Researchers reverse key symptom of muscular dystrophy

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Researchers at the University of Rochester Medical Center have identified a compound that eliminates myotonia – a symptom of muscular dystrophy – in mice. The study was published online today in the *Journal of Clinical Investigation*.

Rochester scientists were able to design a synthetic RNA-based molecule that, when injected into mice with myotonic dystrophy, restored a critical cellular mechanism, or pathway, that controls electrical activity in muscles. In people with the disease, this function is essentially disabled and muscle cells cannot relax properly. The researchers found that once this pathway was re-established, normal muscle function returned.

“The significance of this work is the proof of concept that a fundamental aspect of this genetic disease can be reversed even after it is very well established,” said Charles Thornton, M.D., co-director of the URMC Neuromuscular Disease Center and senior author of the study. “It encourages us to believe that other parts of the disease could be reversible as well.”

Myotonic dystrophy – the most common form of muscular dystrophy in adults – is characterized by progressive muscle wasting and weakness, particularly in the lower legs, hands, neck, and face. People with myotonic dystrophy have prolonged muscle tensing (myotonia) and are not able to relax certain muscles after use. The condition is particularly severe in the hand muscles and can cause a person’s grip to lock, making

it difficult to perform rapid, repeated movements. Consequently, myotonia significantly interferes with a person's ability to work and function. Myotonia is also one of the earliest signs of myotonic dystrophy and is the symptom by which physicians typically recognize the disease.

Five years ago, Thornton and his colleagues in Rochester helped to unravel the genetic flaw that causes the disease by showing that messenger RNA (mRNA) – responsible for transmitting genetic information out of the nucleus and into the main part of the cell where instructions from the molecular blueprint get carried out – is responsible for the symptoms of the disease. In individuals with myotonic dystrophy, a faulty genetic "stutter" results in the over-production of a certain type of mRNA that, in turn, interferes with other important cellular functions including muscle control.

The regulation of muscle activity and relaxation is basically electrical and is governed by the movement of small charged particles into and out of muscle cells in a very controlled manner. This electrical flow goes through very specific pathways, including one called the chloride channel. In individuals with myotonic dystrophy, the chloride channel is essentially disabled, causing electrical signals in muscles stay "on" for too long, resulting in unstable muscle control – like when someone grasps another's hand and can't let go.

The Rochester team, working with the biotechnology company Gene Tools, created a synthetic RNA-based compound that restores the proper genetic instructions for building the chloride channel. When this compound, called a morpholino, was injected into the muscle cells of a set of mice with myotonic dystrophy, the chloride channel was restored and the myotonia all but disappeared and did not return for several weeks.

“This material is incredibly stable in the cells once we get it inside the muscle,” said URMC neurologist Thurman Wheeler, M.D., lead author of the study. “And the effects are surprisingly prolonged, which makes it potentially more attractive as a treatment.”

The Rochester team cautions that more work needs to be done before this new approach can be tested in people. First and foremost, a better method for delivering the compound throughout the body needs to be developed. However, researchers are encouraged by the results and believe that it could ultimately be a step toward a breakthrough treatment for the disease.

“This work should provide hope and encouragement to people with myotonic dystrophy and their families,” said Thornton. “This is a progressive and debilitating condition, but there are early indications that effective treatments are possible. To see a problem like myotonia disappear after it has been present for a long time is certainly a hopeful sign. As we move forward, we should not be content to keep this condition from getting worse. We should set our set our sights on making it better”

Source: University of Rochester