# Neuroprotective properties associated with ligands of the nuclear receptor PPAR-gamma in Parkinson's disease models


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Parkinson's disease (PD) is the second most prevalent neurodegenerative disease after Alzheimer's disease. The nuclear receptor peroxisome proliferator-activated receptor-gamma is a ligand-activated transcription factor with potent insulin sensitizing and anti-inflammatory properties. Recent evidence indicates that PPAR-gamma agonists, such as pioglitazone and rosiglitazone are neuroprotective in rodent models of PD. This thesis sought to further elucidate ligand-activation of PPAR-gamma; as a therapeutic target for PD. We demonstrated that daily oral administration of pioglitazone (5 mg/kg) to hemiparkinsonian monkeys improved clinical rating and fine motor skills, which was accompanied by significant dopaminergic nigrostriatal preservation. Nigrostriatal preservation was associated with reduced neuroinflammation. A separate experiment confirmed blood brain barrier penetration after oral dosing of pioglitazone. We also analyzed the neuroprotective properties of a novel PPAR-gamma agonist, LSN862 (LSN) in a MPTP mouse model. Our results revealed that daily oral administration of LSN (30 mg/kg) starting 3 days prior to MPTP, protected against MPTP-induced dopaminergic nigrostriatal loss. Target validation studies demonstrated that treatment with LSN affected the antioxidant genes NQO1, SOD2, and gp91phox and p67phox were observed in MPTP-treated mice, Moreover, LSN induced a reduction in gliosis as early as 24 hrs post-MPTP. We also showed that striatal PPAR-gamma; and peroxisome proliferator-activated receptor gamma coactivator-1-alpha mRNA levels were affected by treatment with LSN. Last, we validated neuroanatomical targeting of PPAR-gamma for PD by characterizing PPAR-gamma; expression in the basal ganglia of normal and MPTP-treated rhesus monkeys. PPAR-γ was prominently expressed in the basal ganglia. MPTP-treated animals presented an increase in PPAR-gamma expression in the putamen, which was not affected by pioglitazone treatment. Nigral PPAR-gamma; expression was reduced (approximately 50%) ipsilateral to MPTP dosing vs. normal controls that correlated with TH positive neurons. Pioglitazone + MPTP dosing increased PPAR-gamma; nigral positive cells contralateral to MPTP vs.controls. PPAR-gamma-ir was expressed in TH-ir nigral cells, but seldom with microglia. Taken together, the results from this thesis demonstrate that ligand activation of PPAR-gamma can be a potential therapeutic target in PD, as the receptors are localized in key neuroanatomical areas affected by PD, and can be activated by oral, non-invasive agonists that have disease modifying properties.