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Parkinson's Disease: Return of an Old Prime Suspect

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Pacemaking activity in adult substantia nigra (SN) dopamine neurons relies on L-type Ca^{2+} channels, but a surprising study in *Nature* by Chan et al. demonstrates that blockade of these channels by dihydropyridines re-establishes the pacemaking driven by sodium and HCN channels found in juvenile SN. This shift protects SN neurons in chemical models of Parkinson's disease (PD), suggesting that elevated intracellular Ca^{2+} participates in SN cell loss and that dihydropyridines may provide therapy in PD.

Parkinson's disease (PD) is diagnosed by a set of voluntary motor control dysfunctions known as "parkinsonism" that are due to the death of substantia nigra (SN) dopamine (DA) neurons and can be alleviated by DA replacement therapy using L-DOPA (Dauer and Przedborski, 2003; Sulzer, 2007). A major question is why certain neurons are targeted, and particularly why SN neurons die while neighboring midbrain DA neurons of the ventral tegmental area (VTA) are relatively spared (Damier et al., 1999).

A clue is provided by the unusual physiological properties of adult ventral midbrain DA neurons, which exhibit pacemaker activity in the absence of excitatory input (Grace and Onn, 1989), a feature widely suspected to underlie normal voluntary motor control, although there is at present little proof of that conjecture. Pacemaking in SN DA neurons depends on somatodendritic L-type channel-driven Ca^{2+} currents (Nedergaard et al., 1993) and to some extent or in some subpopulations on hyperpolarization-activated and cyclic nucleotide-gated cation (HCN) channels (Mercuri et al., 1995; Neuhoff et al., 2002) together with Ca^{2+}-activated SK K^+ channels that produce an afterhyperpolarization that delays return to threshold (Nedergaard et al., 1993).

The Ca^{2+} flux that underlies SN pacemaking is large, and midbrain DA neurons are to date unique in possessing a greater interspike calcium current than sodium current (Puopolo et al., 2007). Together with high Ca^{2+} flux that occurs during their relatively wide action potentials and presumed additional current when the neurons burst fire with excitatory input (Kuznetsov et al., 2006), normal SN neuron activity seems to entail unusually high Ca^{2+} entry.

In a new study published in *Nature*, James Surmeier's group at Northwestern University reports several surprising features of this pacemaking activity (Chan et al., 2007). First, pacemaking is already present in newborn mouse SN neurons but is driven by sodium channels in conjunction with HCN channels. Then, during the second week following birth, there is a gradual switch as $Ca_v1.3$ current increases, perhaps as the voltage dependence of HCN channels is shifted toward more negative membrane potentials, essentially taking HCN channels "off-line." The development of SN Ca^{2+}-driven pacemaking occurs in tandem with an increased expression of slowly inactivating somatodendritic L-type Ca^{2+} channels that drive the neurons into oscillations, due to the presence of

$Ca_v1.3$ α subunits, which open in a relatively hyperpolarized subthreshold range (~50 mV). In support of these new observations, knockout mice that don't express the $Ca_v1.3$ α subunit of L-type Ca^{2+} channels continue to show SN pacemaking driven by the sodium/HCN currents throughout their lives. While normal adult VTA neurons also have $Ca_v1.3$ channels, they continue for unknown reasons to exhibit pacemaking driven by sodium channels.

L-type Ca^{2+} channels have been pharmacological targets for more than three decades because they regulate the pacemaking currents underlying heart muscle contraction. Dihydropyridines including nimodipine and isradipine have been prescribed to millions of patients for hypertension treatment. These drugs possess an unusual feature in that they show a higher apparent affinity with depolarization (Sanguinetti and Kass, 1984) and are thus particularly efficacious in heart and smooth muscle, as these tissues maintain a relatively high resting potential.

The Surmeier group found that in ventral midbrain slices from normal adult mice, as expected, dihyropyridines halted SN pacemaking. Amazingly, however, pacemaking returned to SN neurons very rapidly, within 2 or 4 hr of exposure, again driven by sodium/HCN currents.

The remarkable compensatory switch in the ionic basis of pacemaker activity by SN neurons following dihydropyridine exposure suggested that dihyrdopyridine treatment might help prevent nigral cell loss in PD. The field of PD research, however, still lacks a mouse line that expresses a familial PD mutation that results in selective PD-like SN neuronal death, and so the investigators tested effects of isradipine on well-established chemical toxin models that selectively kill SN neurons: MPTP, 6-hydroxy-DA, and the mitochondrial complex I inhibitor, rotenone (Dauer and Przedborski, 2003). The dihydropyridines, particularly isradapine, which has a comparatively high affinity for $Ca_v1.3$, effectively blocked the chemically induced neurodegeneration, and a retrospective search of the epidemiological literature revealed an observation that patients taking dihydropyridines had substantially lower than usual incidence of PD.

How do these results contribute to understanding neurodegeneration in PD? All humans presumably have $Ca_v1.3$ L-type Ca^{2+} channels in SN DA neurons, and yet the lifetime incidence of PD is at most 2% (Sulzer, 2007). Other neurons, in particular cochlear hair cells, maintain L-type channel currents that control synaptic exocytosis (Striessnig et al., 2006) but are not known to be damaged in PD. The results, nevertheless, fit with the idea that PD, which exhibits low genetic penetrance, requires "multiple hits" (Sulzer, 2007), unlike some other motor disorders that result from dysfunction of a single enzyme. High cytosolic Ca^{2+} is well known to induce oxidative stress and excitotoxicity and has long been suspected to play a role in PD (Beal, 1998), although there has been little direct evidence. Ventral midbrain DA neurons have among the most extensive neuritic arborization in the CNS, and are likely to express L-type channels in SN dendrites, which contain DA secretory vesicles and mitochondria and presumably require substantial energy supplies. It has long been suspected that PD neurodegeneration begins in neurites, and perhaps high cytosolic Ca^{2+} can initiate oxidative stress and excitotoxicity in dendritic spines.

While the new study does not tie together the role of mutant genes that cause familial PD with high Ca^{2+} levels, mitochondria buffer cytosolic Ca^{2+}, which may link SN death to several genetic mutations that may be associated with mitochondria and are identified to cause familial PD (Sulzer, 2007), including *PINK1*, *DJ-1*, and *LRRK2*. The new results may also help explain one of the long-noted differences between SN and VTA neuron loss in PD (Damier et al., 1999) and in the mouse MPTP model (Liang et al., 1996): most VTA neurons and a subset of SN neurons that are spared in PD and with MPTP express substantially higher levels of calbindin, a protein that additionally buffers cytosolic Ca^{2+}.

More important immediately, however, may be the implication that dihydropyridines could attenuate neurodegeneration in PD. This objective may not be straightforward: these drugs tend to have a higher affinity for $Ca_v1.2$ L-type channels than $Ca_v1.3$ channels that underlie SN pacemaking. The concentration of isradipine used to temporarily halt pacemaking and prevent toxin-induced neurodegeneration in the study is high, and while many hypertensive patients take dihydropyridines with no ill effects, the drugs will cause hypotension in otherwise normal patients: it is possible that doses lower than those used in the study will be efficacious. A note of caution is struck from the observation that mice that lack the $Ca_v1.3$ subunit are deaf (Striessnig et al., 2006), as might be expected from the above-mentioned roles of L-type Ca^{2+} channels in cochlear hair cell activity; fortunately, this has not been reported in humans, perhaps because the voltage dependence of the dihydropyridine block makes them poor blockers of channel opening driven by rapid voltage fluctuations but effective blockers during the slow depolarizations associated with pacemaking. Finally, L-type channels further appear to underlie forms of synaptic plasticity, including the regulation of synaptic input and morphological changes that occur in dendritic spines (Day et al., 2006), and L-type channel inhibition may interfere with these normal synaptic functions.

Sill, most neurons and smooth muscle cells contain mainly the $Ca_v1.2$ α subunits, and it may be that identification of a relatively specific $Ca_v1.3$ channel antagonist would provide a means to turn off SN Ca^{2+}-driven pacemaking and return it to a normally acting but "rejuvenated" sodium-driven pacemaker, thus protecting the SN downstream from the initial underlying cause of PD with little disturbance of other important L-type channel-driven functions.

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