosine formation as a marker for NO-mediated cell damage were completely blocked, whereas the decrease in striatal dopamine was only partially prevented by pioglitazone (Dehmer et al., 2004). Treatment with pioglitazone also

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induced expression of the NF-κB-inhibitor IκB-α in substantia nigra and striatum and probably thereby blocked shuttling of the p65 subunit of NF-κB to the nucleus of dopaminergic neurons and mitigated activation of astrocytes and microglia. These two studies mainly implicated anti-inflammatory actions of pioglitazone as the mechanism underlying the neuroprotection, but recently it has also been shown that pioglitazone inhibits MAO-B in the striatum. Therefore, reduced conversion of MPTP to its active form MPP^+ could contribute to the protective effect of pioglitazone (Quinn et al., 2008).

Another recent study showed a neuroprotective effect of the other TZD in clinical use, rosiglitazone, in the chronic MPTP plus probenecid mouse model of PD (Schintu et al., 2009). Treatment with rosiglitazone completely prevented motor deficits and impairment of olfactory function and loss of dopaminergic neurons in the substantia nigra. Rosiglitazone partially protected against loss of striatal dopamine, whereas decreases in DOPAC and dynorphin mRNA in the striatum were completely abolished. Administration of rosiglitazone also reduced astrogliosis and the number of activated microglia as assessed by GFAP and CD11b staining, respectively, without affecting the conversion of MPTP to MPP^+.

In the aforementioned studies, TZDs had been given prior to administration of MPTP. Using a similar chronic MPTP plus probenecid model of PD, another recent publication extended previous findings to the fact that delayed treatment with rosiglitazone was also effective in arresting ongoing neuronal loss and limiting inflammation when administered at a later stage of the disease (Carta et al., 2011). The prolonged therapeutic time window of rosiglitazone is encouraging for translating this finding into the clinics.

In a very interesting recent study Swanson and coworkers presented evidence that pioglitazone also exerts neuroprotective and anti-inflammatory effects in a MPTP model in rhesus monkeys. They observed significant improvement in a clinical rating score by pioglitazone treatment that was associated with less dopaminergic neurodegeneration and less infiltrating CD68-positive macrophages in the nigrostriatal area (Swanson et al., 2011). This study further supports a potential clinical use of TZDs in the treatment of PD, although the protective effect on neuronal loss was not as pronounced as in the rodent models and the effect of pioglitazone on the conversion of MPTP to MPP^+ was not addressed in this study.

Besides injection of MPTP, administration of the mitochondrial complex-I inhibitor rotenone and of 6-hydroxydopamine (6-OHDA) has been used to model PD. Pioglitazone protected against rotenone-induced motor impairments and decline in striatal dopamine levels (Ulusoy et al., 2011). A recent study confirmed the protective effects of pioglitazone on neuronal loss and on motor behavior in the acute MPTP model, but did not find pioglitazone to exert any protection in the 6-OHDA model in rats (Laloux et al., 2012). The lack of effect in this model might be attributed to the severity of the damage caused by bilateral intracerebral injections of 6-OHDA.

Intrastriatal injection of lipopolysaccharide (LPS) has also served to model degeneration of dopaminergic neurons in PD. Hunter et al. (2007) found pioglitazone administered prior to striatal LPS injection to prevent the loss of dopaminergic neurons and to ameliorate the decline in striatal dopamine levels in rats, and to limit the inflammatory response. Intrastriatal LPS administration led to increased expression of COX-2 and iNOS, to mitochondrial dysfunction in the striatum and the substantia nigra, and to increased oxidative stress. Pioglitazone normalized COX-2 expression and mitochondrial function, reduced iNOS induction, and reduced oxidative stress as measured by tyrosine nitrosylation and protein carbonylation. The authors attributed the protective effects to the blunted inflammatory response, attenuated oxidative stress, and restored mitochondrial function.

The report by Teismann and coworkers in a recent issue of Experimental Neurology (Exp Neurol. 2012 Jun;235(2):528–38) adds important new information on the mechanism of the protective action of TZDs in PD (Martin et al., 2012). Most studies implicate anti-inflammatory mechanisms of the TZDs to underlie neuroprotection. In this study, the authors show that rosiglitazone ameliorated MPP^+-induced reactive oxygen species formation and cell death in neuronal SH-SY5Y cells in vitro and that this was associated with increased glutathione S-transferase activity. Thus, rosiglitazone showed direct protective effects on neuron-like cells as well, in addition to its anti-inflammatory effect on glial cells. Importantly, the protective effect could not be blocked by the PPARγ antagonist GW9662, suggesting that the exerted neuroprotection is PPARγ-independent. The authors also raised concerns with regard to the use of the MPTP-model to evaluate the neuroprotective properties of rosiglitazone. They show that rosiglitazone treatment decreased the striatal conversion of MPTP to the active toxin MPP^+. The reduced conversion is most likely due to an inhibition of MAO-B. A similar finding has been reported for pioglitazone (Quinn et al., 2008). This important observation will likely prohibit the further use of the MPTP model to study the protective effects of TZD, although it does not explain the therapeutic efficacy of TZD in other PD models or of MPP^+ in vitro. Besides the PPARγ-independent neuroprotective effects of rosiglitazone, the report by Martin et al. also shows that blocking PPARγ function with the antagonist GW9662 in vivo caused dopaminergic neuronal loss in the substantia nigra, demonstrating a role of PPARγ-dependent processes in neuronal survival. PPARγ activation is known to be neuroprotective in other brain disorders. In a mouse model of cerebral ischemia PPARγ neuronal KO mice suffered from significantly bigger infarcts than their control littermates (Zhao et al., 2009).

To our knowledge, the neuroprotective properties of TZDs have only been shown in toxin-based models of PD so far, that do not mimic all pathologic aspects of PD seen in humans (Blandini and Armentero, 2012). Furthermore, in most studies, TZDs were given prior to application of the respective toxin which does not adequately reflect the clinical situation. It will be interesting to see whether TZDs also exert neuroprotection in genetic PD models. Viral overexpression of α-synuclein in the nigro-striatal system, for example, has been shown to model the progressive course of PD quite accurately and is suitable to increase the predictive value of preclinical studies in rodents and monkeys (Decressac et al., 2012; Kirik et al., 2003; Lo Bianco et al., 2002).

Potential mechanisms involved in TZD-exerted neuroprotection. There are several potential mechanisms that could explain the neuroprotective effects of TZDs in preclinical models of PD. Microglial activation has been implicated in the pathogenesis of PD and is believed to aggravate neuronal injury (Carta et al., 2011; Gupta et al., 2008). Most studies in preclinical PD models consistently found reduced astrogliosis and microglial activation concomitant to neuroprotection after TZD administration (see previous paragraph), but demonstration of a direct causal link is still lacking. Stimulation of pro-inflammatory signaling pathways by administration of LPS elicited cell death in neuron–microglia co-cultures, which could be blocked by administration of pioglitazone (Xing et al., 2007). The protective effect of pioglitazone was associated with reduced induction of COX-2, iNOS, and NO production, reduced phosphorylation of JNK and p38 MAPK, and inhibition of phosphorylation and of nuclear translocation of the p65 subunit of NF-κB in microglia (Xing et al., 2007, 2008). Also two other TZD compounds exerted a neuroprotective effect in neuron–glia co-cultures possibly by blunting LPS-induced expression of IL-6, TNF, iNOS and COX-2 (Luna-Medina et al., 2005). Importantly, the protective effect of these TZDs was inhibited by co-administration of the PPARγ antagonist GW9662. A recent study also implicated IL-4 as a potential mediator of the anti-inflammatory effect of rosiglitazone (Loane et al., 2009). Pretreatment of glia prepared from wild-type mice with rosiglitazone attenuated LPS-induced increases in MHCII expression and IL-1β release, while not having any effect in IL-4-deficient glia. In addition to these effects on immune cells within the CNS, modulation of the peripheral immune