Calcium channel blockers key to reversing myotonic dystrophy muscle weakness, study finds

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New research has identified the specific biological mechanism behind the muscle dysfunction found in myotonic dystrophy type 1 (DM1) and

further shows that calcium channel blockers can reverse these symptoms in animal models of the disease. The researchers believe this class of drugs, widely used to treat a number of cardiovascular diseases, hold promise as a future treatment for DM1.

"The main finding of our study is that combined calcium and chloride channelopathy is highly deleterious and plays a central role in the function impairment of muscle found in the disease," said John Lueck, Ph.D., an assistant professor at the University of Rochester Medical Center (URMC) in the Departments of Pharmacology and Physiology, and Neurology.

"Our research also suggests that muscle impairment in DM1 is potentially mitigated by common clinically available calcium channel blockers and that calcium channel modulation is a potential therapeutic strategy." Lueck is lead author of the study, which appears in the *Journal of Clinical Investigation*.

Toxic RNA disrupts muscle function

Myotonic dystrophy is one of the most common forms of muscular dystrophy. People with the disease have muscle weakness and prolonged muscle tensing (myotonia), making it difficult to relax muscles after use. The disease also affects the eyes, heart, and brain, leading eventually to difficulty walking, swallowing, and breathing.

More than 20 years ago, URMC neurologist Charles Thornton, MD, and others uncovered how a genetic flaw—a "stutter" that results in thousands of repetitions of code on a segment of chromosome 19—gives rise to DM1. This repeat expansion, which grows longer over time, results in the creation of abnormal RNA which accumulates in the nucleus of cells and affects the normal processing of many other RNAs. Thornton is a co-author of the current study and the research was a

collaboration between the Lueck and Thornton labs.

This toxic RNA specifically disrupts the function of muscleblind-like (MBNL) proteins responsible for regulating the splicing of transcripts important for maintaining healthy muscle function. Among other things, these splicing defects impair the function of receptors for calcium and chloride channels, gateways in muscle cells that help convert electrical signals from motor neurons into chemical signals within the muscle cells. Specifically, the release of stored calcium causes muscle cells to contract, a process called excitation-contraction coupling (ECC), while lowering the concentration of the chemical depolarizes the cell and allows it to relax.

Calcium channel blockers to the rescue

Lueck and his colleagues were particularly interested in understanding this cycle as it held the potential to explain the muscular dysfunction in DM1. The first challenge was to focus on the muscle impact of the disease and eliminate the "noise" of the dozens of other defects wrought by the toxic RNA. "Myotonic dystrophy is a really complicated disorder, which you can think of as almost like an aggregate of many diseases," said Lueck.

To accomplish this, the team created a mouse model that mimicked four of the splicing defects found in DM1 in genes associated with the calcium and chloride channels. These mice exhibited severe myotonia, muscle weakness, impaired mobility, respiratory defects, and a marked reduction in lifespan.

The involvement of the calcium channel in muscle dysfunction presented an opportunity and a target—calcium channel blockers are widely used to treat, among other things, high blood pressure, cardiac arrhythmias, and migraines. When the team treated the mice with verapamil, a

calcium channel blocker used to treat hypertension and chest pains, the mice quickly recovered muscle function and began to resemble their healthy, wild type peers.

The findings were made possible by years of close observation of the animals by Lily Cisco, a graduate student in the Lueck lab who is first author of the study.

The researchers are quick to emphasize that verapamil is NOT an appropriate treatment for DM1 in humans due to its potential cardiac side effects. "We think that the calcium channel is a new therapeutic target and if we can target it correctly, pharmacologically that it will improve muscle function and health. Our goal now is to find the appropriate and safe calcium channel blocker that will do the job and we believe it exists."

More information: Verapamil mitigates chloride and calcium bi-channelopathy in a myotonic dystrophy mouse model, *Journal of Clinical Investigation* (2023). DOI: 10.1172/JCI173576

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