

Cardiac Dysautonomia and Neurodegeneration in Parkinson's Disease: A Nonhuman Primate Model

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Parkinson's disease (PD) is classically described as a movement disorder associated to the loss of dopaminergic neurons in the substantia nigra pars compacta. Yet today, PD is recognized as a multisystem disorder affecting several components of the central and peripheral nervous system. Dysautonomia or the dysfunction of the autonomic system, greatly affects PD patients' quality of life, and often its symptoms are more disabling than motor deficits. Cardiac dysautonomia or the abnormal autonomic control of the heart, and cardiac sympathetic neurodegeneration are frequently observed in PD patients, although they are frequently under diagnosed. The lack of established preclinical monkey models of PD with cardiac dysautonomia has hampered the development and testing of new treatments to alleviate or prevent cardiac dysautonomia in PD. This thesis is centered on developing a nonhuman primate model to help understand cardiac dysautonomia and neurodegeneration in PD. First, we aimed to develop and characterize *in vivo* a model of cardiac dysautonomia and neurodegeneration. We demonstrated that intravenous dosing of 50 mg/kg of the neurotoxin 6-hydroxydopamine (6-OHDA) induced a nonuniform pattern of sympathetic denervation in the left ventricle detected by ¹¹C-meta-hydroxyephedrine (¹¹C-MHED) uptake using positron emission tomography (PET), as well as a reduction in circulating catecholamines. Second, to confirm the cardiac sympathetic neurodegeneration in the model, we assessed postmortem the sympathetic innervation of the left ventricle. Our results revealed that systemic 6-OHDA significantly reduced tyrosine hydroxylase-immunoreactivity (TH-ir; marker of sympathetic innervation) and protein gene product marker 9.5 (PGP9.5; a pan-neuronal marker) in nerve structures of the left ventricle. Moreover, the ratio of TH/PGP9.5-ir in nerve fibers of the left ventricle reproduced the same pattern of nerve loss as found with ¹¹C-MHED PET, resulting in the least sympathetic innervation in the inferior wall. In addition, 6-OHDA-treated animals had decreased catecholamine enzyme production in the chromaffin cells of the adrenal medulla. Third, we investigated if systemic 6-OHDA had an effect on the nigrostriatal system. We found that systemic 6-OHDA variably reduced the number of dopaminergic neurons in the substantia nigra and upregulated human leukocyte antigen (HLA-DR) expression in the brain microvasculature. We demonstrated that nigral cell counts correlated with the intensity of HLA-DR in blood vessels in the same area. Overall, this body of work demonstrates that systemic administration of 6-OHDA to rhesus monkeys induces cardiac dysautonomia presented as cardiac sympathetic nerve loss and dysfunction of the adrenal medulla. The data presented here support the use of this animal model to test disease-modifying strategies aiming to alleviate symptoms of cardiac dysautonomia and for peripheral neuroprotection.