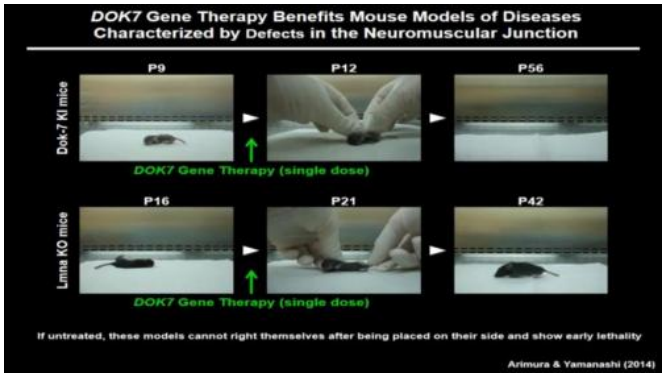
Gene therapy in mice improves defects in neuromuscular junction reversing neuromuscular disease symptoms

19 September 2014, by Bob Yirka



(Medical Xpress)—A team of researchers working in Japan has found that injecting a genetically engineered virus into the muscle of mice afflicted with two types of neuromuscular disease caused a reversal of symptoms. In their paper published in the journal *Science*, the team describes how they genetically modified a harmless virus to allow for carrying a corrected mouse gene into mouse muscle, causing the muscle to begin producing a missing protein, and reversing symptoms in the mice.

Neuromuscular diseases such as muscular dystrophy or ALS impact what is known as the neuromuscular junction—the connecting point between nerves and muscles. Scientists have learned that in some instances, the reason problems develop in this critical part of the body is because of defective genes that cause the muscle protein Dok7 to be created by the body—the protein allows for activation of receptors—without it, muscles atrophy and eventually become useless, leading to death as the heart weakens or victims can no longer breathe. In this new effort, the researchers found a way to replace the defective Dok7 producing genes in afflicted mice.

The team genetically engineered a harmless virus to carry good copies of the genes responsible for causing mouse muscle to create Dok7—they injected it directly into the muscle of an afflicted mouse, whereupon the virus promptly released it, allowing the muscle cells to respond to the presence of the new gene. When tested on mice with familial limb-girdle myasthenia, muscles cells began creating Dok7, which after seven weeks, led to restored muscle ability, weight gain, a longer lifespan and normal scores on motor skill tests. Pleased with their success the team tried the same technique on mice with another neuromuscular diseases—Emery-Dreifuss muscular dystrophy. Once again, the mice regained muscle ability, though they didn't recover completely, as the disease had damaged their hearts.

The team is moving on to testing the technique in mice with other neuromuscular diseases to learn more about which types of diseases the therapy is likely to help. They'll also be testing the technique with other animals, leading to even more research that will at some point look into whether the same type of therapy could work to help humans with neuromuscular diseases.

More information: DOK7 gene therapy benefits mouse models of diseases characterized by defects in the neuromuscular junction, *Science* 19 September 2014: Vol. 345 no. 6203 pp. 1505-1508 . DOI: 10.1126/science.1250744

Abstract

The neuromuscular junction (NMJ) is the synapse between a motor neuron and skeletal muscle. Defects in NMJ transmission cause muscle weakness, termed myasthenia. The muscle protein

Dok-7 is essential for activation of the receptor kinase MuSK, which governs NMJ formation, and DOK7 mutations underlie familial limb-girdle myasthenia (DOK7 myasthenia), a neuromuscular disease characterized by small NMJs. Here, we show in a mouse model of DOK7 myasthenia that therapeutic administration of an adeno-associated virus (AAV) vector encoding the human DOK7 gene resulted in an enlargement of NMJs and substantial increases in muscle strength and life span. When applied to model mice of another neuromuscular disorder, autosomal dominant Emery-Dreifuss muscular dystrophy, DOK7 gene therapy likewise resulted in enlargement of NMJs as well as positive effects on motor activity and life span. These results suggest that therapies aimed at enlarging the NMJ may be useful for a range of neuromuscular disorders.

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