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The Thorny Problem of Dyskinesias: Dendritic Spines, Synaptic Plasticity, and Striatal Dysfunction

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Abnormal involuntary movements, particularly levodopa-induced dyskinesia (LID) and antipsychotic drug-elicited tardive dyskinesia, are among the most difficult to manage adverse effects associated with the treatment of Parkinson's disease (PD) and schizophrenia, respectively. The mechanisms underlying dyskinesias in levodopa-treated PD have been studied for decades. Over this time, there has been a gradual shift from a focus on mechanisms associated with surviving dopamine (presynaptic) neurons to changes in dopaminergic cells in the striatum.

The medium spiny neurons (MSNs) of the striatum account for more than 90% of striatal neurons. Medium spiny neurons share a common morphology of medium-sized cell bodies with radially extending dendrites that are richly invested with dendritic spines, the thorny excrescences noted by Santiago Ramon y Cajal in the late 18th century. Displaying his usual brilliant ability to predict functional correlates of his structural observations, Cajal suggested that these spines were the site of interaction between presynaptic axons and their postsynaptic targets, and today it is clear that the dendritic spine is the primary site at which excitatory inputs regulate neurons.

There are two major subtypes of MSNs, defined on the basis of the dopamine receptor present on the cell, the peptide co-transmitter in these neurons, and the projection target of the cell: MSNs that express dopamine D₁ receptors, preprotachykinin messenger RNA, and project to the pars reticulata of the rodent substantia nigra (direct pathway cells), and D₂ receptor-expressing MSNs that contain preproenkephalin and innervate that globus pallidus before routing to the substantia nigra (indirect pathway cells).

In this issue, Suárez *et al.* (1) report that dopamine denervation of the striatum results in a loss of dendritic spines but not dendritic length or cell body size in MSNs, with levodopa treatment reversing the spine loss observed in dopamine-denervated mice. The authors used either D₁ receptor td-Tomato or D₂ receptor-enhanced green fluorescent protein bacterial artificial chromosome (BAC) transgenic mice subjected to unilateral intrastriatal injections of 6-hydroxydopamine or vehicle. Two to three weeks later, the animals were started on 2 weeks of daily levodopa/ benserazide or vehicle injections, resulting in contralateral fore-

limb and orofacial dyskinesias and trunk dystonia. Suárez *et al.* (1) used the fluorescent reporters in the two mouse lines to guide intracellular fills of the MSNs with Lucifer Yellow, permitting full structural reconstructions of the cells, as well as the ability to selectively define physiological changes in D₁ and D₂ MSNs.

Suárez *et al.* (1) found that the overall decrease in MSN spine density was not attributable to a selective loss of spines in one of the two types of MSNs but occurred in both D₁- and D₂-expressing MSNs. Dendritic spine loss was restricted to striatal territories suffering extensive (>90%) dopaminergic deafferentation but not contiguous striatal sectors in which the loss of dopamine axons was less marked. Repeated levodopa treatment, which induced dyskinesias, reversed the overall decrease in MSN dendritic spine density. However, examination of MSNs expressing either the D₁ or D₂ receptor revealed that the reversal of spine loss was restricted to D₂-enhanced green fluorescent protein MSNs and was not seen in D₁-positive MSNs. Physiological studies of the D₁ MSNs in mice with LID uncovered an increased excitability of these cells.

The loss of MSN dendritic spines in both postmortem studies of idiopathic PD and animal models of parkinsonism has long been known [(2); see (3) for review], with considerable attention devoted to understanding the mechanisms underlying LID. The report by Suárez *et al.* (1), in large part, confirms the results of previous studies on MSN spine loss and the changes in MSN structure and function that underlie LID. The advantages of the new report are the use of BAC transgenic mice to unambiguously define D₁- and D₂-expressing MSNs and the fact that the study is the most comprehensive and detailed set of experiments on MSN dendritic changes in LID to date, allowing one to decipher the relative degree of involvement of spines (and therefore indirectly synapses) expressing either D₁ or D₂ receptors.

There are some observations in the current study that differ from earlier reports. Suárez *et al.* (1) found that for the spine changes to be manifest, the extent of the dopaminergic innervation of the striatum must exceed ~90%. However, in 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP)-treated monkeys, in which the striatal dopamine loss is typically less extensive than seen after 6-hydroxydopamine treatment, a loss of spines occurs both in striatal territories suffering extensive dopamine depletion and less severely affected areas, although the degree of spine loss differs (3). Similarly, postmortem studies of PD have reported a marked loss of dendritic spines in the striatum (4), despite the fact that the striatal dopamine loss (particularly in the caudate nucleus) rarely reaches 90% in idiopathic PD. To some degree Suárez *et al.* (1) findings that striatal dopamine loss must be nearly complete for significant spine loss to occur may reflect differences in methods of ascertaining the dopamine innervation: Suárez *et al.* (1) carefully used two indices of the extent of striatal dopamine loss. The duration of striatal dopaminergic denervation may also contribute to discrepant observations. In the current study, animals survived for 5 to 6 weeks, in contrast to the years or decades of striatal dopamine loss in monkeys with experimentally induced parkinsonism or patients with idiopathic PD. In postmortem studies, the length of the dendritic arbor is significantly decreased (4), in contrast to the lack of change in dendritic length in the current study. Finally, the various methods used to lesion the striatal dopamine

innervation and the duration of survival may be important factors, particularly regarding local inflammatory changes.

Using single-cell reverse transcriptase polymerase chain reaction to define the phenotype of MSNs, Day *et al.* (5) reported that mice treated with reserpine lost spines on D₂ but not D₁ MSNs. In the current study, with the definition of the dopamine receptor offered by the use of BAC transgenic mice, Suárez *et al.* (1) found that both D₁ and D₂ MSNs lost dendritic spines after dopamine denervation. Their data are consistent with the earlier observations in MPTP-treated monkeys, in which both D₁- and non-D₁ (presumptive D₂)-immunoreactive spines are decreased (2). It is unclear if there is an evolving temporal pattern of dendritic spine loss that differentially results in D₁ and D₂ MSNs showing spine loss at different times after dopamine denervation.

Unexpectedly, Suárez *et al.* (1) found that levodopa treatment, which elicited dyskinesias, reversed the spine loss—but only on D₂ MSNs. The D₁ MSNs, in which spine loss was not reversed, instead became hyperexcitable, as reflected by an increased number of action potentials in response to injection of depolarizing currents into the cells. This observation is consistent with previous literature indicating enhanced D₁ receptor signaling in LID.

How do the findings of the current study and earlier data guide us in developing strategies to attenuate LID? The current study points to the D₁ receptor as critical. However, chronic treatment with D₁ agonists is likely to lead to cognitive deficits. Moreover, D₁-containing MSNs undergo a phenotypic change after chronic levodopa treatment, expressing the dopamine D₃ as well as the D₁ receptor (6); D₃ partial agonists have been reported to attenuate LID in MPTP-lesioned monkeys (6). The difficulties in developing a D₃ partial agonist for human use or for selectively activating D₃ receptors without concomitant activation of D₂ receptors suggest that some approach to the treatment of LID other than direct modulation of dopamine receptors is needed.

A large number of nondopaminergic strategies for pharmacologic amelioration of LID have been advanced (7), ranging from serotonergic agents to peptides. Among these, glutamatergic agents are arguably the best candidates. Single corticostriatal glutamatergic axons synapse with MSN spine heads in a one-to-one ratio. However, in LID, this characteristic synaptic architecture between corticostriatal axons and MSN dendritic spines no longer holds, with multiple corticostriatal (but not thalamostriatal) glutamatergic axons synapsing onto MSN spines (8). Thus, simple reversal of dendritic spine loss may not be a viable approach to attenuating dyskinesias. Instead, treatments that prevent or attenuate MSN dendritic spine loss in the first place may be a better strategy than directly targeting LID that has already developed. Increased intracellular calcium levels are thought to be the major mechanism contributing to MSN spine loss (5,9). Thus, postglutamate receptor strategies aimed at limiting the rate of increase and ultimate amount of calcium in spines by treatment with L-type voltage-gated calcium channel antagonists may be a useful strategy, preventing both spine loss and LID (5,9). Alternatively, metabotropic glutamate receptors type 2 and 3 agonists, which dampen glutamate release from corticostriatal axons and thereby limit the intraspinal surge in calcium, prevent and reverse dopamine denervation-elicited spine loss (10). The side effect profiles in human studies of both dihydropyridine

antagonists of L-type calcium channels and metabotropic glutamate receptors type 2 and 3 agonists have been very good, suggesting that the adverse effects that have plagued *N*-methyl-D-aspartate antagonist trials could be avoided in treating LID. Both approaches offer the potential advantage of minimizing spine loss if instituted early in the course of PD and preventing the development of dyskinesias. In attempts to reduce the burden of dyskinesias, an ounce of prevention may be worth more than a pound of cure.

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