Three proteins found that help fine tune movement

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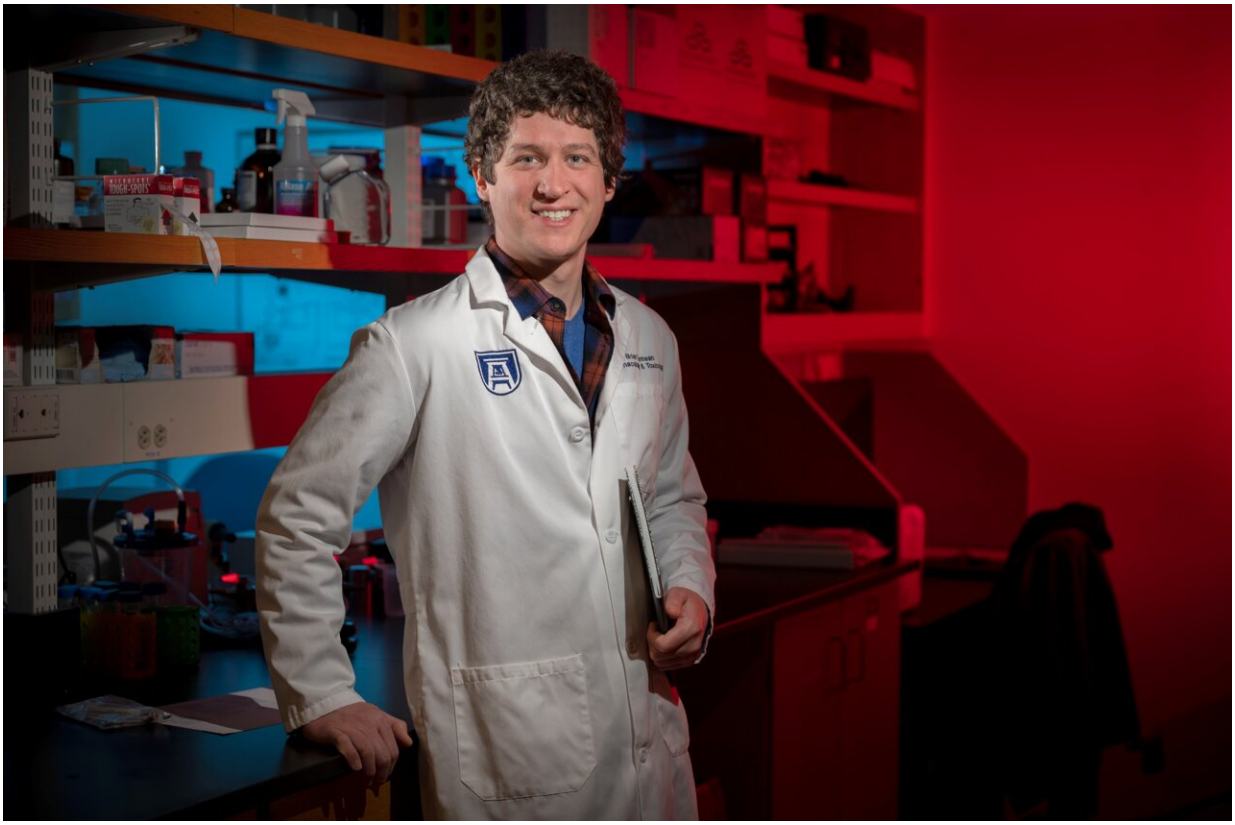

Dr. Brian Muntean. Credit: Michael Holahan, Augusta University

Three members of a family of proteins have been identified that are important to helping us fine tune the activity of brain chemicals which enable us to walk or stand at will, scientists report.

The findings point toward the proteins KCTD5, KCTD17 and KCTD2 as potential new therapeutic targets in conditions like Parkinson's and dystonia where control of movement is lost, says Dr. Brian Muntean, pharmacologist and toxicologist at the Medical College of Georgia at Augusta University and co-corresponding author of the study published in the journal *PNAS*.

Dr. Kirill A. Martemyanov, chair of the Department of Neuroscience at the Florida Campus of the Scripps Research Institute in Jupiter, Florida, also is a corresponding author.

The fine tuning these KCTD family members appear to enable is called neuromodulation, which involves hundreds if not thousands of proteins inside neurons that are part of the complex pathway that precisely fine tunes the fast-moving sharing of neurotransmitters, or chemical messengers, between these brain cells so we can accomplish a desired function of our brain and body like walking across the room.

It's the first discovery about the role these KCTD proteins play in neurons called striatal neurons, which are essential to movement and a variety of other fundamental functions.

One of the key pathways neuromodulators use is cyclic AMP, or cAMP, which is called a "second messenger" because it's a response inside a cell that occurs in response to something that happens outside a cell.

In the case of movement, a key external influence is the neurotransmitter dopamine, known to be important to controlled movement and known to be deficient in Parkinson's. As a neurotransmitter, dopamine works by interacting with a receptor on the surface of neurons, which triggers a lot of activity inside the cell including triggering proteins, which they now know include these three members of the KCTD family. In this complex scenario, dopamine also functions as a neuromodulator by helping

regulate cAMP levels inside neurons.

"People can still move but sometimes they can't stop moving because the neurotransmission keeps going but the cells aren't being modulated correctly to interpret the neurotransmission," Muntean says.

The scientists have found that these three KCTD proteins are doing at least two things simultaneously to modulate the fast work of neurotransmitters.

They are helping regulate the way dopamine is making cAMP both by interacting with the proteins that directly make it and by interacting with proteins that put zinc, which is also known to regulate cAMP, into the neurons.

"Modulating the cAMP level is what can kind of dictate the long-term ability of these neurotransmitters to work perfectly," Muntean says.

KCTD is a family of about two dozen proteins, which scientists have begun to realize are involved in this complicated pathway of regulating the regulators, by binding to some of the proteins in the pathway that regulate cAMP.

The scientists found that the three KCTDs do bind to proteins that make cAMP. But they also found they interact with proteins that put zinc into neurons, something they had not really considered before. Zinc in an essential mineral important to a lot of processes like making proteins and cell division, as well as regulating cAMP levels. About 10% of the proteins inside cells bind to zinc, which can help the proteins work better or less well, so it can modulate the activity of a lot of these proteins in the cell, Muntean notes.

In this scenario, the scientists found zinc appears important in the "very

layered" process of modulating cAMP and that KCTD5 regulates zinc levels by controlling levels of the transporter, Zip 14, which brings zinc inside cells.

They started by looking at a total of six members of the KCTD family known to have a role in G protein coupled receptor signaling, the biggest family of receptors on the cell surface including dopamine receptors on neurons.

To learn more about the function of these proteins, they used the precise gene editing ability of CRISPR/Cas9 to selectively stop neurons from the striatum, a small area of the brain key to movement, from making the proteins.

When they eliminated KCTD5, KCTD2 and KCTD17, they found cAMP production enhanced in response to dopamine, with the largest response resulting from eliminating KCTD5. KCTD5 elimination also increased the neurons' sensitivity to dopamine.

To look more closely at exactly what is regulating cAMP activity, they used the root extract forskolin, which is known to regulate the activity of the enzyme adenylyl cyclase which makes cAMP.

When they added forskolin, it generated a "rapid and robust" increase in cAMP in neurons where KCTD2, KCTD5 and KCTD17, were present. When they used CRISPR to eliminate these KCTD family members, it also eliminated the positive response to the root extract. Deletion of the other members of the KCTD family of proteins they were looking at had no effect on generation of cAMP or sensitivity to dopamine.

Additionally, they found that mice without sufficient KCTD5 had major motor deficits that could be reversed by removing some of the now excessive zinc, more evidence that one way KCTD5 helps fine tune

movement is by regulating zinc levels and of the importance of that modulation.

Muntean and his colleagues hope that by better understanding what these proteins do to enable this ongoing process of neuromodulation, they can help identify new pathways for treating problems like Parkinson's as well as a number of movement disorders that can put children in wheelchairs like dystonia, in which muscles contract involuntarily as a result of problems such as a lack of oxygen during birth as well as some infections and drug reactions, and chorea, a neurological disorder that can produce jerky, involuntary movement of the shoulders, hips and face, and can result from over activity of dopamine.

"There is no cure," Muntean says flatly, and most often no effective treatment for these movement disorders. "I argue it's because we don't know enough about how brains cells are transferring information. I think our findings help us better understand how the neurons in the brain are transferring information relevant to motor coordination. They help further unravel the complexities of these signaling pathways in neurons, and then hopefully that is going to allow us to have some better therapeutic targets and innovation for treating patients down the line," he says. "I think this opens up a whole new door."

The KCTD gene family has 25 members, which early work indicates are involved in a myriad of neurodevelopmental and neuropsychiatric disorders, including bipolar disorder, autism and schizophrenia. It's known that some patients with dystonia have a mutation in KCTD17 and variations in the gene that makes Zip-14 have recently been implicated in Parkinson's and dystonia, the authors write.

"You perturb the cAMP neuromodulation pathway and, it's very delicate, and that results in movement disorders," Muntean says.

cAMP is a common pathway involved in nearly every cell and tissue type.

In addition to movement, dopamine has key roles in enabling us to feel pleasure, like enjoying a good meal, and pleasure also can prompt our brain to produce more dopamine. Too little dopamine can decrease normal excitement and motivation levels; some foods like dairy foods, fish with high level of omega-3, bananas and dark chocolate can prompt dopamine release.

Several neurotransmitters, including serotonin and acetylcholine, also function as neuromodulators, which essentially help police their own activity.

More information: Brian S. Muntean et al, Members of the KCTD family are major regulators of cAMP signaling, *Proceedings of the National Academy of Sciences* (2021). DOI: 10.1073/pnas.2119237119

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