Homeostatic regulation of dopaminergic neurons without dopamine

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A n astonishing number of psychomotor disorders stem from alterations of the function of brain neurons that release or respond to the neurotransmitter dopamine. Synthesized from the amino acid tyrosine, dopamine is implicated in drug abuse, attention deficit hyperactivity disorder, Tourette’s syndrome, dystonia, schizophrenia, and Parkinson’s disease (PD), where the control of internally generated movement or thought is disturbed (1). In PD, dopaminergic neurons in a region of the mesencephalon, the substantia nigra pars compacta, stop releasing dopamine and eventually die, leading to the emergence of bradykinesia, tremor, and rigidity (2). The neural adaptations in target structures, like the striatum, that accompany the gradual loss of dopaminergic neurons and the symptoms of the disease are beginning to be understood. But what happens to the dopaminergic neurons that remain? How do they respond to falling levels of dopamine? The prevailing view is that dopamine release and the activity of dopaminergic neurons is controlled by homeostatic mechanisms (3). That is, activity is regulated to maintain an optimal basal level of dopamine in target structures by feedback mechanisms that sense dopamine. The work by Robinson et al. (4) in this issue of PNAS challenges the completeness of this view. The authors show that dopaminergic neurons that do not release dopamine exhibit normal activity patterns in awake, behaving mice. This finding suggests that, although dopamine may be important, other signaling factors must control the activity patterns of dopaminergic neurons. The existence of other homeostatic signals has fundamental implications not only for our understanding of the compensations in early-stage PD but also for mechanisms contributing to other dopaminergic disorders like attention deficit hyperactivity disorder and drug abuse.

A major figure in the story told by Robinson et al. (4) is the experimental subject. Previous studies focusing long-term adaptations to dopamine depletion have relied on chemical toxins like 6-hydroxydopamine or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (1). Although both agents lower brain dopamine levels effectively, they do so by poisoning dopaminergic neurons, making subsequent study of them problematic. These models also suffer from the inability to distinguish between compensations that are induced by the depletion of dopamine and those that are triggered by the loss of dopaminergic neurons. This distinction is crucial, particularly when thinking about therapeutic strategies in disorders like PD, because “dopaminergic” neurons may be releasing neurotransmitters or neurotrophic factors other than dopamine that are important to the proper functioning of target tissues. To overcome this limitation, Richard Palmiter’s group (5) engineered a mouse in which the dopaminergic neurons in the mesencephalon were normal in every respect except that they were incapable of converting tyrosine to L-dihydroxyphenylalanine (L-DOPA), the precursor for dopamine. After weaning, these dopamine-deficient (DD) animals resemble those in which dopaminergic neurons have been lesioned in that they don’t move around readily, eat, or drink. Without treatment, they die. However, like PD patients, L-DOPA rescues them.

What Is the Homeostatic Signal?

Robinson et al. (4) show that in unanesthetized, awake but essentially akinetic DD mice the activity of dopaminergic neurons is surprisingly normal both in terms of basal firing rates and pattern. Just as in control mice, DD dopaminergic neurons (identified by their distinctive spike waveform) discharged in a single spike pacemaker mode, an irregular mode, and a “bursty” mode (6–8). This result argues that there is a fundamental gap in our understanding of how the activity of dopaminergic neurons is regulated. The prevailing view is that there are two homeostatic feedback mechanisms that serve to keep activity and dopamine release within a preferred range. One involves a short-loop feedback through dendritic autoreceptors, the other involves long-loop, dopamine-responsive basal ganglia circuits. Obviously, without dopamine, neither of these mechanisms should operate properly. This is a little like discovering that your home heating system works beautifully year-round when the thermometer in the control system is disconnected. Clearly, there is some other homeostatic signal that we don’t know about. Because dopaminergic neurons are autonomous pacemakers, it is possible that the homeostatic signal is one directly linked to spiking, like transmembrane calcium flux. There are precedents for this type of regulation that allow for alterations in both synaptic and intrinsic processes governing activity (9, 10). However, the elevated susceptibility of dopaminergic neurons in DD mice to anesthetics shown by Robinson et al. (4) is difficult to reconcile with an autonomous regulation of this sort. It may be that dopaminergic neurons release another neurotransmitter, like glutamate (11), that serves the homeostatic purpose. If so, it could prove to be extremely important in managing dopaminergic neuron function and designing stem cell replacements in PD.

L-DOPA Activates Long-Loop Circuits

One striking difference between dopaminergic neurons in control and DD mice is their response to systemic administration of the dopamine precursor L-DOPA. Understanding how L-DOPA shapes the activity of the basal ganglia is important because in the early stages of PD, patients respond well to it (12). Robinson et al. (4) show that in DD mice L-DOPA dramatically reduced the firing of dopaminergic neurons but had no effect in control mice. This finding means that the discharge of dopaminergic neurons fell in DD mice at the same time as they began to move and feed. This paradoxical effect seems not to be caused by any alteration in the sensitivity of autoreceptors (13) but rather by an elevated sensitivity of synaptically
striatum are the most attention to the striatum, locomotion. Previous studies have paid the most attention to the striatum, which is the principal recipient of the dopaminergic innervation lost in PD. The vast majority of the neurons in the dopaminergic innervation lost in PD. Robinson et al.‘s work (4) strongly argues that dopamine itself is critical to the development of supersensitivity, a widely held, yet largely untested, assumption (cf. ref. 15). But to this day very little is known about the neuronal populations that become supersensitive and their relationship to locomotion. Previous studies have paid attention to the striatum, which is the principal recipient of the dopaminergic innervation lost in PD.

There also is a component of the response to L-DOPA that is mediated by D2 dopamine receptors. Autoreceptors of this type and may play some role, but Robinson et al. make the case that a longer loop circuit is likely to be involved. Several circuits could mediate this response, including one involving the globus pallidus and subthalamic nucleus: two nuclei that serve as an interface between the basal ganglia and the rest of the brain. Dopaminergic neurons in the substantia nigra pars compacta, where Robinson et al.’s recordings were largely made, receive a direct striatal innervation (16) that appears to be derived from a distinct subset of medium spiny neurons found in patches or striosomes (17). These neurons express D1 dopamine receptors that enhance their responsiveness to excitatory cortical synaptic inputs (18). Robinson et al. (4) show that the effects of L-DOPA in DD mice are attenuated by D2 receptor antagonists and mimicked by D1 receptor agonists, suggesting that medium spiny neurons in this direct GABAergic pathway are supersensitive. There also is a component of the response to L-DOPA that is mediated by D2 dopamine receptors. Autoreceptors of this type and may play some role, but Robinson et al. make the case that a longer loop circuit is likely to be involved. Several circuits could mediate this response, including one involving the globus pallidus and subthalamic nucleus: two nuclei that play a critical role in the motor symptoms in PD (19–21).

As with all good work, the studies by Robinson et al. (4) raise more questions that they answer. What factors, other than dopamine, contribute to the homeostatic regulation of activity in dopaminergic neurons? Is glutamate important? Growth factors like brain-derived neurotrophic factor? Which neural circuits contribute to this regulation, and how do they adapt as dopamine levels fall? Are they restricted to the basal ganglia or are other circuits involved? Answering these questions and the ones they spawn will push us closer to not only better treatments for PD but also better treatments for the staggering array of other dopamine-related disorders.