SOUTHWESTERN NEWS

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

EMBARGOED UNTIL 11 A.M. CST, WEDNESDAY NOV. 2, 2005

Disease-causing protein protects against nerve damage in Parkinson's disease

DALLAS – Nov. 2, 2005 – Researchers at UT Southwestern Medical Center have discovered that a protein associated with causing neurodegenerative conditions may, when appearing in normal amounts, actually protect against neurodegeneration.

The findings, appearing in the Nov. 3 issue of the journal *Cell*, have surprised the researchers, because an excess of the same specific protein – alpha-synuclein – causes Parkinson's disease.

"It's the first time that anyone has shown that synuclein has any positive function at all in the body, and this is important because it's been known to be involved in neurodegeneration," said Dr. Thomas Südhof, senior author of the study and director of the Center for Basic Neuroscience. Dr. Südhof also is an investigator in the Howard Hughes Medical Institute.

The key to their findings was determining the interaction between alpha-synuclein and another protein – cysteine-string-protein-alpha, or CSP-alpha. The researchers' investigation involved several strains of mutant mice, which produced differing amounts of CSP-alpha or alpha-synuclein.

CSP-alpha is a "co-chaperone," meaning that it helps other proteins fold into their normal shapes, a vital process in the instantaneous reactions that occur at terminals of a nerve cell. When mutant mice lack only CSP-alpha, they appear normal for their first three weeks, then undergo rapid nerve degeneration and die at one to four months of age.

When mutant mice lack only alpha-synuclein, on the other hand, they continue to appear normal as they age, indicating that alpha-synuclein might not be essential in healthy nerve cells.

But mice that have been bred to produce an excess of human alpha-synuclein undergo a slowly progressing nerve degeneration resembling Parkinson's.

The researchers bred mice lacking CSP with mice with excessive human synuclein in their brains, expecting to see a faster descent into the Parkinson's-like symptoms in the offspring. Instead, they produced apparently healthy animals. In their terms, the alpha-synuclein "rescued" the mice from the harmful effects of lacking CSP-alpha.

The results were "exactly the opposite of what I expected," said Dr. Sreeganga Chandra,

(MORE)

instructor in the Center for Basic Neuroscience and lead author of the study. "The rescued animals can live for one year or longer."

The researchers also bred mice that produced neither CSP-alpha nor alpha-synuclein and found they suffered neurodegeneration faster than mice just lacking CSP-alpha – another sign that alpha-synuclein protects against a lack of CSP-alpha.

In humans, clumps of alpha-synuclein, called Lewy bodies, are found in the brain cells of patients with Parkinson's, Alzheimer's and other degenerative diseases. The researchers speculate that the formation of Lewy bodies may take alpha-synuclein out of circulation in cells, thus removing its protective action.

Testing this hypothesis would involve looking for mutations in the genes for CSP-alpha or alpha-synuclein in patients with neurodegenerative diseases. "Trying to understand what's going on in a dying brain is very difficult," said Dr. Südhof, who directs the Gill Center for Research on Brain Cell Communication and the C. Vincent Prothro Center for Research in Basic Neuroscience.

The researchers also found that alpha-synuclein doesn't bind to or react with the same proteins that CSP-alpha does, so it doesn't simply act as a substitute. However, both molecules bind to the membranes of synaptic vesicles – small spheres that contain the nerve cell's neurotransmitters, chemicals that carry signals between brain cells – indicating that they both act at the vesicles' surface.

"There's a pathway, but we don't really know all the players in this pathway," Dr. Chandra said.

Other researchers involved in the work were Gilbert Gallardo, student research assistant at the Center for Basic Neuroscience, and researchers from Germany and Spain.

The work was supported in part by the National Institutes of Health, the American Parkinson Disease Association and the Spanish Ministry of Education.

###