Researchers reveal how protein mutation is involved in rare brain development disorder

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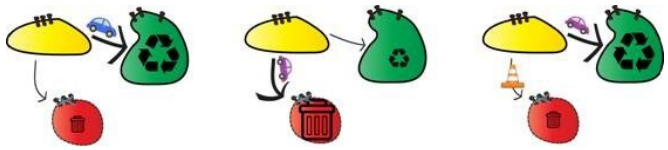

Credit: McGill University

Rearing its head in infancy, Christianson Syndrome is a rare disorder whose symptoms include intellectual disability, seizures and difficulty standing or walking. Although it is becoming increasingly diagnosed, with little being known about the neural mechanism behind the disease, therapeutic options for patients remain limited.

Now, researchers at McGill University focusing on the intellectual disability aspect of the disease, have shown for the first time how a specific mutant form of the SLC9A6 encoding gene for the NHE6 protein affects the ability of neurons to form and strengthen connections. The findings, which the researchers hope could eventually lead to new treatments for patients, are published online in the journal *Neurobiology of Disease*.

"NHE6 functions like a GPS inside of brain cells, helping other proteins navigate to the correct location to allow the neurons to function properly and remodel the connections they form between themselves during learning and memory situations," explains Dr. Anne McKinney, Professor in the Department of Pharmacology and Therapeutics at McGill's Faculty of Medicine and the study's senior author. "This protein regulates pH of the vesicles, which contain the cargo that moves inside the brain cell. It prevents it from becoming too acidic or too alkali. We now show that if this protein loses its function because of a mutation, then other proteins can no longer be sent to the right places, and thus these neurons are unable to properly undergo learning-type mechanisms. Using methods to regulate the pH of the vesicles we can rescue the cargo trafficking and learning of the neuron."

Using mouse models to study the hippocampus

To make their discovery, the researchers grew mouse neurons on a dish, expressing a mutant version of SLC9A6 discovered in patients. Using high-resolution microscopy and electrophysiology they examined changes in appearance of these brain cells as well as how they responded to artificial learning and memory-type stimulations in a dish.

"We found that by attempting to rescue the 'GPS function' of the protein by compensating with other pharmacological agents, we were able to restore at least some of the proper mechanisms to allow other proteins to be trafficked around the cell normally and thus restore their ability to 'learn,'" notes Andy Gao a Ph.D. student in Dr. McKinney's lab and the study's first author.

A hope for potential therapies

The first study to clearly demonstrate that mutations in SLC9A6 can lead to changes in synaptic function that could be related to the cognitive deficits associated with Christianson Syndrome, the researchers hope that these insights will eventually provide more clues as to how to modify the impact of the mutation in order to provide clinical benefit.

"Interestingly enough, other groups are starting to show that the implicated protein is actually expressed less as well in other more common neurodegenerative disorders, such as Parkinson's and Alzheimer's Diseases," notes Dr. McKinney, who is also Associate Dean, Academic Affairs at the Faculty of Medicine. "Through our work, we can start to develop potential therapeutic targets to

improve the quality of life, not only for those suffering from Christianson Syndrome, but from other disorders as well where NHE6 is perturbed."

More information: Andy Y.L. Gao et al. A Christianson syndrome-linked deletion mutation (?287ES288) in SLC9A6 impairs hippocampal neuronal plasticity, *Neurobiology of Disease* (2019). DOI: 10.1016/j.nbd.2019.104490

Provided by McGill University

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