Parkinson's disease study identifies possible new treatment target

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Treatments for Parkinson's disease have most recently focused on increasing dopamine, a chemical messenger in the brain that affects reward-based behaviors and motivation, as well as movement. A new study by Yale researchers challenges long-held assumptions about dopamine's sole role in this disorder.

In people with Parkinson's disease, nerve cells that produce dopamine slowly die. The loss of dopamine leads to slower movements, resting tremors, and other symptoms that worsen over time. To reverse parkinsonism—the collection of symptoms seen in Parkinson's disease—doctors provide a treatment that increases dopamine levels in the striatum, a portion of the brain that is responsible for motor learning. However, medical treatments do not consider the effects of parkinsonism on another neurotransmitter, acetylcholine.

Scientists had previously believed that when dopamine levels dropped, acetylcholine levels increased. However, this relationship had never been thoroughly investigated, despite acetylcholine's likely role in creating a movement disorder called dyskinesia, which develops in most patients after several years of dopamine treatment for parkinsonism.

To investigate, senior author Nigel S. Bamford and the research team studied healthy mice and mice genetically modified to exhibit parkinsonism with progressively decreasing dopamine levels. In healthy mice, the researchers observed, the ratio of dopamine and acetylcholine remains in equilibrium, and small changes in these chemicals do not significantly impact motor function. In mice with parkinsonism, the reduction in dopamine decreases the activity of a small population of cells within the striatum that are responsible for making acetylcholine. While the concentrations of both dopamine and acetylcholine decline, the balance between these two neurotransmitters shifts to favor acetylcholine. Under these conditions, Bamford and his co-authors learned, motor function in parkinsonism becomes dependent on both dopamine and acetylcholine.

These findings suggest that treating parkinsonism may require targeted therapies that restore the balance between these two chemicals, instead of focusing solely on dopamine, said the researchers. The study is published in the journal *Neuron*.

More information: Jonathan W. McKinley et al. Dopamine Deficiency Reduces Striatal Cholinergic Interneuron Function in Models of Parkinson's Disease, *Neuron* (2019). DOI: 10.1016/j.neuron.2019.06.013

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