Challenging Parkinson's dogma

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Scientists may have discovered why the standard treatment for Parkinson's disease is often effective for only a limited period of time. Their research could lead to a better understanding of many brain disorders, from drug addiction to depression, that share certain signaling molecules involved in modulating brain activity.

A team led by Bernardo Sabatini, Takeda Professor of Neurobiology at Harvard Medical School, used mouse models to study dopamine neurons in the striatum, a region of the brain involved in both movement and learning. In people, these neurons release dopamine, a neurotransmitter that allows us to walk, speak and even type on a keyboard. When those cells die, as they do in Parkinson's patients, so does the ability to easily initiate movement. Current Parkinson's drugs are precursors of dopamine that are then converted into dopamine by cells in the brain.

The flip side of dopamine dearth is dopamine hyperactivity. Heroin, cocaine and amphetamines rev up or mimic dopamine neurons, ultimately reinforcing the learned reward of drug-taking. Other conditions such as obsessive-compulsive disorder, Tourette syndrome and even schizophrenia may also be related to the misregulation of dopamine.

In the October 11 issue of *Nature*, Sabatini and co-authors Nicolas Tritsch and Jun Ding reported that midbrain dopamine neurons release not only dopamine but also another neurotransmitter called GABA, which lowers neuronal activity. The previously unsuspected presence of GABA could explain why restoring only dopamine could cause initial

improvements in Parkinson's patients to eventually wane. And if GABA is made by the same cells that produce other neurotransmitters, such as depression-linked serotonin, similar single-focus treatments could be less successful for the same reason.

"If what we found in the mouse applies to the human, then dopamine's only half the story," said Sabatini.

The surprising GABA story began in the Sabatini lab with a series of experiments designed to see what happens when cells release dopamine. The scientists used optogenetics, a powerful technique that relies on genetic manipulation to selectively sensitize cells to light. In laboratory dishes, researchers tested brain tissue from mice engineered to show activity in dopamine neurons. Typically in such experiments, other neurotransmitters would be blocked in order to highlight dopamine, but Tritsch, a postdoctoral fellow in the Sabatini lab, decided instead to keep the cell in as natural a state as possible.

When Tritsch activated the dopamine neurons and examined their effects on striatal neurons, he naturally expected to observe the effects of dopamine release. Instead, he saw rapid inhibition of the striatal neurons, making it clear that another neurotransmitter – which turned out to be the quick-acting GABA – was at work. This was so unusual that the team launched a series of experiments to confirm that GABA was being released directly by these dopamine neurons.

A standard way to detect GABA is to look for vesicular GABA transporter, or VGAT, a protein that packages and carries GABA into neurotransmitter vesicles. The scientists silenced the gene that makes VGAT in mice and found that the dopamine neurons released GABA even in the absence of VGAT.

The researchers then tested other transporters, zeroing in on one that

ferries dopamine and a variety of other neurotransmitters. For reasons they don't yet understand, this protein – the vesicular monoamine transporter – also shuttles GABA.

"What makes this important now is that every manipulation that has targeted dopamine by targeting the vesicular monoamine transporter has altered GABA as well. And nobody's paid any attention to it," said Sabatini. "Every Parkinsonian model that we have in which we've lost dopamine has actually lost GABA, too. So we really have to go back now and think: Which of these effects are due to loss of GABA and which are due to loss of dopamine?"

Anatol Kreitzer, an assistant investigator at the Gladstone Institute of Neurological Disease in San Francisco, who was not involved in the research, called the findings remarkable.

"It was totally unexpected," said Kreitzer, who is also an assistant professor of physiology and neurology at the University of California, San Francisco. "At the molecular level, nobody really expected dopamine neurons to be releasing significant amounts of GABA. At the functional level, it's surprising that this major modulator of plasticity in the brain, which is so critical for Parkinson's, for learning and rewards, and for other psychiatric illnesses, can also release GABA. That raises a question as to what role GABA has."

GABA can very quickly change the electrical state of cells, inhibiting their activity by making them less excitable. Sabatini wonders if the loss of GABA in dopamine neurons could explain why hyperactivity is sometimes seen after chronic loss of these neurons.

The next challenge will be to explore whether other neurons that express the vesicular monoamine transporter also release GABA in addition to neurotransmitters such as serotonin and noradrenaline.

"These findings highlight how little we actually know about the most basic features of cell identity in the brain," said Sabatini.

Tritsch said what started out as a straightforward project to understand dopamine quickly changed direction, with lots of starts and stops on the way to some exciting new findings.

"It can be nice to come up with a hypothesis, test it, verify it, and have everything fall into place," he said. "But biology rarely works that way."

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