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The Missing, the Short, and the Long: Exploring the Borderland Between Psychiatry and Neurology

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Albin and Leventhal have presented compelling rationales for the different mechanisms of the short (SDR) and long (LDR) duration responses to levodopa in Parkinson's disease (PD).¹ As the authors remark, their unusual character caught the attention of Cotzias soon after his introduction of the drug and have been studied by his successors; yet, they remain unexplained. Neither known pharmacodynamic nor synaptic mechanisms completely account for them.

By the mid-1970s, a decade after levodopa's first use, it became clear that vivid dreams and visual hallucinations were common in patients, but only after years on the drug, appearing even in those without dementia or other evidence of psychosis.² Particularly curious was the reappearance of hallucinations after a drug holiday, which, at the time, was commonly prescribed for those whose motor symptoms had become refractory. Hallucinations usually reappeared at a much lower dose of levodopa than before the drug holiday, even in the absence of a motor response. The phenomenon was thought to be attributed to drug-induced hypersensitivity of a subset of dopamine (DA) neurons, that is, representing effects similar to those produced by cocaine and amphetamine, which are indirect agonists that also produce reverse tolerance. However, this explanation was never convincing, because potent direct-acting DA agonists (such as bromocriptine or apomorphine) did not provoke hallucinations in those patients who had them on levodopa. Consequently, drug companies promoted this mental-motor dissociation in their marketing of direct DA agonists.

Although Albin and Leventhal discuss some of the dopaminergic and glutamatergic nigrostriatal, thalamic, and cortical projections affecting the motor system, learning, and reward, they omit consideration of other aspects of subjective experience and observable behavior. Might they be similar to those underlying the motor SDR and LDR, particularly those influenced

by DA in the sensory and limbic temporal lobes or frontal and parietal structures?

The mental manifestations of PD and its treatment are at the borderland between psychiatry and neurology, as are those of Huntington's disease, Lewy body dementia, schizophrenia, and other DA-associated diseases. Given the understanding now being achieved using functional imaging and new systems-mapping techniques, perhaps it is time to reconsider the artificial barrier between these two fields.

Potential Conflicts of Interest

Nothing to report.

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Reply to “The Missing, the Short, and the Long: Exploring the Borderland Between Psychiatry and Neurology”

Roger L. Albin, MD and Daniel K. Leventhal, MD, PhD

We thank Dr Moses for his interest in and generous comments about our article. His comments highlight a critical and inadequately explored aspect of striatal dopaminergic neurotransmission; the nature and roles of long-term plastic changes. Aberrant plasticity of striatal dopaminergic neurotransmission has been explored in the context of treatment-induced dyskinesias, but as Dr Moses points out, there may be other important clinical phenomena involving chronically altered striatal dopaminergic neurotransmission. Hallucinations can be induced, even in normal subjects, by Pavlovian conditioning, a form of reinforcement learning associated with striatal dopaminergic neurotransmission.¹ Recent functional imaging data suggest striatal involvement in the phenomenon of induced hallucinations, raising the possibility that chronic alterations in striatal dopaminergic neurotransmission associated with Parkinson's disease mediate hallucinosis.¹ Alterations of dopaminergic neurotransmission in nonstriatal circuits may also be involved. Arnulf et al suggested that hallucinations in Parkinson's disease are elements of dream activity intruding into wakefulness, a process possibly driven by aberrant dopaminergic modulation of hypothalamic and brainstem circuits controlling sleep.^{2,3} We agree with Dr Moses that further research in this area may be fruitful.

Author Contributions

Both authors contributed equally to drafting this reply.

Potential Conflicts of Interest

Nothing to report.

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