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For treating advanced Parkinson's, new research points to serotonin

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For most people with Parkinson's disease, the only relief from the tremors, rigidity and impaired movement associated with the progressive loss of their motor skills is a drug called L-DOPA. But as the disease progresses, L-DOPA can cause prominent side effects that counteract its effectiveness.

Now, Rockefeller University's Paul Greengard and colleagues in Sweden provide evidence that serotonin, a well-studied neurotransmitter involved in regulating mood, appetite, sexuality and sleep, also plays a crucial role in Parkinson's disease. Using a mouse model of the disease, Greengard's team shows that side effects associated with repeated L-DOPA treatment can be blocked by manipulating a specific serotonin receptor. The finding, reported this week in *Proceedings of the National Academy of Sciences Early Edition* online, points to a new target for developing treatments for this disorder, which is the second most common neurodegenerative disease after Alzheimer's.

"Our study provides a scientific rationale for developing drugs that act on the serotonin 1B receptor for the treatment of advanced Parkinsonism," says senior co-author Per Svenningsson, a visiting professor in Greengard's lab and a group leader at the Karolinska Institute in Sweden.

The neurotransmitter dopamine has several functions in the brain, including the regulation of movement. Parkinson's disease is characterized by a progressive degeneration of dopamine-producing

neurons, which causes tremors, rigidity and lack of movement control. These neurons project from the midbrain to an area of the brain called the corpus striatum. Although dopamine signaling is impaired in Parkinson's patients, serotonin production remains strong. In addition, several serotonin receptors are highly expressed in the striatum and available to modify the action of L-DOPA.

Two years ago, Greengard and Svenningsson identified a protein, called p11, that acts as a regulator of serotonin signaling in the brain. The researchers showed that p11 increases the concentration of the serotonin 1B receptor at synapses, thereby increasing the efficiency of serotonin signaling, and linked this interaction to an individual's susceptibility to depression and his or her response to antidepressant treatments.

In the new study, Greengard, Svenningsson and their colleagues show that p11 and serotonin also play a role in the L-DOPA-induced symptoms of advanced Parkinson's disease. Svenningsson and Xiaoqun Zhang, a graduate student at Karolinska, used a mouse model of Parkinson's disease in which a substance called 6-OHDA causes the destruction of dopamine neurons in one hemisphere of the brain. L-DOPA, because it is a dopamine replacement and a stimulant, causes the 6-OHDA-treated mice to rotate their bodies in the opposite direction of the dopamine-depleted brain hemisphere.

When the researchers gave these mice L-DOPA, they found increased levels of the serotonin 1B receptor and the protein p11 in the striatum. The researchers then used a molecule called CP94253, which binds to the serotonin 1B receptor and mimics the action of serotonin. CP94253 was given to two sets of 6-OHDA-treated mice: one in which p11 was "knocked out" and another with p11 intact.

After treatment with CP94253, rotational behavior and involuntary movements decreased in the p11-intact 6-OHDA-treated mice, but not in

the p11 knockout mice — suggesting that CP94253 works through p11. The researchers believe that CP94253, and similar serotonin 1B receptor agonists, may counteract L-DOPA-induced behaviors by reducing the release of GABA, a chemical messenger that inhibits the transmission of nerve impulses. GABA is released from neurons that contain the dopamine D1 receptor.

“Blocking the dopamine D1 receptor is not a treatment option for L-DOPA-induced side effects, since it would diminish the therapeutic efficiency of L-DOPA,” says Greengard, who is Vincent Astor Professor and head of the Laboratory of Molecular and Cellular Neuroscience at Rockefeller. “Developing compounds that target the serotonin 1B receptor may offer an alternative approach for treating advanced Parkinson’s disease.”

Source: Rockefeller University