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NEWS

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Muscle pathology is key to nerve cell death in mice with Kennedy disease, say U-M scientists

Faulty signals between muscle cells and motor neurons could be key factor in human neuromuscular disorders

Editors: Color images of mice being tested for fore-limb strength are available on request.

ANN ARBOR, Mich. – Healing damaged muscle could be critical to preventing the death of nerve cells in patients with Kennedy disease and other incurable neuromuscular disorders, such as ALS or Lou Gehrig's disease, according to a new research study from the University of Michigan Medical School.

Using a mouse model of Kennedy disease, U-M scientists have found that pathological changes in skeletal muscle develop long before the motor neurons that control these muscles begin to die. U-M researchers believe defective muscle cells disrupt the flow of signaling molecules between muscle and nerve, which appears to be a crucial factor in progression of the disease.

"Our most surprising finding was the early onset of muscle pathology in Kennedy disease mice and how it preceded what we found in the spinal cord," says Andrew P. Lieberman, M.D., Ph.D., U-M's assistant professor of pathology who directed the study. "This suggests that muscle degeneration comes on early and plays an important role in disease pathology."

Results of the U-M study will be published in the October 2006 issue of the *The Journal of Clinical Investigation,* which will be posted Sept. 14 on the journal's Web site at www.jci.org.

Kennedy disease, or Spinal Bulbar Muscular Atrophy, is a rare inherited disorder caused by a mutation in the androgen receptor gene. Its symptoms – progressive neuromuscular weakness in the arms, legs, face and throat; breast enlargement and testicular atrophy – are triggered by the presence of male hormones called androgens.

Because Kennedy disease is hormone-dependent, it only affects men and symptoms don't develop until after adolescence when the testes begin producing testosterone and other androgen hormones. Because women normally produce only small amounts of testosterone, the disease has no effect or only mild effects in women, although they can still pass the mutation on to their children.

Hormones are signaling molecules that circulate through the bloodstream until they latch on to specialized receptor molecules. When a hormone binds to its matching receptor, it triggers physical, behavioral and biochemical changes in the body. Since the androgen receptor for testosterone is defective in men with Kennedy disease, the hormone's signal doesn't function properly.

Kennedy disease is one of nine related diseases – including Huntington disease and several spinocerebellar ataxias – called polyglutamine expansion disorders. All these diseases are caused by the same kind of mutation. The equivalent of a "genetic stutter," the mutation is an elongated stretch of repeating DNA code for glutamine. The excess glutamine has a toxic effect on cells where the mutant protein is active.

"We think there is a shared mechanism in how the mutation causes neurodegeneration in all these polyglutamine disorders," Lieberman says. "One common factor that contributes to disease pathogenesis appears to be abnormal interactions between different types of cells. If we can figure out exactly how this occurs in Kennedy disease, it could have implications for all the polyglutamine disorders and other motor neuron diseases, like ALS." (ALS refers to amyotrophic lateral sclerosis, which is also known as Lou Gehrig's disease.)

To study Kennedy disease, Lieberman and his U-M collaborators developed a mouse model of the disorder by replacing the mouse androgen receptor gene with a copy of the human gene that included 113 glutamine repeats. Male mice with the mutated androgen receptor gene developed severe Kennedy disease, while female mice had minimal symptoms.

Male mice in the study appeared normal at birth, but neuromuscular weakness and other symptoms developed when the mice became sexually mature and started producing testosterone. About 80 percent of the male mice died suddenly between the ages of eight and 20 weeks old.

"The time of death varied depending on the amount of circulating testosterone in the bloodstream," says Zhigang Yu, M.D., a U-M post-doctoral fellow and first author on the paper. "Animals with testicular atrophy lived longer, because they didn't produce as much testosterone. Castrating male mice removed the source of testosterone and prevented early death."

To determine why the mice died at such a young age, U-M scientists conducted necropsies. They discovered that all the dead mice had distended bladders and signs of acute urinary tract obstruction, but no actual obstructions were found. Using genetic and physiologic tests, U-M scientists determined that the mice died because specialized skeletal muscles in their lower urinary tract couldn't relax enough to allow the bladder to empty. These muscles, which also are used during sexual activity, contained large amounts of defective androgen receptor protein.

"For a long time, we thought of Kennedy disease as a motor neuron disease, with secondary effects on muscle," Lieberman says. "But our findings in these mice suggest that muscle defects lead the way and contribute to the motor neuron pathology."

In future research, Lieberman hopes to isolate and identify the critical biochemical signals between skeletal muscle and motor neurons that are disrupted by the toxic effects of the Kennedy disease mutation.

"Our data indicate that a loss of trophic support from the diseased muscle may be involved in lower motor neuron degeneration," he adds. "This suggests that skeletal muscle could be an important therapeutic target for treating patients with Kennedy disease."

The U-M study was supported by the National Institutes of Health, the Department of Defense, the Muscular Dystrophy Association, the Kennedy's Disease Association, the U-M Nathan Shock Center Rodent Core and the U-M Biomedical Research Council.

U-M collaborators in the study included Nahid Dadgar, research associate; Megan Albertelli, D.V.M., graduate student; Kirsten Gruis, M.D., assistant professor of neurology; Diane Robins, Ph.D., professor of human genetics and Cynthia Jordan, an associate professor of psychology at Michigan State University.

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