UT SOUTHWESTERN MEDICAL CENTER NEWS

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Drug protects brain cells in Huntington's disease model, researchers find

DALLAS – July 24, 2007 – A drug used in some countries to treat the symptoms of Huntington's disease prevents death of brain cells in mice genetically engineered to mimic the hereditary condition, UT Southwestern Medical Center researchers have found.

The research sheds light on the biochemical mechanisms involved in the disease and suggests new avenues of study for preventing brain-cell death in at-risk people before symptoms appear.

"The drug can actually prevent brain cells from dying," said Dr. Ilya Bezprozvanny, associate professor of physiology at UT Southwestern. "It's much more important than people thought."

The study, of which Dr. Bezprozvanny is senior author, appears in the July 25 issue of *The Journal of Neuroscience*.

The drug, called tetrabenazine (TBZ), is commercially distributed as Xenazine or Nitoman and blocks the action of dopamine, a compound that some nerve cells use to signal others. TBZ is approved for use in several countries, but not the U.S., to treat uncontrollable muscle movements in Huntington's and other neurological conditions.

Huntington's is a fatal genetic condition that usually manifests around ages 30 to 45, according to the Huntington's Disease Society of America. About one in 10,000 people in America have the disease, with another 200,000 at risk. One of the most famous people with Huntington's was folk singer Woody Guthrie, who died in 1967.

Huntington's is caused by a dominant gene, meaning that a person carrying the gene is certain to develop the disease and has a 50 percent chance of passing it on to his or her children. Symptoms include jerky, uncontrollable movements called chorea and deterioration of reasoning abilities and personality. Symptoms begin after many brain cells have already died.

Although a genetic test exists, some people with a family history of Huntington's choose not to be tested because there is no cure and because they fear loss of health insurance. There are treatments to lessen the symptoms, but there is currently no way to slow or halt the progression of the disease.

In the current study, the UT Southwestern researchers used mice that were genetically engineered to carry the mutant human gene for Huntington's, causing symptoms and death of brain cells

(MORE)

similar to those seen in the disease. The study focused on an area of the brain called the striatum, which plays a critical role in relaying signals concerning motion and higher thought and receives signals from several brain regions.

The striatum is primarily made up of nerve cells called medium spiny neurons, which undergo widespread death in Huntington's. One major input to the striatum comes from an area called the substantia nigra, which controls voluntary movements and sends signals to the striatum via nerve cells that release dopamine.

The researchers conducted various coordination tests on both normal and genetically manipulated mice. Engineered mice given a drug that increased brain dopamine levels performed worse on these tasks, while TBZ protected against this effect. Most importantly, TBZ appears to reduce significantly cell loss in the striatum of the engineered mice, the scientists report.

"More research is needed to determine whether this protective effect might also be present in humans, and also whether at-risk people would benefit from the drug," Dr. Bezprozvanny said.

Clinical trials in humans would be very difficult, however, because trials require many participants and there is no easy way to score effectiveness of a presymptomatic drug, Dr. Bezprozvanny said. Thus, his future studies in animals will look at the effectiveness of TBZ given just after initial symptoms have developed. This situation simulates what would probably happen in a human trial, he said.

Other UT Southwestern researchers involved in the study were Dr. Tie-Shan Tang, instructor in physiology; and Dr. Xi Chen and Dr. Jing Liu, postdoctoral researchers in physiology.

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