DIFFERENTIAL CONTRIBUTION OF IH IN DENDRITIC EXCITABILITY IN SUBSTANCIA NIGRA AND VENTRAL TEGMENTAL AREA DOPAMINERGIC NEURONS

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AIMS

The selective vulnerability of substantia nigra pars compacta (SNc) dopaminergic (DA) neurons is an enigmatic trait of Parkinson's disease, especially if compared to the remarkable resistance of closely related DA neurons in the neighboring Ventral Tegmental Area (VTA).

We recently demonstrated that MPP+, a neurotoxin able to cause selective nigrostriatal degeneration in rodents and primates, alters the electrophysiological properties of SNc DA neurons in vitro by inhibiting the Hyperpolarization-activated current (Ih). The goal of this work is to identify the functional role of Ih in the integration of synaptic inputs in identified SNc and VTA DA 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 DA 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 excitatory potentials at somatic level. The effect size of this response depends on postsynaptic Ih magnitude and is significantly greater in SNc compared to VTA DA neurons. In vivo, local administration of specific Ih blockers causes a DA degeneration pattern reminiscent of MPTP-intoxication.

CONCLUSIONS

These results indicate that Ih regulates the responsiveness to dendritic excitability differentially within midbrain DA neurons and suggest that Ih loss of function may be linked to PD trigger mechanisms, resulting from metabolic stress in early phases of disease, and act in concert with SNc-specific connectivity to promote selective vulnerability.