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Lessons from the worm: How the elderly can live an active life

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When the tiny roundworm *C. elegans* reaches middle age—at about 2 weeks old—it can't quite move like it did in the bloom of youth. But rather than imposing an exercise regimen to rebuild the worm's body-wall muscles, researchers can bring the wriggle back by stimulating the animal's neurons. And, they say, pharmaceuticals might have a similar effect in mammals.

Scientists at the University of Michigan's Life Sciences Institute and Medical School have found that the loss of motor ability associated with aging begins in neurons and spreads to muscles, and that chemically stimulating neurons could "rejuvenate" old roundworms by improving the animals' motor function.

Researchers in the lab of Shawn Xu, the Bernard W. Agranoff Collegiate Professor in the Life Sciences Institute and Department of Molecular and Integrative Physiology, in collaboration with Ao-Lin Hsu in the Department of Internal Medicine at the Medical School, determined that the motor decline in older worms had roots in early changes in the function of the nervous system that began long before visible deterioration in the structure of the animals' tissues. They were able to reverse the decline in motor ability by giving the worms arecoline, an alkaloid found in the areca nut.

In parts of India and Southeast Asia, where the areca palm grows, people chew the nut as a stimulant, often combined with betel leaf and other ingredients. However, the practice is associated with cancer.

"The pharmacological stimulation of neurons with the chemical improved motor functions in old animals," Xu said. "Understanding the neuron-to-muscle sequence can help find treatments for motor decline in humans. It would be ridiculous to chew areca nuts in hopes of rejuvenating muscle, of course, but the findings suggest that there's potential to develop a drug that works in a similar way for humans."

The research is scheduled for online publication Sept. 3 in *Cell Metabolism*.

Aging is characterized by gradual, progressive declines in performance of multiple tissues, called functional aging, which ultimately lead to death. While much research has illuminated how genes and the environment affect life span, the mechanisms underlying functional aging in tissues throughout the body have been largely elusive, Xu said.

To understand the role of tissue deterioration in motor-function decline in aging animals, Xu's lab, in collaboration with Hsu, evaluated the functional status of neurons and muscles in the roundworm *C. elegans* throughout the worms' lifespan, which is about three weeks.

Like other animals, aging *C. elegans* worms exhibit a decline in motor activity, and old worms are less active than young ones. Was this because of decline in motor neurons controlling muscles in the worms, or because the muscles themselves were weaker?

The researchers in Xu's lab, working with Hsu, outlined a sequence of changes related to the worms' deteriorating ability to move as they grew older. First, relatively early in a nematode's life, the function of motor neurons begins to decline. Later, in nematode middle age the worm's body-wall muscles, which are controlled by the weakened neurons, begin to lose function. Stimulating the neurons with arecoline restored the muscles' function.

"Pharmacological stimulation of the aging nervous system can improve motor functions in aged animals—maybe even mammals," Xu said. "Our studies not only illustrate an example of how functional aging may occur in a genetic model organism, but also provide insights into how genetic and pharmacological interventions may help slow down the rate of such functional aging."

Xu is a faculty member in the Life Sciences Institute, where his laboratory is located and all of his research is conducted. He is also an associate professor in the Department of Molecular and Integrative Physiology at the Medical School.

Provided by University of Michigan