Investigators eye new target for treating movement disorders

19 January 2018, by Bill Snyder

Blocking a nerve-cell receptor in part of the brain that coordinates movement could improve the treatment of Parkinson's disease, dyskinesia and other movement disorders, researchers at Vanderbilt University have reported.

Their findings, published recently in the journal *Neuron*, focus on M4, a subtype of the muscarinic acetylcholine family of nerve cell (neuron) receptors activated by binding the neurotransmitter acetylcholine.

The Vanderbilt scientists found that M4 neurons project into the substantia nigra pars reticulata, a small structure near the base of the brain important in regulating movement. Here M4 receptor activation opposes signaling by another class of receptors that binds the neurotransmitter dopamine .

When, in Parkinson's disease, dopamine -producing neurons begin to die off, the opposing action of M4 neurons can suppress dopamine signaling even further.

Drugs called M4 selective antagonists, which selectively block the M4 receptor, thus may relieve symptoms of the disease.

"M4 muscarinic receptor activation has a much more pivotal role in controlling dopamine signaling than we thought," said the paper's corresponding author, P. Jeffrey Conn, Ph.D.

This finding "gives much greater strength to the notion that we could use M4 selective antagonists to treat Parkinson's disease," he said.

Drugs that block muscarinic acetylcholine receptors can relieve symptoms of Parkinson's disease including tremors and muscle rigidity. But because they block the whole muscarinic acetylcholine family of receptors, these drugs cause adverse side effects patients can't tolerate, said Conn, who directs the Vanderbilt Center for Neuroscience Drug Discovery.

For years L-DOPA, a precursor to dopamine that can replenish the brain's supply of the neurotransmitter, has been the main treatment for Parkinson's disease. But L-DOPA is not without its side effects, either.

The identification of different subtypes of the muscarinic acetylcholine receptor raised the possibility of selectively targeting treatment in a way that avoids unwanted side effects.

Conn and his colleagues have been developing potential drugs called positive allosteric modulators that can boost the activity of the M4 receptor like the dimmer in an electrical circuit.

"In schizophrenia there's excessive dopamine transmission," he said. "We've studying M4 as a way to dampen dopamine function in schizophrenia patients. It's actually those studies that led us to develop these insights into M4 regulation of dopamine signaling" in movement disorders.

"We used genetic approaches and now have very selective compounds that have anti-parkinsonian activity in animal models," said Conn, the Lee E. Limbird Professor of Pharmacology in the School of Medicine.

"We've shown that with the first one. Now we have much better compounds that we're going to follow."

Provided by Vanderbilt University