REVERTING THE ELECTROPHYSIOLOGICAL ALTERATIONS CAUSED BY HCN LOSS OF FUNCTION TO PROTECT VULNERABLE DOPAMINERGIC NEURONS IN MITOPARK MOUSE MODEL

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Introduction: Mitochondrial dysfunction is a common pathogenic event at the crossroads of multiple Parkinson's Disease (PD)-related pathways. In recent years, the interplay between diseased mitochondria and membrane ionic mechanisms has been suggested to underlie selective degeneration of vulnerable dopaminergic (DA) neurons. The current carried by hyperpolarization-activated cyclic nucleotide–gated (HCN) channels is a key electrophysiological marker of midbrain DA neurons. Recently, we discovered that HCN current is functionally downregulated by low intracellular ATP and PD-related mitochondrial toxins in vulnerable DA neurons of the Substantia Nigra pars compacta (SNc), suggesting that HCN channels act as downstream effectors of mitochondrial stress. In turn, HCN loss of function (LOF) increases voltage-dependent calcium inflow during synaptic activity in vitro. In agreement with our findings, HCN current was found downregulated in SNc DA neurons of MitoPark mice, a transgenic mitochondrial model showing selective nigrostriatal degeneration, long before the appearance of neuropathology and motor symptoms. Based on these premises, we tested the hypothesis that HCN LOF is causally linked to differential DA degeneration by performing (1) local administration of selective blockers of HCN current in adult rats and (2) pharmacological rescue of defective HCN current with the HCN enhancer lamotrigine (LTG) in presymptomatic MitoPark mice

Materials and methods: Inactivation of HCN current *in vivo* was obtained by stereotaxic injection of ZD7288or ivabradine in adult rats. MitoPark C57BL/6J at 6weeks old mice received an intra-peritoneal dose of LTG 15mg/kg daily or saline. Locomotor activity such as Open Field (OFT), rotarod test and apomorphine-induced rotations.

Results: Our results demonstrate that intracerebral administration of HCN current blockers cause SNc-specific neurodegeneration and parkinsonian motor phenotype. Moreover, we generated preliminary data indicating that pharmacological rescue of defective HCN current with LTG ameliorates motor decay in MitoPark mice. In particular, we observed reduced motor decay, as measured with open field and rotarod test, in LTG-treated MitoPark mice, compared to vehicle-treated MitoPark mice.

Discussion and conclusions: These findings support the proposition that HCN LOF is sufficient and necessary to PD-related nigrostriatal degeneration, at least in specific preclinical settings. Further study will be required to estimate the potential of LTG or other HCN modulators as neuroprotective therapeutics in PD.