Flexible and age-dependent modulation of pacemaker activity of substantia nigra dopaminergic neurons by distinct types of voltage-gated calcium channels

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Dopamine neurons within the substantia nigra (SN DA) are particularly important, as their selective and progressive degeneration causes the major motor-related symptoms of Parkinson’s disease (PD). While metabolic stress, mitochondrial dysfunction and impaired Ca²⁺ homeostasis have been identified as PD trigger factors, aging is the most prominent risk factor. Voltage-gated Ca²⁺ channels (VGCCs), especially those of the CaV1.3 L-type, generate an activity-related oscillatory Ca²⁺ burden selectively in SN DA neurons that contributes to their high vulnerability to degeneration. In humans, epidemiological studies indicate that blood–brain barrier-permeable L-type Ca²⁺ channel (LTCC) blockers of the dihydropyridine-type reduce the risk for PD by about 30%. However, while LTCC blockers are already in clinical trials as neuroprotective PD therapy, the age-dependent functional roles of distinct types of VGCCs in SN DA neurons remain unclear.

We addressed this by combining electrophysiological (patch clamp and multi-electrode array approaches) and cell-specific molecular analysis of postnatal juvenile and adult mice with pharmacological and genetic tools. Our findings suggest that (CaV1.3) LTCCs are not crucial for SN DA pacemaker-activity at either postnatal age, but their activity rather stabilizes pacemaker-precision. Moreover, they can control SN DA activity by sensitizing inhibitory dopamine D2-autoreceptor (D2-AR) responses [1]. In addition, we identified that voltage-gated T-type Ca²⁺ channels (TTCCs) can also modulate SN DA neuron activity, and they can compensate for CaV1.3 LTCC D2-AR modulation in SN DA neurons. Accordingly, SN DA neurons from juvenile CaV1.3 KO mice displayed significantly larger amplitudes of TTCC-currents. The increase in current was accompanied by a corresponding 2-fold increase in CaV3.1 TTCC mRNA. Moreover, with unbiased stereology, we detected an about 30% lower number of SN DA neurons already in juvenile CaV1.3 KO mice. In summary, the here identified homeostatic interplay of CaV1.3 and CaV3.1 VGCCs, and their complex modulation of SN DA activity pattern provides new insights into flexible age- and Ca²⁺-dependent activity control of SN DA neurons, and has implications for PD pathophysiology and its pharmacological therapy.

Reference


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