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Oral treatment with sphingosine-1-phosphate receptors modulator prevents Parkinson symptoms concomitantly to reduced brain inflammation in MPTP mouse models

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Here we explore the efficacy of an oral treatment with fingolimod (FTY720), a selective sphingosine-1-phosphate receptors modulator, to prevent MPTP induced nigrostriatal loss and motor deficits in mice. In addition, potential molecular mechanisms have been assessed. Sphingosine-1-phosphate is a potent bioactive lipid mediator that acts as a natural ligand upon binding to five different receptors that are located in astrocytes, oligodendrocytes, microglial and neuronal cells. Modulation of these receptors has been shown to provide neuroprotection in multiple sclerosis and in mouse model of Alzheimer's disease. Whether the selective sphingosine-1-phosphate receptors modulator FTY720 exhibits neuroprotection in Parkinson's disease is unclear. Adult male mice were disseminated into four independent groups: vehicle (saline), FTY720, MPTP/vehicle and MPTP/FTY720. Chronic oral FTY720 (1 mg/kg) administrations began two days before the MPTP (30 mg/kg, i.p., 5 days) treatments. Motor behavioral tests and Western blot analyses on striatum tissues were assessed on these mice. We revealed diminutions of ~50% in the levels of tyrosine hydroxylase and dopamine transporter proteins in the striatum of MPTP mice. At the behavioral level, these mice exhibited motor deficits at the Pole and Beam tests. Interestingly, FTY720 oral treatment has the capacity to prevent these known detrimental signs associated to MPTP treatment. Further study has revealed that while striatal levels of phosphorylated extracellular signal-regulated kinases and S1PR subtype 1 were unaffected, tumor necrosis factor-alpha and glial fibrillary acidic protein levels were robustly increased in MPTP-treated mice, an outcome that was totally prevented by FTY720 treatments. Notably, FTY720 treatments was also able to prevent the reduction of brain-derived neurotrophic factor levels observed in the striatum of mice treated with MPTP. Our findings propose that oral FTY720 treatments prevent the damaging effects of MPTP on striatal dopamine terminals and motor behaviors. The mechanism of action may involve inhibition of inflammatory pathways and the modulation of brain-derived neurotrophic factor synthesis. This study is providing novel evidence for the clinical utility of targeting S1PR in Parkinson's disease therapy.

Biography

Michel C Y R is a PhD holder in Pharmacy from Laval University in Canada and a Post-Doctoral Trainee in Cellular Biology at Duke University in the USA. He is currently a Full Professor at the Medical Biology Department at the University of Trois-Rivieres. As the Director of the Canada Research Chair in Molecular Neuropharmacology, he is leading the effort to understand the molecules in the brain that are responsible for learning and executing motor actions. He is also investigating the molecular bases for movement disorders such as Parkinson disease and makes it possible to better target and develop new treatments.

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