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MEETING ABSTRACT

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Differential sensitivity of SN and VTA neurons to stress in vitro
Se Joon CHOI¹, Ori J. LIEBERMAN¹, Ellen KANTER¹, D. James SURMEIER², David SUZER¹ and Eugene V. MOSHAROV¹,*
¹Department of Neurology, Columbia University, New York, NY, United States of America; ²Department of Physiology, Northwestern University Feinberg School of Medicine, Chicago, IL, United States of America

Systemic administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a neurotoxin that was first identified to induce parkinsonism in humans, selectively kills dopaminergic neurons of substantia nigra (SN), while leaving the neighboring ventral tegmentum area (VTA) neurons relatively intact, closely mimicking the difference in vulnerability of these neuronal populations in Parkinson's disease. It is, however, controversial whether higher sensitivity of SN neurons to MPTP results from extra-neuronal toxin metabolism and transport, or from the intrinsic properties of these cells that predispose them to neurodegeneration. Here, we compared metabolic changes induced by MPP⁺ in cultured mouse SN and VTA neurons. In this system, which excludes extra-neuronal metabolism and transport of MPTP and MPP⁺, we found significantly higher concentrations of cytosolic Ca²⁺, NO and DA in toxin-treated SN neurons, which resulted in higher mitochondrial oxidation and neurotoxicity. Contribution of complex I inhibition and DA production to MPP⁺-induced toxicity was different between the two neuronal populations with a larger role played by disrupted DA homeostasis in SN neurons and energy depletion in VTA neurons. DAT activity was higher in SN compared to VTA neurons, although this was not sufficient to fully explain the difference in toxicity. Importantly, pharmacological blockade of L-type Ca²⁺ channels normalized MPP⁺-induced alterations in Ca²⁺, NO and DA in SN neurons, also decreasing mitochondria oxidation and neurotoxicity. Overall, our data suggest that higher sensitivity of SN neurons to MPP⁺ reflects general susceptibility of these cells to some types of insults, a large portion of which is dictated by the presence of L-type Ca²⁺ channels and downstream upregulation of NO and DA production.

*Submitting author e-mail: em706@columbia.edu