HCN channels constrain dendritic excitability in substantia nigra dopaminergic neurons in vitro and promote their survival in vivo

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AIMS

The molecular mechanisms underlying the differential vulnerability between substantia nigra pars compacta (SNc) and Ventral Tegmental Area (VTA) dopaminergic (DAergic) neurons in Parkinson's Disease (PD) are still unclear. We recently demonstrated that MPP+, a neurotoxin able to cause selective nigrostriatal degeneration in rodents and primates, alters the electrophysiological properties of SNc DAergic neurons in vitro by inhibiting the Hyperpolarization-activated current (Ih). The goal of this work is to identify physiological determinants of differential vulnerability within DAergic neurons.

METHODS

Whole-cell recordings were performed in acute midbrain slices from juvenile WH rats or TH-GFP mice. Simultaneous determination of changes in cytosolic calcium concentration was achieved by loading the recorded neuron with Fluo-4 or Oregon Green. Inactivation of Ih in vivo was obtained by stereotaxic intranigral injection of ZD7288 or ivabradine in adult WH rats or TH-GFP mice.

RESULTS

In midbrain DAergic neurons from TH-GFP mice, pharmacological suppression of Ih increases the amplitude and duration of evoked Excitatory Post-Synaptic Potentials (EPSPs) leading to temporal summation of multiple EPSPs. The extent of this response depends on postsynaptic Ih magnitude and is significantly greater in SNc compared to VTA DAergic neurons. In vivo, local administration of specific Ih blockers causes a DAergic degeneration pattern reminiscent of MPTP-intoxication.

CONCLUSIONS

These results indicate that Ih regulates dendritic excitability differentially within midbrain DAergic neurons and suggest that Ih loss of function, possibly resulting from metabolic stress in early phases of PD, may act in concert with SNc-specific connectivity to promote selective vulnerability.