Hyperpolarization-activated current, midbrain dopamine neurons and Parkinson's disease

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1-methyl-4-phenylpyridinium (MPP+) is the active metabolite of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) metabolism, a compound long used to generate animal models for Parkinson's disease (PD) research. MPP+ is believed to kill dopamine (DA) neurons by blocking mitochondrial complex I, thereby impairing ATP production and elevating reactive oxygen species. Yet well accepted, this mechanism is hardly consistent with the observation that DA neurons of the substantia nigra pars compacta (SNc) are strikingly more vulnerable than DA neurons located in the neighboring ventral tegmental area (VTA), a histopathological hallmark also present in spontaneous PD. Hence, additional, extra-mitochondrial pathogenic pathways may account for this remarkable discrepancy. With patch clamp recordings from rat and mouse midbrain slices we recently demonstrated that MPP+ acutely inhibits the hyperpolarization-activated inward current (Ih) in SNc and VTA DA neurons. The effect is voltage- and concentration-dependent and, importantly, unrelated to complex I inhibition/ATP depletion. Moreover, we found that MPP+-dependent inhibition of Ih enhances temporal summation of evoked excitatory post-synaptic potentials, a phenomenon linked to calcium-mediated toxicity in other structures and one proposed cell-death mechanism in PD. Although quantitatively similar in SNc and VTA DA neurons, MPP+-dependent inhibition of Ih may result in an exacerbated toxic action on SNc DA neurons when combined to an elevated excitatory synaptic input from the subthalamic nucleus, abnormally active in PD. Interestingly, Ih loss-of-function has also been described in Mitopark mice, a genetic mitochondrial model, suggesting that the hypothetical pathogenic relevance of the proposed mechanism may extend to other animal models and, perhaps, to sporadic PD.