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NEURODEGENERATIVE DISEASE

SNc neurons' Achilles heel

In Parkinson's disease, degeneration of dopamine neurons in the substantia nigra pars compacta (SNc) is thought to result from oxidative stress. However, why SNc neurons are particularly vulnerable to degeneration has been a long-standing conundrum. Surmeier and colleagues now show that these neurons have a high basal level of mitochondrial oxidative stress, and that this is exacerbated by loss of DJ-1 protein, which has been associated with Parkinson's disease.

Dopaminergic SNc neurons show spontaneous, pacemaker-like firing that opens L-type Ca^{2+} channels. This could create an oxidative burden on mitochondria because Ca^{2+} has to be removed by pumps that burn energy that the mitochondria supply through oxidative phosphorylation. Pacemaking also occurs in dopamine neurons in the ventral tegmental area (VTA), but much less Ca^{2+} is allowed to enter here. Because VTA neurons are less affected in Parkinson's disease than SNc neurons, the authors investigated whether Ca^{2+} entry actually creates a measurable mitochondrial oxidative stress.

Monitoring the oxidation of mitochondrial matrix proteins revealed that basal mitochondrial oxidative stress was higher in SNc neurons than in VTA neurons in slices from mature — but not from juvenile — wild-type mice, and higher still in SNc neurons from *DJ-1* knockout mice. These differences disappeared when L-type Ca^{2+} channels or Ca^{2+} entry into mitochondria were pharmacologically blocked.

SNc mitochondria, but not VTA mitochondria, showed transient spontaneous depolarization (mitochondrial flickering), which was reduced by blocking L-type channels, by blocking Ca^{2+} entry into mitochondria and by applying a cell-permeant antioxidant. This suggests that oxidative stress resulting from Ca^{2+} entry causes mitochondrial depolarization. How might this happen? Superoxide — which is produced during oxidative stress — can trigger the opening of uncoupling proteins (UCPs), which are mitochondrial H^+ channels, resulting in mitochondrial depolarization. UCPs can also prevent further superoxide production through a negative feedback reaction. In accordance with this, applying a UCP antagonist both reduced mitochondrial flickering and increased mitochondrial oxidative stress in SNc neurons.

SNc neurons from *DJ-1* knockout mice had lower levels of *Ucp4* and *Ucp5* mRNA and showed reduced mitochondrial flickering compared with wild-type mice. This suggests that in *DJ-1* knockout mice, reduced UCP expression in SNc dopamine neurons exacerbates mitochondrial stress in these already vulnerable neurons.

By elevating mitochondrial oxidative stress, Ca^{2+} entry into the cell during normal pacemaking activity renders SNc dopamine neurons more vulnerable to toxins and could accelerate their loss with aging — the number one risk factor for Parkinson's disease. These findings suggest that L-type Ca^{2+} channel blockers, some of which have already been approved for use in humans, may be neuroprotective.

Leonie Welberg

ORIGINAL RESEARCH PAPER Guzman, J. N. *et al.* Oxidant stress evoked by pacemaking in dopaminergic neurons is attenuated by DJ-1. *Nature* 10 Nov 2010 (doi: 10.1038/nature09536)