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Mighty mice: Treatment targeted to muscle improves motor neuron disease

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New research with transgenic mice reveals that a therapy directed at the muscle significantly improves disease symptoms of a genetic disorder characterized by destruction of the neurons that control movement. The study, published by Cell Press in the August 13th issue of the journal *Neuron*, highlights a promising new treatment for this currently incurable and nontreatable neurodegenerative disorder.

Spinal and bulbar muscular atrophy (SBMA), or Kennedy's disease, is a neurodegenerative disease that attacks the neurons that control muscle movement. The disease, which only fully affects males, is characterized by substantial weakness and wasting in the muscles that have lost innervation. Previous research has shown that a specific mutation in the gene for the androgen receptor (AR) causes the disease. The mutation causes the accumulation of a mutant protein that damages the motor neurons.

Recent evidence has suggested that the mutant AR may also exert a direct toxic effect on the muscle. "Although the extent to which SBMA pathogenesis is a consequence of neuron degeneration and secondary muscle atrophy, or primary damage to the muscle, is not known, these observations suggest that skeletal muscle may be an important target for disease treatment," offers senior study author, Dr. Maria Pennuto from the Department of Neuroscience at the Italian Institute of Technology in Genova.

Dr. Pennuto and colleagues had previously shown that phosphorylation

of AR by Akt blocked the activation of the AR, and that insulin-like growth factor 1 (IGF-1), which activates Akt, is a protective factor for muscle and reduced mutant AR toxicity in cells grown in the lab. "These observations suggest IGF-1 and Akt-mediated inactivation of AR as a potential therapy for SBMA," says Dr. Pennuto. In the current study, the researchers extended these findings and demonstrated that IGF-1 reduces AR activation in cultured cells through phosphorylation of AR by Akt.

The group also generated SBMA mice that expressed high levels of IGF-1 in skeletal muscle. Notably, the IGF-1 used in this experimental paradigm is a form of IGF-1 that is specifically produced by muscle. The mice exhibited increased Akt activation and AR phosphorylation, specifically in the muscle, and this correlated with reduced accumulation of the disease protein in the tissue.

Importantly, augmentation of IGF-1/Akt signaling also improved motor performance, body weight, and muscle and spinal cord pathology, and extended survival in the SBMA mice. "Our study establishes IGF-1/Akt-mediated inactivation of mutant AR as a strategy to counteract disease in living animals and is the first to demonstrate that skeletal muscle is a viable target tissue for therapeutic intervention in SBMA," concludes Dr. Pennuto.

Source: Cell Press (news : web)