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MEETING ABSTRACT

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The neuronal calcium sensor NCS-1 modulates age-dependent sensitization of dopamine D₂ autoreceptor responses as well as survival of substantia nigra dopaminergic neurons
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The preferential and progressive degeneration of substantia nigra dopamine midbrain (SN DA) neurons causes the major motor-related symptoms of Parkinson’s disease (PD). While the molecular mechanisms of the particularly high vulnerability of SN DA neurons to degeneration in PD and during aging remain unresolved, a variety of disease triggering factors have been identified. Among them are e.g. genetic factors (PARK genes), metabolic stress, mitochondrial dysfunction, and activity-related Ca²⁺ load. However, age remains the most prominent risk factor for PD. In addition, the electrical activity of SN DA neurons itself seems to affect their vulnerability to PD-triggers and to degeneration. This activity is intrinsically generated and controlled by a range of different ion channels and receptors, and it is crucial for presynaptic as well as somatodendritic dopamine release. Dopamine itself, in a negative feedback loop, modulates the activity of SN DA neurons by activating GIRK2 K⁺ channels via inhibitory dopamine autoreceptors of the D₂ type (D₂AR).

With cell-specific electrophysiological, pharmacological and molecular analysis of postnatal juvenile (PN13) and adult (PN90) mouse DA midbrain neurons, we identified that SN DA neurons—in contrast to neighboring and less vulnerable VTA DA neurons—display prominent somatodendritic D₂AR responses that sensitize during postnatal maturation. This sensitization was Ca²⁺-dependent, and it required the interaction of the neuronal calcium sensor NCS-1 with the D₂AR. Sensitized D₂AR responses were absent in NCS-1 KO mice, and they could provide a molecular mechanism for protecting SN DA neurons from overexcitability and degeneration. Therefore, we analyzed numbers of SN DA and VTA DA neurons in WT and NCS-1 KO mice at PN13, PN90, PN360 and PN580, by combining immunohistochemistry and unbiased stereology. We detected that the loss of NCS-1 indeed selectively affected the progressive age-dependent loss of SN DA neurons. We currently investigate whether that is also the case in the chronic MPTP PD mouse model.

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