Liver X receptors (LXRs) activation decreases neuroinflammation in Parkinson's disease

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Parkinson's disease (PD) is a neurodegenerative disorder characterized by the degeneration of dopaminergic nigrostriatal neurons, progressive loss of substantia nigra and inflammation. Recent works have identified liver X receptors (LXRs) as potent anti-inflammatory molecules in macrophages and neuronal cells (Xu et al. , 2013; Crisafulli et al., 2010). The aim of this study was to investigate the role of LXRs in neurodegenerative disorders like PD using *in vivo*, *in vitro* and *ex vivo* models; for this purpose, we studied the effect of the synthetic LXR agonist, T0901317, in neuro-inflammatory pathway related to PD.

For *in vitro* study, differentiated human neuroblastoma cell line SH-SY5Y was used. Cells were pre-treated with T0901317 (10μM) for 2 hrs before damage induced by neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) that produces clinical, biochemical and neuropathological changes similar to PD. Twenty-four hrs after damage, cell death assay (MTT) and western blot analysis were carried out. For *ex vivo* study, the organotypic cultures were performed from the ventral mesencephalons of P6 mice. Seven-day-old cell cultures were pre-treated for 2h with T0901317 (10μM) and damaged with MPTP for 24hrs; western blot analysis were assessed for proinflammatory proteins expression. Moreover, for *in vivo* PD model, C57Bl/6 mice received four intraperitoneal injections of MPTP-HCl (20 mg/kg) in saline at 2 hr intervals in 1 day (total dose per mouse 80 mg/kg) and treated with TO901317 (20mg/kg) for 7 days. After this time point, the behavioral testing and biochemical analysis were performed.

In this study we showed a reduction in MPTP-induced cell death, iNOS and COX-2 expression, IkB-a degradation, and NF-kB translocation after treatment with T0901317. Moreover, in SH-SY5Y cells we demonstrated an important restoration of neuthrophic factors (GDNF) and nNOS expression. Moreover, mice exhibited a significantly recovery of motor function after TO901317 treatment. In the light of the results obtained, TO901317, a synthetic LXR agonist, is able to modulate the neuroinflammatory pathway involved in PD increasing the locomotors function. Therefore, LXRs could be considered as a possible therapeutic target in a neurodegenerative disorders like PD.

Xu et al.(2013). *Mol Neurobiol.*
Crisafulli et al. (2010). *J Leukoc Biol*. 309-21