Published in final edited form as:

Mov Disord. 2017 August ; 32(8): 1164. doi:10.1002/mds.27078.

Make Dopamine Neurons Great Again: An Exciting New Therapeutic Option in Parkinson's Disease

Luis Bonet-Ponce¹ and Andrew B. Singleton²

¹Cell Biology and Gene Expression Section, Laboratory of Neurogenetics, National Institute of Aging, National Institutes of Health, Bethesda, Maryland, USA

²Molecular Genetics Section, Laboratory of Neurogenetics, National Institute of Aging, National Institutes of Health, Bethesda, Maryland, USA

Available pharmacological treatments of PD are purely symptomatic and are not able to stop the midbrain dopaminergic (mDA) neuronal loss at the SNpc. Among the possible therapeutic targets, the transcriptional factor Nurr1 is of special interest because of its role in the differentiation, development, and survival of the mDA neurons.¹ Spathis and colleagues describe their efforts in the development of a Nurr1:RxR α heterodimer activator (BRF 110) that has a neuroprotective effect in different in vitro and in vivo PD models.²

First, the authors perform an assay of multiple Nurr1:RxR α possible activators by developing and testing several compounds on the human Dopaminergic (DA) SH-SY5Y cell line with a luciferase reporter construct. They identified BRF 110 as a highly selective and specific compound able to activate the Nurr1:RxR α heterodimer in vivo and in vitro. Further in vivo experiments demonstrate that BRF 110 is bioactive and reaches the brain with a half life of approximately 1.5 hours.

To test the cytoprotective effect of the compound, SH-SY5Y cells were exposed to toxins (1-methyl-4-phenylpyridinium (MPP)⁺ and hydrogen peroxide (H₂O₂)). The cells cotreated with BRF 110 had a better survival rate than those exposed to the vehicle. Comparable results were detected with human induced pluripotent stem cells (iPSC)-derived DA neurons exposed to MPP⁺, thus suggesting a protective effect of BRF 110 on DA cells. Because of the limitations of toxin-based PD models, the authors tested BRF 110 on genetic models of PD (expressing the leucine-rich repeat kinase 2 (*LRRK2*)-G2019S mutation). Indeed BRF 110 treatment reduces cell death in either primary rat cortical neurons transfected with the G2019S vector and in iPSC-derived DA neurons from patients carrying the G2019S mutation. However, caution should be taken as the authors do not show LRRK2 protein expression in iPSC-derived DA neurons. The neuroprotective role of BRF 110 seems to be driven by Nurr1, as BRF 110 exposure increases the expression of 3 DA biosynthesis genes (Tyrosine hydroxylase (*TH*), Aromatic L-amino acid decarboxylase (*AADC*) and GTP cyclohydrolase 1 (*GCHI*)-Nurr1 targets) and because Nurr1 knockdown abolished the BRF 110 protection.

The most exciting data came when the authors tested BRF 110 in preclinical mouse models of PD. First, BRF 110 was administrated to mice exposed to MPTP and 6-Hydroxydopamine (6-OHDA), showing a robust increase in the number of TH⁺ neurons at

the SNpc, as well as the number of TH+ axons reaching the striatum. In addition, BRF 110 treatment improved some functional tests of performance. The authors also confirmed these data using a genetic model of PD injecting a AAV-alpha-synuclein (*ASYN*) virus in the SN. Remarkably, BRF 110 affords neuroprotection in pharmacological and genetic PD models without inducing dyskinesia. Although the in vivo data carry limitations because the animal models show a sudden neurodegeneration, these findings point to an interesting therapeutic option in PD.■

References

1. Decressac M, Volakakis N, Björklund A, et al. NURR1 in Parkinson disease—from pathogenesis to therapeutic potential. *Nat Rev Neurol*. 2013; 9:629. [PubMed: 24126627]
2. Spathis AD, Asvos X, Ziavra D, et al. Nurr1:RXRα heterodimer activation as monotherapy for Parkinson's disease. *Proc Natl Acad Sci U S A*. 2017; 114:3999–4004. [PubMed: 28348207]