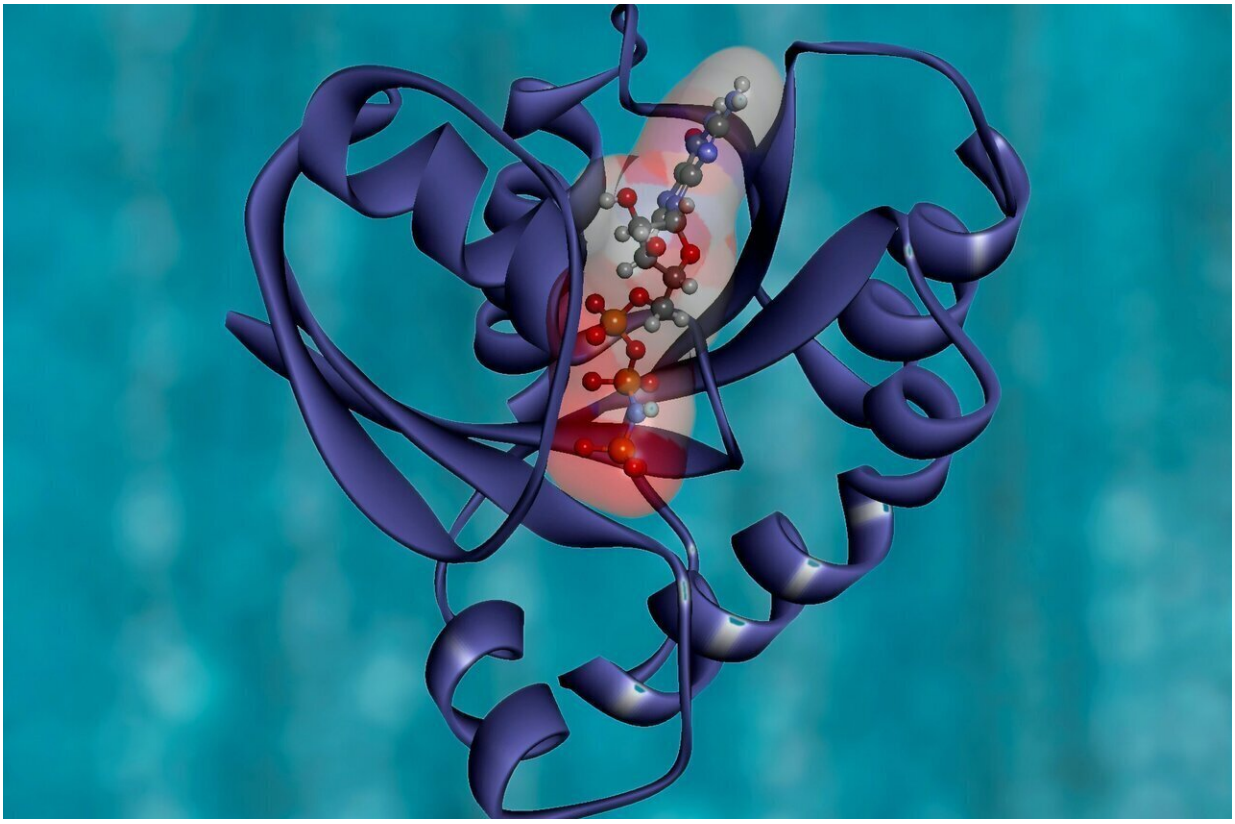
Unraveling the mystery of Gαo, a protein implicated in movement disorders

February 3 2021



Credit: Unsplash/CC0 Public Domain

Scientists at Scripps Research have clarified the workings of a mysterious protein called Gαo, which is one of the most abundant proteins in the brain and, when mutated, causes severe movement

disorders.

The findings, which appear in *Cell Reports*, are an advance in the basic understanding of how the brain controls muscles and could lead to treatments for children born with Gαo-mutation movement disorders. Such conditions—known as GNAO1-related neurodevelopmental disorders—were discovered only in the past decade, and are thought to affect at least hundreds of children around the world. Children with the disease suffer from severe developmental delays, seizures and uncontrolled muscle movements.

"We were able to figure out what this protein does in the nervous system, and then use that knowledge to find out why its mutation leads to this devastating disorder," says study senior author Kirill Martemyanov, Ph.D., professor and Chair of the Department of Neuroscience at Scripps Research in Florida.

Understanding a lesser-known G protein

Gαo is a member of a family of proteins called G proteins, best known for their roles in carrying signals into cells from cell-surface receptors called G-protein-coupled receptors (GPCRs). These receptors are found on many cell types in the brain and elsewhere in the body, and mediate dozens of biological processes from inflammation to mood and vision.

Because GPCRs are so important and relatively well studied, a large fraction of medicines target them to treat diseases. However, unlike most other G proteins, Gαo has a role in GPCR signaling that has remained somewhat obscure.

"My lab has been studying this protein for quite some time," says Martemyanov, "and there was really no connection to anything immediately disease-related until a few years ago, when mutations in the

gene encoding Gαo were found to cause a set of rare genetic syndromes featuring seizures and uncontrollable movements."

The neuroscientist was soon attending meetings of the Virginia-based Bow Foundation and the European organization Famiglie GNAO1, which support families of children with these syndromes. Ultimately, the Bow Foundation helped fund his study through a fellowship award to the study's first author Brian Muntean, Ph.D., a postdoctoral researcher in the Martemyanov lab.

A 'dominant negative effect'

Gαo protein is found at high levels in brain cells, and the syndromes caused by the mutation of its gene, GNAO1, involve disruptions in brain signaling that controls movements. Therefore, in the study, Martemyanov and colleagues focused on the role of Gαo in a major motor control hub in the brain called the striatum.

They found that mice engineered with a disrupted GNAO1 gene in striatal neurons had a severe movement disorder, with impairments in muscle coordination and in their ability to learn physical tasks. Comparing those mice with their healthy counterparts, the researchers teased apart the complex molecular mechanisms by which Gαo affects GPCR signaling in these brain cells.

These striatal neurons express GPCRs for the neurotransmitters dopamine and adenosine, and the scientists were able to show that Gαo supports key elements of the signaling pathways that feed into striatal neurons from these receptors—helping to maintain the proper amplification and coordination of dopamine and adenosine signals and enabling seamless control of movements.

The team engineered mice to have several of the same GNAO1

mutations that have been reported in children with GNAO1 disorders. The scientists found that these mutations could be classified along a range of deficiencies, but in each case the resulting mutant Gαo was not entirely functional.

GNAO1 disorders usually involve only one mutant copy of the gene out of the two copies that exist in each person's genome. Martemyanov and colleagues discovered, however, that the mutant Gαo proteins often interfere with the workings of the remaining non-mutant Gαo proteins—what biologists call a "dominant negative" effect. The scientists also found that this interference takes different forms depending on the particular GNAO1 mutation, creating a variety of disease patterns, but generally appears to cause severe disruption to motor control even when the normal functional copy of Gαo is present.

"These findings can now guide our thinking about possible corrective strategies," Martemyanov says.

More information: Brian S. Muntean et al. Gαo is a major determinant of cAMP signaling in the pathophysiology of movement disorders, *Cell Reports* (2021). DOI: 10.1016/j.celrep.2021.108718

Provided by The Scripps Research Institute