Understanding acetylcholine drive of striatal dopamine transmission in an animal model of Parkinson’s

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Understanding acetylcholine drive of striatal dopamine transmission in an animal model of Parkinson's

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Research Abstract

Current mainstream pharmacotherapy of Parkinson’s involves boosting dopamine release with the precursor l- DOPA. While initially effective, side effects limit its long-term use. It is critical that we identify new therapies. A balance between dopamine and ACh released from cholinergic interneurons (ChIs) has long been thought important to normal movement, but the precise roles for ChIs are only now emerging. New findings suggest that ChIs play critical roles, and show

dysfunction in Parkinson’s, that could be targeted in PD therapies. Using an optogenetic approach, we recently identified that ChIs operate a direct means of driving striatal DA release: synchronised action potentials in a few ChIs powerfully drives dopamine release by activating presynaptic nicotinic receptors, bypassing activity in dopamine neurons.

We propose in this timely project, to understand how this powerful ChI-dopamine axis operates in a new mouse model of Parkinson’s. Current ideas about ChI dysfunction have arisen largely from toxin models which do not recapitulate PD progression. Within the Oxford Parkinson’s Disease Centre we have developed a mouse model of human a-synuclein expression which shows age-related motor dysfunction and deficits in striatal DA transmission. We propose to test the hypothesis that ChIs show dysfunction, and to explore whether ChIs can be targeted to drive DA transmission in Parkinson’s, using this new model in a pioneering combination with optogenetic technology. By identifying how striatal ChIs function in this model we will understand better whether ChIs can promote dopamine function as a future direction for alternative treatment strategies for Parkinson’s.

Further information available at:

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