SOUTHWESTERN NEWS

Media Contact: Amy Shields
214-648-3404
amy.shields@utsouthwestern.edu

UT SOUTHWESTERN RESEARCHERS FIND POSSIBLE LINK BETWEEN ENZYME AND PROGRESSION OF FATAL CHILDHOOD DISEASE

DALLAS – Dec. 5, 2000 – Researchers at UT Southwestern Medical Center at Dallas have uncovered clues to what may accelerate the progression of the fatal childhood disease Duchenne dystrophy, the most common childhood muscular dystrophy.

The researchers found that an enzyme that produces nitric oxide in the skeletal muscle plays a pivotal role in blood-flow regulation during physical activity. When nitric oxide is released, blood flow increases to the exercising muscle. The study was published in the Nov. 21 issue of *Proceedings of the National Academy of Sciences*.

The enzyme, called neuronal nitric oxide synthase, or nNOS, is missing in the skeletal muscle of children with Duchenne dystrophy. The study suggests that the lack of nNOS results in functional muscle ischemia, or low blood flow, which may accelerate the progression of the disease.

"Our study suggests that the presence of nNOS allows nitric oxide to be produced when muscles contract," said Dr. Ronald Victor, chief of hypertension and senior author of the study.

"In children with Duchenne dystrophy, nitric oxide is not produced, and there is not enough blood flow that should normally occur to the working muscle. The working muscle is deprived of oxygen and blood when nitric oxide is not present. We think that limits the exercise capacity of children with the disease and that this contributes to the progressive destruction of the muscle over time."

There is currently no cure for Duchenne dystrophy, which causes the leg and chest muscles to weaken and occurs in about 2 out of 10,000 people. Symptoms usually appear in boys 1 to 6 years old. Females can carry the gene but rarely develop symptoms.

The disease is caused by the absence of an integral protein called dystrophin.

"Dystrophin is a large protein that is necessary for the correct assembly of other proteins in the skeletal muscle. It's like the backbone upon which all of the other proteins function. It

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seems to be very essential for structural purposes," said Dr. Gail Thomas, assistant professor of internal medicine.

The researchers believe that the presence of dystrophin and nNOS are both needed for nitric oxide to be produced when muscles contract.

During physical activity, the sympathetic nervous system – which prepares the body to react to situations of stress or emergency – is activated causing blood vessels to constrict. Nitric oxide is activated to partially counteract this mechanism and to maintain the correct balance of blood flow and oxygen delivery to working muscles.

"In children with Duchenne dystrophy the sympathetic nervous system goes on unchecked, so they get too much constriction in the working muscles because they don't have nitric oxide to offset it," Victor said.

Thirty-three subjects aged 7 to 15 years old participated in the study. Thirteen of those studied were healthy, 10 had Duchenne dystrophy, and the remaining 10 had other forms of muscle disease.

The researchers reported that in the exercising muscles of the healthy subjects, nitric oxide was produced in the working muscle allowing blood vessels to dilate and blood to flow freely through the exercising muscle. The researchers reported similar findings in the subjects with other forms of muscular dystrophy.

In subjects with Duchenne dystrophy, this protective mechanism was defective.

The researchers believe that replacing nNOS in children with Duchenne dystrophy might lead to an effective treatment.

"If you could make the muscles produce nitric oxide again, some of the blood flow abnormalities would be alleviated. It would not be a cure for the disease, but it's possible that it might help," Thomas said.

Potential treatments would be drug- or gene-based therapies, Victor added.

In 1998, the researchers found that nitric oxide plays a major role in the regulation of blood flow to contracting muscles in mice with a disease resembling human muscular dystrophy.

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Dr. James T. Stull, chairman of physiology; Dr. Susan Iannaccone, professor of pediatrics; and Mikael Sander, Bahman Chavoshan and Shannon Harris, all hypertension research fellows, also participated in this study.

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