Role of LXRs in midbrain dopamine neuron development and Parkinson’s disease

https://neurodegenerationresearch.eu/survey/role-of-lxrs-in-midbrain-dopamine-neuron-development-and-parkinson%c2%92s-disease/

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Role of LXRs in midbrain dopamine neuron development and Parkinson’s disease

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Research Abstract

Our group has identified nuclear receptors of the LXR family, LXR? and LXR?, as key regulators of midbrain dopaminergic (mDA) neurogenesis (Sacchetti et al, 2009, Cell stem cell). With the support of Hjärnfonden we identified endogenous brain LXR ligands as an entirely new family of very selective and potent regulators of neurogenesis and survival: While 24,25-EC selectively increases mDA neurogenesis, CA regulates both neurogenesis and survival of midbrain red nucleus neurons, and 3?,7?-diHCA selectively promotes motor neuron survival (Theofilopoulos et al., 2013 and 2014,
Nature Chem. Biol and J. Clin. Invest.). More recently, with the support of Hjärnfonden, we

began to elucidate the mechanism by which Lxr regulate mDA neurogenesis. Using a combined transcriptomic, cistromic and system biology approaches, we recently identified the transcription factor, Srebf1, as a direct target of Lxr required for mDA neurogenesis. However, many mechanistic and functional questions still remain. In the continuation of this project we propose to delve more
into the mechanism of Srebf1-induced mDA neurogenesis and complete our ongoing analysis of the molecular mechanism by which LXRs are differentially activated in response to distinct endogenous LXR ligands. In addition of that we propose to investigate the role of Lxr/Srebf1 is A9 vs A10 mDA
neurogenesis. We also plan to examine whether cholesterol metabolites and Lxr ligands are altered in the CSF of patients with diverse forms of Parkinson's disease (PD) and examine whether such alterations may play a role in PD. Finally, we also propose to use Lxrs to: (1) Generate in vitro models of PD using PD-iPS cells and gene editing technology, in order to examine mechanisms of disease; and (2) Improve cell replacement strategies for PD using either stem cells or direct
reprogramming. This project thus aims at providing further mechanistic insights into the function of LXR in development and disease and at contributing to the development of novel therapies for PD.

Further information available at:

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