UT SOUTHWESTERN MEDICAL CENTER NEWS

Media Contact: Aline McKenzie
214-648-3404
aline.mckenzie@utsouthwestern.edu

'Deranged calcium signaling' contributes to neurological disorder, UT Southwestern researchers find

DALLAS – Nov. 25, 2008 – Defective calcium metabolism in nerve cells may play a major role in a fatal genetic neurological disorder that resembles Huntington's disease, researchers at UT Southwestern Medical Center have found in a mouse study.

The disease, called spinocerebellar ataxia 3 – also known as SCA3, or Machado-Joseph disease – is a genetic disorder that, like Huntington's, impairs coordination, speech, and vision and causes brain atrophy. Although rare, the condition is one of the most common inherited forms of ataxia and most frequently affects people of Portuguese descent.

The UT Southwestern researchers previously had found that calcium flow within nerve cells is disrupted in Huntington's disease. The latest findings, appearing in the Nov. 26 issue of the *Journal of Neuroscience,* suggest that SCA3, which is caused by a genetic defect similar to the one found in Huntington's, involves the same "deranged calcium signaling," researchers said.

Both SCA3 and Huntington's are caused by repeating segments of DNA, although the repeats associated with each disease appear in different genes that code for different proteins. The genetic mutations cause repeated units of the amino acid glutamine to appear in the respective proteins. The more repeats there are, the earlier the onset of the disease.

In Huntington's disease the mutated protein is Huntingtin; in SCA3 it is ataxin-3.

The researchers determined that the mutant human ataxin-3 activates a molecule that acts as a channel in the membrane of a sequestered chamber inside cells called the endoplasmic reticulum, or ER. The channel then releases calcium into the cell as a whole. Normal ataxin-3 did not activate the channel or cause calcium release.

The researchers also found that cells from a person with SCA3 showed abnormally high levels of calcium release when treated with bradykinin, a substance that also activates the calcium channel.

Such abnormal calcium release is toxic to cells and results in impaired motor function, said Dr. Ilya Bezprozvanny, professor of physiology at UT Southwestern and senior author of the study. "We're generalizing the idea of calcium toxicity for this group of diseases, which are called polyglutamine expansion disorders," he said.

(MORE)

The researchers also studied mice that had been genetically engineered to overexpress the human ataxin-3 protein containing excessive glutamine repeats. The mutant mice performed poorly on tests of motor coordination compared with normal mice and displayed age-dependent neuronal loss in the same brain regions that are affected in SCA3 patients.

To test whether blocking calcium release would alleviate symptoms in the mice, the researchers treated them for a year with dantrolene, a drug that blocks excessive calcium release from the ER in skeletal muscle cells. Dantrolene is approved for use in humans as a one-time emergency treatment for a reaction to anesthesia.

Treatment with dantrolene improved the coordination of the mutant mice and slowed brain atrophy.

Dantrolene is not suitable for long-term use in humans, however, because of side effects that can potentially harm the liver and the heart and cause neurological problems, said Dr. Bezprozvanny.

"The take-home message is not so much that dantrolene is the solution for treating SCA3, but that this shows a direction for research into a better drug to block similar targets with fewer side effects," Dr. Bezprozvanny said.

The researchers now are studying whether blocking calcium release from the endoplasmic reticulum also can improve function in mouse models of Huntington's and other neurodegenerative diseases such as spinocerebellar ataxia type 2 and Alzheimer's disease.

Other UT Southwestern researchers involved in the study were Dr. Xi Chen, postdoctoral researcher in physiology; Dr. Tie-Shan Tang, instructor of physiology; Dr. Huiping Tu, former instructor of physiology; graduate student Omar Nelson; and Dr. Robert Hammer, professor of biochemistry. Researchers from Brunel University in London and RIKEN Brain Science Institute in Japan also participated.

The study was funded by the National Institutes of Health, the Robert A. Welch Foundation, the McKnight Endowment Fund for Neuroscience, the National Ataxia Foundation, Ataxia UK, Ataxia MJD Research Project Inc. and MEXT of Japan.

###