

# Insight into dopamine role suggests new treatment pathway for Parkinson's

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Dopamine (DA) not only functions as a neurotransmitter, a chemical messenger between neurons by which one neuron triggers another, researchers have found. It also appears to coordinate the activity of a particular neural circuitry. In studies with mice, they found evidence that the dopamine deficiency in Parkinson's and other related movement disorders may cause loss of muscle control and paralysis due to disruption of coordinated activity in this circuit.

The finding is in contrast with the widely held belief that such pathology is caused by an overall inhibition of brain activity due to lack of dopamine in such disorders as Parkinson's.

The researchers said their findings suggest new treatments for Parkinson's and other such disorders aimed at restoring this dopamine-regulated circuitry coordination.

Rui Costa and colleagues published their findings in the October 19, 2006, issue of the journal *Neuron*, published by Cell Press.

In their experiments, the researchers used knockout mice genetically altered to lack the dopamine transporter--the protein that recycles dopamine after it has been released during neuronal triggering. Since such animals lack a store of dopamine, the researchers could quickly deplete the animals of dopamine using a drug that blocked its synthesis. And conversely, they could quickly restore dopamine by administering a mix of L-Dopa and carbidopa. To analyze the effects on neural circuitry

of such manipulations, the researchers used an array of electrodes to measure brain activity across ensembles of many neurons in the "corticostriatal" regions of the animals' brains that control motor function.

The researchers recorded neuronal activity under four conditions:

- when the animals were undisturbed in their cage
- when they were placed in a novel environment, which triggers hyperactivity, or "hyperkinesia," in such knockout mice
- when they were depleted of dopamine using a drug, which causes muscle paralysis, or "akinesia," and
- during restoration of motor activity by administration of L-Dopa/carbidopa.

"We found that contrarily to a commonly adopted view the overall levels of cortical activity did not change during transition from a state of extreme hyperdopaminergia to a state of profound DA depletion with akinesia," wrote the researchers. "Instead, we observed dramatic and rapid changes in corticostriatal neuronal ensemble coordination during hyperdopaminergia-related hyperkinesia and after acute DA depletion. These alterations were DA dependent and were reversed by the administration of L-Dopa."

The researchers concluded that "our data indicate that rapid alterations in dopamine transmission cause substantial changes in the coordinated activity of neuronal ensembles in corticostriatal circuits, leading to the emergence of striking behavioral abnormalities. Thus, although slow adaptations that take place following chronic dopamine depletion or psychostimulant treatment can be important for some aspects of the pathophysiology of DA-related disorders, many functionally important changes may stem from rapid alterations in network synchrony.

Costa and colleagues also concluded that their findings could have implications for treating Parkinson's and related movement disorders, writing that "therapeutic interventions that restore normal synchronicity in these circuits, using either pharmacological or electrophysiological manipulations, and targeted not only to basal ganglia but also directly to motor cortex can be potentially beneficial to DA-related motor dysfunction and Parkinson's disease."

Source: Cell Press

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