Better models of early-stage Parkinson's disease can speed up the development of new treatments

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A rat model of early-stage Parkinson's disease was characterized and

utilized in the Ph.D. study of Juuso Leikas, MSc (Pharm). A common anesthetic, isoflurane, was shown to relieve Parkinson-like symptoms in the model.

The progressive degeneration of the nigrostriatal dopaminergic neurons and the resulting striatal dopamine depletion are the primary causes for the characteristic motor symptoms of Parkinson's disease (PD), including resting tremor, rigidity, bradykinesia and postural instability. Current PD drug therapies offer only symptomatic relief and do not influence the progression of the underlying pathology. Known processess associated with neurodegeneration and endogenous reparative mechanisms offer promising targets for novel disease-modifying treatments, but these kinds of treatments have not yet been introduced into clinical practice. To assess novel disease-modifying treatments, valid and well-characterized animal models of early-stage PD and sensitive test batteries are needed.

The aim of Leikas' thesis was to devise a rat model of early-stage PD based on the intrastriatal infusion of 6-hydroxydopamine (6-OHDA) for the assessment of disease-modifying therapies. Several lesioning protocols were examined; it was observed that a single 10 µg infusion of the toxin into striatum gradually decreased the striatal dopamine content by 40-60 % and produced mild motor deficits that were detectable by a sensorimotor test battery. Imaging findings revealed functional connectivity (FC) changes in this model which resembled those observed in early-stage PD. Exercise induces neuroplasticity and can contribute to a neuroprotective or a restorative effect in PD, thus walking exercise was used to test the ability of the model to detect the effects of PD treatments. The combined ipsilateral limb use score calculated by combining a battery of non-drug-induced sensorimotor tests proved to be a good way to assess the effects of therapies in this model. Finally, the model and test battery were used to provide evidence suggesting that isoflurane, a commonly used volatile anesthetic with putative effects on

brain TrkB neurotrophin receptor and glycogen synthase kinase 3β (GSK3β) signaling could ameliorate 6-OHDA-induced motor deficits in rats.

In conclusion, the findings of the present study demonstrated that a unilateral single 10 µg infusion of 6-OHDA into the rat striatum produced the biochemical, behavioral and functional alterations reminiscent of early-stage PD. Repeated, brief exposures to isoflurane anesthesia evoked antiparkinsonian-like effects in this model, encouraging further studies to clarify the underlying mechanisms and potentially to discover new PD treatments among widely used anesthetics.

The doctoral dissertation of Juuso Leikas, Master of Science (Pharmacy), titled "Partial 6-OHDA lesion model of early-stage Parkinson's disease for the assessment of disease-modifying treatments," will be examined at the Faculty of Health Sciences.

More information: Partial 6-Ohda Lesion Model of Early-Stage Parkinson's Disease for The Assessment of Disease-Modifying Treatments. urn.fi/URN:ISBN:978-952-61-3775-9

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