Study shows voluntary running reduces neuromuscular decline in aging mice

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Research led by The Ohio State University Wexner Medical Center and College of Medicine explored the neurobiological effects of exercise in mice with age-related loss of physical function.

Their study, published online in *Neurobiology of Aging*, investigated aging rodents that underwent voluntary running exercise between the ages of 22 and 27 months, which represents roughly 55 to 80 years of age in humans.

"These experiments showed that running significantly improved the neuromuscular decline in mice that underwent running compared to sedentary mice. Our findings support the mantra of 'use it or lose it' in regards to the connection between the nervous system and muscles, namely the neuromuscular junction," said senior author Dr. W. David Arnold, neuromuscular specialist and associate professor at Ohio State Wexner Medical Center.

"We found that voluntary exercise, initiated at old age, improves neuromuscular junction (NMJ) transmission. This is important because NMJ is responsible for the chemical transmission of the electrical impulse from a nerve to the muscle to produce an appropriate muscle contraction," said Arnold, who's also an avid runner and open water swimmer.

He and his laboratory team are investigating mechanisms of loss of function with age to develop strategies for reducing the burden of sarcopenia on older adults. Sarcopenia is the pathological loss of muscle size and strength, an important contributor to loss of physical function in older adults.

"Sarcopenia can have severe consequences on older adults leading to immobility, falls, and loss of independence. Regular physical activity is one of the most important strategies that an individual can use to ward off loss of physical function with aging," Arnold said.

Postdoctoral researcher Deepti Chugh led the study of 22-month-old mice, which are the equivalent age of about 55 to 60 years old in humans. The mice were randomized into three treatment groups: running, sedentary, and an additional running group also that received a gene therapy to increase expression of follistatin.

Follistatin is a protein that blocks the action of another protein called

myostatin and, in doing so, triggers increased muscle size or hypertrophy.

The goals of the study were to understand the neuroprotective effects on motor neurons and their connections with muscle at the NMJ.

Motor neurons are the nerve cells located in the spinal cord that serve as the final connection between the nervous and muscular systems. These are the cells that degenerate and die during Amyotrophic Lateral Sclerosis (ALS), also known as Lou Gehrig's disease.

The findings show that while exercise didn't slow age-related loss of motor neurons, it did show striking improvement of NMJ transmission or communication between the nervous and muscular systems. Additionally, while follistatin induced muscle enlargement, this provided no added benefits over exercise alone in regards to neurological function.

In 2020, the Arnold team published a study in the journal *Neurobiology of Aging* that revealed a novel mechanism of age-related loss of muscle function at the NMJ. They showed that loss of muscle responsiveness (excitability) to nervous system signaling may be an important mechanism of age-related decline.

In their future work, Arnold's team plans to explore the mechanisms of these improvements with exercise and to develop ways to help prevent or treat sarcopenia in individuals who can't exercise.

Additionally, Arnold and Ohio University researcher Brian Clark are co-principal investigators on an ongoing clinical STAMINA study looking at NMJ failure as a mechanism of weakness in older adults.

"Our STAMINA study aims to understand if failure of communication

between the nervous system and the muscular system might be a target for therapeutic development to address weakness and loss of mobility in older adults. This study builds on the recent work in Dr. Arnold's lab using aging rodent models," said Clark, executive director of the Ohio Musculoskeletal & Neurological Institute at Ohio University in Athens, Ohio.

More information: Deepti Chugh et al. Voluntary Wheel Running with and without Follistatin Overexpression Improves NMJ Transmission but not motor unit loss in Late Life of C57BL/6J Mice, *Neurobiology of Aging* (2021). DOI: 10.1016/j.neurobiolaging.2021.01.012

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