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Research suggests new direction for ALS treatment

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A research team from Wake Forest University School of Medicine is the first to show that injections of a protein normally found in human cells can increase lifespan and delay the onset of symptoms in mice with ALS (amyotrophic lateral sclerosis), or Lou Gehrig's disease.

Reporting in the Nov. 28th issue of the Journal of Neuroscience, the researchers said treatments of recombinant heat shock protein 70 (Hsp70) increased total lifespan by 10 percent – significantly more than Riluzole®, the only ALS treatment approved by the U.S. Food and Drug Administration. They cautioned that while the research suggests a new treatment approach for ALS, it is not ready for studies in patients.

"This is another piece in the puzzle of what causes ALS and how to best treat it," said David Gifondorwa, lead author and a Ph.D. candidate at Wake Forest. "It's possible that one day a treatment based on this finding could be part of a 'cocktail' for attacking the disease from different fronts."

ALS is a disease that causes death of motor neurons, the nerve cells that control muscles. There are two sets of motor neurons affected in ALS: upper motor neurons that are located in the brain and brainstem, and lower motor neurons that are located in the spinal cord but send out nerve fibers, or "transmission lines," to connect with muscles.

The study focused on the lower motor neurons. Previous research by Wake Forest and others had shown that before the motor neuron dies, it

first detaches, or denervates, from the muscle.

“There is a growing amount of research that suggests denervation is what happens first,” said Carol Milligan, Ph.D., senior researcher. “Our hope is that the results of our study will help steer thinking into focusing on what happens at the junction of nerve and muscle. It is possible that if we can develop treatments to maintain the contact of nerves and muscle, we can maintain the health of the motor neurons longer.”

The current study involved mice that are genetically engineered to develop ALS. They have the same genetic defect found in about 2 to 3 percent of human ALS cases. The mice were treated with either a placebo, Riluzole, or Hsp70, a protein made by the cells of both animals and humans. Heat shock proteins are produced by cells as part of the stress response to protect themselves from injury. In several animal models of ALS, motor neurons do not mount a typical stress response.

The researchers tested whether injecting the mice with Hsp70 would help protect the motor neurons. The mice in the study got injections of Hsp70 three times a week beginning 50 days after birth. The injections were effective at increasing lifespan, delaying symptom onset, preserving motor function and prolonging motor neuron survival. Lifespan increased by 10 days in the Hsp70 treated mice, compared to one day in the Riluzole group. Ten days represents about 10 percent increase in the lifespan of this animal model of ALS. In humans, Riluzole increases lifespan by about 60 days.

The treatment was not detected in the central nervous system, leading the researchers to believe that it acts not in the spinal cord, but where the neurons attach to muscle. Treatment with Hsp70 resulted in an increased number of innervated muscles, compared to the other groups.

“The protein seems to work at the neuromuscular junction,” said

Gifondorwa. “Because current ALS treatments work at the spinal cord, our finding suggests the possibility of a cocktail that works to prevent damage in both locations may prove more beneficial.”

Wake Forest is currently studying new ALS treatments, as well as working to better understand what goes wrong to cause the disease. The Wake Forest ALS Center, under the directorship of James Caress, M.D., will soon be part of the clinical trial of Arimoclomol, a drug that works to enhance the stress response of nerve cells. And, a team of nine researchers from five departments that includes Milligan and Caress is developing a series of projects with the goal of understanding more about the early events in the development of ALS.

In mice, the researchers will study changes that occur in the muscles, nerves and spinal cord with denervation. They will also work to determine which nerves and muscles are affected first. In humans with ALS, they hope to look at early muscle changes using advanced imaging technology.

Source: Wake Forest University Baptist Medical Center