FFAR4 and nigrostriatal function: A novel target for treatment of PD?

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Research Abstract

? DESCRIPTION (provided by applicant): Parkinson’s disease (PD) is amongst the most prevalent of brain neurodegenerative diseases, and is characterized by movement symptoms including rigidity, tremor, and postural instability. Though an absolute cause of PD has not been discovered, the clinical symptomology evolves due to selective destruction of neurons in the nigrostriatal brain region that are responsible for synthesis of the key neurotransmitter dopamine

(DA). Since nigrostriatal neurons regulate coordinated movement in mammals, their destruction as occurs in PD, leads to movement dysfunction. The gold-standard for treatment of PD over the last 4 decades has been administration of the DA precursor L-DOPA, which increases the levels of DA in the nigrostriatal pathway. Importantly, DA synthesis in the brain is regulated by the critical enzyme tyrosine hydroxylase (TH) and as such, approaches that increase TH activity would be expected to increase DA synthesis, and alleviate movement dysfunction. Our laboratory has demonstrated that agonism of the recently discovered free-fatty acid receptor-4 (FFAR4) leads to activation of TH in the rat PC12 cell line that is well-accepted as a model system for neuronal DA synthesis. Additionally, we show that FFAR4 agonism offers significant protection against neurotoxin-mediated cell death in PC12 cells, suggesting that FFAR4 may also have a distinct neuroprotective role. Importantly, FFAR4 is agonized by long-chained saturated fats, including the dietary polyunsaturated omega-3 fatty acids (?3FA), which have long been known to provide neuroprotective roles in degenerative diseases, including PD. Based on these results, we hypothesize that FFAR4 agonism by ?3FA and synthetic FFAR4 agonists will lead to TH activation and DA synthesis in the rat brain, and may offer neuroprotection in a rat model of PD. This project seeks to test this hypothesis by directly assessing the role of FFAR4 in TH activity and DA synthesis in rat nigrostriatal tissue, and evaluating the neuroprotective role that FFAR4 may play in a rat model of PD. Results of this work will establish a knowledge base towards understanding the physiological role of FFAR4 in nigrostriatal DA neurons and reveal if FFAR4 is a valid physiological target for treatment of PD.

Further information available at:

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