A Lethal Convergence of Dopamine and Calcium

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The controversy about whether dopamine contributes to cell loss in Parkinson's disease takes a new turn as Mosharov et al. in this issue of *Neuron* demonstrate that Ca^{2+} influx through L-type channels elevates dopamine synthesis to potentially toxic levels in vulnerable ventral mesencephalon neurons.

Parkinson's disease (PD) afflicts millions. It is the second most common neurodegenerative disease, robbing sufferers of many capacities, including the ability to move and speak fluidly. Age is the greatest risk factor for PD, which means that as improvements in health care drive up the average life span, the number of people suffering from PD will increase. Projections are that the number of Americans suffering from PD will double by 2025 (Dorsey et al., 2007).

To make matters worse, nothing is known to slow the inexorable progression of the disease. In large measure, this is because we don't know what causes it. The paper by Mosharov et al. (2009) in this issue of *Neuron* appears to provide a potentially important piece of the puzzle. The cardinal symptoms of PD—rigidity, tremor, bradykinesia—result from the death of a small group of dopaminergic neurons in a region of the mesencephalon, the substantia nigra pars compacta (SNc; Hornykiewicz, 1966; Riederer and Wuketich, 1976). We know this in part because boosting the production of dopamine by oral administration of the dopamine precursor L-3,4 dihyroxyphenylalanine (L-DOPA) does a good job of ameliorating symptoms, at least in the early stages of the disease.

The question Mosharov and colleagues (2009) asked was why SNc dopaminergic neurons were vulnerable. Dopamine itself has long been suspected to be a culprit in PD. Dopamine catabolism or oxidation can generate molecules capable of wreaking all sorts of havoc inside cells (Burke et al., 2004; Eisenhofer et al., 2004; Greenamyre and Hastings, 2004). But there are problems with this model. One is that not all dopamine neurons in the brain die in PD (e.g., Damier et al., 1999; Saper et al., 1991). As a matter of fact, neighboring dopaminergic neurons in the ventral tegmental area (VTA) are largely spared in PD. So, while the use of dopamine as a transmitter was potentially dangerous, it alone couldn't explain vulnerability.

Mosharov et al. (2009) reasoned that maybe it was the quantity of dopamine, not the quality. But how to measure dopamine where it really matters, in the cytoplasm? By using an innovative combination of patch clamp and amperiometric approaches, Mosharov et al. (2009) were able to measure cytosolic dopamine concentrations in living neurons, albeit after bumping concentrations up by exposing them to L-DOPA. After carefully characterizing how cytosolic dopamine levels were controlled by precursor (L-DOPA) availability, enzymatic synthesis, vesicular sequestration, and catabolism, Mosharov et al. (2009) made a key discovery—cytosolic DA concentrations in vulnerable SNc DA neurons were 2- to 3-fold higher than in resistant VTA DA neurons, rendering them much more sensitive to the toxic effects of an acute L-DOPA challenge. This difference was not attributable to precursor uptake, dopamine storage or dopamine degradation, leaving differences in synthesis as the most likely culprit.

Why was there a difference in synthesis? The study doesn't provide a definitive answer but does provide a tantalizing clue. Cytoplasmic Ca^{2+} concentrations are higher in SNc dopaminergic neurons than neighboring VTA neurons because they use L-type Ca^{2+} channels to help maintain autonomous pacemaking (Chan et al., 2007). When these channels are antagonized or cytoplasmic Ca^{2+} extrinsicially buffered, the differences in cytosolic dopamine went away—arguing that Ca^{2+} was boosting dopamine synthesis. More importantly, antagonizing L-type Ca^{2+} channels significantly diminished the toxic effects of L-DOPA. This model fits nicely with the early observation that expression of calbindin, a Ca^{2+} buffering protein, is negatively correlated with vulnerability in PD (Damier et al., 1999; German et al., 1992). Mosharov et al. (2009) also show that alpha-synuclein (a major component of Lewy bodies associated with PD) factors into this equation, perhaps by being converted into an inhibitor of chaperone mediated autophagy by dopamine (Martinez-Vicente et al., 2008; see Figure 1).

So, are SNc dopaminergic neurons particularly vulnerable in PD not because they make dopamine per se, but because they make too much? The ability of L-type Ca^{2+} channel antagonists to diminish the sensitivity of SNc dopaminergic neurons to toxins used to create animal models of PD is certainly consistent with this idea (Chan et al., 2007), as is the diminished risk of developing PD with the use of Ca^{2+} channel antagonists to treat hypertension (Becker et al., 2008). But it should be remembered that Ca^{2+} itself poses a challenge to cellular longevity (Mattson, 2007; Nicholls, 2009). Sustained Ca^{2+} influx, like that seen in pacemaking SNc dopaminergic neurons (Chan et al., 2007), creates a particularly thorny problem for mitochondria which have long held center stage in thinking about the etiology of PD (Schapira, 2008). Not only are they largely responsible for producing the adenosine triphosphate (ATP) necessary to keep intracellular Ca^{2+} concentrations within acceptable limits, they directly participate in Ca^{2+} buffering (Nicholls, 2009). Because aging diminishes the mitochondrial capacity to generate ATP through oxidative phosphorylation, neurons with a Ca^{2+} reliant

pacemaking phenotype should be operating nearer and nearer their peak metabolic capacity, diminishing their ability to withstand episodic challenges (Nicholls, 2009) or the additional proteostatic burden created by reactive dopamine metabolites (Sulzer, 2007; Figure 1).

As fascinating and plausible as this story is, a 300 pound gorilla is sitting in the corner. Is PD really a dopaminergic disorder? To be sure, loss of SNc dopaminergic neurons is responsible for the motor symptoms of the disease, but there are a host of nonmotor symptoms that plague PD patients that have their origins elsewhere (Chaudhuri et al., 2006). Braak and colleagues (2004) have argued that the Lewy body pathology characteristic of PD actually begins in the caudal brainstem in the non-dopaminergic neurons of the dorsal motor nucleus of the vagus. Regardless of whether you are convinced of the caudal-to-rostral staging in PD proposed by Braak (Burke et al., 2008; Lees, 2009), there is no arguing with the distributed LB pathology and loss of non-dopaminergic neurons in PD. What makes these neurons vulnerable is unresolved, but the work by Mosharov et al. (2009) elegantly drives home the lesson that figuring this out is likely to come from understanding how cellular risk factors converge to determine vulnerability.

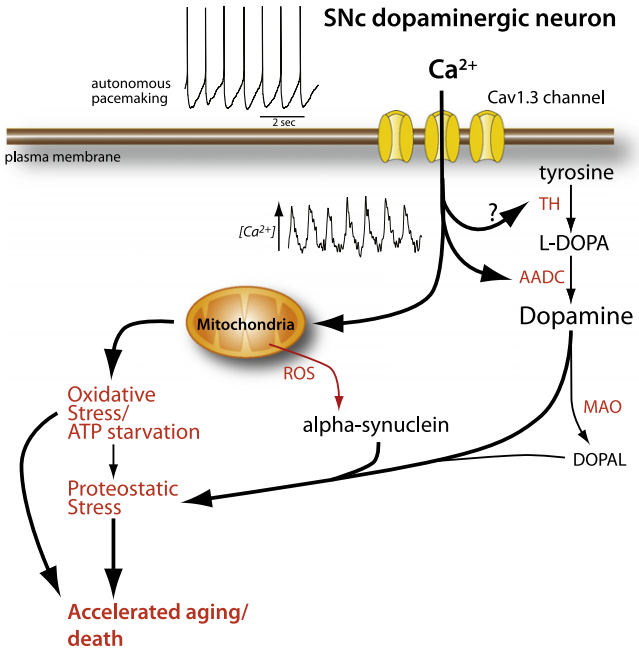

Figure 1. Calcium Enhancement of Dopamine Synthesis Leads to Increased Stress in Substantia Nigra Dopaminergic Neurons

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