Test reveals effectiveness of potential Huntington's disease drugs

October 30 2006

Researchers led by Dr. Ilya Bezprozvanny, associate professor of physiology, and including Dr. Jun Wu, research associate, have shown an effective test for screening Huntington's disease drugs and that two compounds -- memantine and riluzole -- are most effective at keeping cells alive under conditions that mimic the disorder. Credit: UT Southwestern Medical Center

A test using cultured cells provides an effective way to screen drugs against Huntington's disease and shows that two compounds – memantine and riluzole – are most effective at keeping cells alive under conditions that mimic the disorder, UT Southwestern Medical Center researchers report.

"These drugs have been tested in a variety of Huntington's disease models and some HD human trials and results are very difficult to

interpret," said Dr. Ilya Bezprozvanny, associate professor of physiology and senior author of the study, available online and published in today's issue of Neuroscience Letters. "For some of these drugs conflicting results were obtained by different research groups, but it is impossible to figure out where the differences came from because studies were not conducted in parallel.

"We systematically and quantititatively tested the clinically relevant drugs side-by-side in the same HD model. That has never been done before," said Dr. Bezprozvanny.

Huntington's disease is a fatal genetic disorder, manifesting in adulthood, in which certain brain cells die. The disease results in uncontrolled movements, emotional disturbance and loss of mental ability. The offspring of a person with Huntington's have a 50 percent chance of inheriting it.

More than 250,000 people in the United States have the disorder or are at risk for it. There is no cure, but several drugs are used or are being tested to relieve symptoms or slow Huntington's progression.

The disease affects a part of the brain called the striatum, which is involved in the control of movement and of "executive function," or planning and abstract thinking. It primarily attacks nerve cells called striatal medium spiny neurons, the main component of the striatum.

Dr. Bezprozvanny's group previously demonstrated that Huntington's striatal neurons are oversensitive to glutamate, a compound that nerve cells use to communicate with each other.

In the latest UT Southwestern study, the researchers cultured striatal spiny neurons from the brains of mice genetically engineered to express the mutant human Huntington gene. As predicted, glutamate killed the

Huntington's neurons, but the scientists also tested five clinically relevant glutamate inhibitors to assess their protective ability.

Folic acid has been suggested as a treatment for people with Huntington's because it interacts with homocysteine, a compound that makes nerve cells more vulnerable to glutamate. Gabapentin and lamotrigine, both glutamate inhibitors, are used in epilepsy treatment and as a mood stabilizer, respectively. These three compounds did not significantly protect the cultured cells.

However, a drug called memantine, which is used to treat Alzheimer's disease, and riluzole, used in amyotrophic lateral sclerosis, did protect the cells. Memantine demonstrated a stronger effect in the study. Memantine has also shown evidence of retarding the progression of Huntington's in people, while riluzole has helped relieve some symptoms.

"Our results provide the first systematic comparison of various clinically relevant glutamate pathway inhibitors for HD treatment and indicate that memantine holds the most promise based on its in vitro efficacy," Dr. Bezprozvanny said. "Whole animal studies of memantine in an HD mouse model will be required to validate these findings."

Source: UT Southwestern Medical Center