DISSECTING THE ROLE OF ALPHA-SYNUCLEIN IN DOPAMINE BIOLOGY USING HUMAN DOPAMINERGIC CELL MODELS

L. Lourenco Venda, J. Alegre, M. Lufino, S. Senior, S. Cragg, R. Wade-Martins

Oxford Parkinson's Disease Centre, University of Oxford, Oxford, UK

Introduction: Alpha-synuclein is central to the Lewy body neuropathology of Parkinson's disease (PD), in which cardinal motor symptoms are linked to death of dopaminergic neurons. Recent advances suggest alpha-synuclein links genetics and neurodegeneration in sporadic PD. We have previously reported BE(2)-M17 as a human dopaminergic cell line which endogenously expresses tyrosine hydroxylase (TH); synthesises dopamine and takes up 3HDA in a dopamine transporter (DAT)-dependent manner. Consistent with previous findings, suppression of alpha-synuclein decreases DAT function, possibly due to a reduction in DAT membrane localisation.

Aims: To understand the role of alpha-synuclein in dopamine homeostasis.

Methods: BAC-SNCA-HA vectors carrying the entire human SNCA genomic locus under the control of endogenous promoter sequences have been successfully used to deliver and stably express WT or PD-associated alpha-synuclein mutations in BE(2)-M17 cells, at levels equivalent to endogenous alpha-synuclein.

Results: Expression of A30P and A53T, but not WT, significantly decreases 3HDA uptake. Work undergoing seeks to investigate the mechanism underlying the effect of mutated alpha-synuclein on DAT function. In addition, expression of WT alpha-synuclein leads to a decrease in dopamine content. Interestingly, A30P but not A53T mutated alpha-synuclein increases total dopamine content. Current work is looking at dopamine synthesis, specifically with regard to TH and AADC activities.

Conclusions: Our work highlights important roles for alpha-synuclein in pathways related to PD neurodegeneration. Understanding these processes is fundamental for deciphering the cellular and biological processes underlying PD aetiology.