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Scientists shed new light on cause of inherited movement disorder

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University of Utah School of Medicine researchers and their colleagues at University of Texas (UT) Southwestern Medical Center have found strong evidence that abnormal calcium signaling in neurons may play an important role in the development of spinocerebellar ataxia type 2 (SCA2), a disorder causing progressive loss of coordination, speech difficulty, and abnormal eye movements. Their findings are published in the July 27, 2009 issue of *Journal of Neuroscience*.

SCA2 is an inherited neurodegenerative disease that predominantly affects neurons called Purkinje cells in the cerebellum, the region of the brain that controls voluntary muscle movements, balance, and posture. It is one of a group of genetic disorders characterized by ataxia, or loss of muscle coordination.

"We have known for some time that, at a molecular level, SCA2 is caused by glutamine repeat mutations in the ataxin-2 gene, but the exact mechanism of Purkinje cell degeneration is not well understood," says Stefan-M. Pulst, MD, University of Utah professor and chair of neurology, member of the Brain Institute at the University of Utah, and contributor author on this study. Pulst's group also discovered the ataxin-2 gene in 1996.

The glutamine repeat mutations found in SCA2 are also found in other neurodegenerative diseases, including Huntington disease (HD) and spinocerebellar ataxia type 3 (SCA3). It is commonly assumed that these disorders share a common pathogenic mechanism. Ilya Bezprozvanny,

PhD, associate professor of physiology at UT Southwestern Medical Center, and his group had previously uncovered evidence that deranged calcium signaling played an important role in the pathology of HD and SCA3, so they thought that abnormal calcium signaling might also be involved in SCA2.

Calcium signaling refers to the movement or release of calcium ions as a form of cellular communication. Bezprozvanny and his colleagues demonstrated that the mutant ataxin-2 gene strongly associated with an intracellular calcium release channel, increasing the sensitivity of the channel to activation. They also found that enhanced calcium signaling contributed to the death of Purkinje cells in cell culture, but this effect could be attenuated by dantrolene, a stabilizer of intracellular calcium signaling. Bezprozvanny and his colleagues then approached Pulst, who had developed a mouse model of SCA2, in order to test whether these results could be replicated in genetically modified mice.

The authors discovered that dantrolene was effective in alleviating motor coordination deficits in mice with a mutant ataxin-2 gene. After being fed dantrolene for a period of nine months, these mice were found to have motor coordination that was similar to normal mice and they did not suffer any significant adverse effects from long-term treatment with the calcium signaling stabilizer. The scientists also discovered that, beyond the positive effects on coordination, feeding dantrolene to mice with a mutant ataxin-2 gene reduced the death of Purkinje cells in the cerebellum.

"We were all elated to find that dantrolene had a pronounced effect in our mice," says Pulst. "It prevented deterioration in motor function and Purkinje cell death. "

Dantrolene is approved for use in humans for the treatment of muscle spasticity. "Although it showed effects in mice with ataxia, it could have

major side effects in human patients with ataxia because it may cause sedation and muscle weakness. Therefore, this drug should be evaluated in controlled clinical trials before wide-spread use in SCA2 patients," cautions Pulst.

Taken together with their previous studies on HD and SCA3, the research group now has evidence that deranged calcium signaling contributes to the pathogenesis of at least three inherited ataxias. This strongly suggests that abnormal neuronal calcium signaling may also be involved in other neurodegenerative diseases caused by glutamine repeat mutations.

It is estimated that SCA2 affects as many as one or two in every 100,000 people. "Neurodegenerative diseases like HD and SCA2 are progressive and have no known cures at this moment," according to Pulst. "Calcium signaling stabilizers such as dantrolene or similar compounds may provide a new avenue for investigation in the laboratory and in clinical trials to limit disability and disease progression."

Source: University of Utah Health Sciences (news : web)