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UCSD Findings Could Lead to New Therapy for Spinal Cord Injury-Induced Spasticity and Rigidity

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Research led by scientists at the University of California, San Diego (UCSD) School of Medicine has identified a target with potential as an effective new therapy for chronic spasticity and rigidity, a painful condition that often results from spinal cord injury.

In work with rats, Martin Marsala, M.D., a professor in the Department of Anesthesiology at the University of California, San Diego (UCSD) School of Medicine, demonstrated that an AMPA receptor antagonist called NGX424 (tezampanel), being developed by TorreyPines Therapeutics, Inc., of La Jolla, California, is highly potent in suppressing spasticity and rigidity. The study will be published in the October 17 issue of the *Journal of Neuroscience.*

Paraplegia from spinal cord ischemia is a serious complication that occurs in 20 to 40 percent of patients undergoing a surgical process called aortic cross-clamping. When the surgeon works on the aorta to correct a potentially lethal aneurysm, this large vessel carrying all of the blood flow from the heart must be temporarily blocked. If clamping occurs for more than 30 minutes, the procedure can result in the loss of specialized spinal cord neurons called spinal inhibitory neurons. Loss of these neurons can lead to irreversible spasticity and rigidity, or loss of muscle control, in the lower limbs.

"This exaggerated muscle tone, or uncontrolled spasms, is a serious complication of either ischemic or traumatic injury to the spinal cord -- such as injuries resulting from a diving or car accident," said Marsala. Several other conditions can lead to spasticity/rigidity, including brain trauma, multiple sclerosis, cerebral palsy or Parkinson's disease - all of which lead to increased peripheral muscle tone.

The most effective treatment for the spastic muscle condition - which results in pain and tremendous spasms, even in those patients who have partial motor recovery - has been a drug called Baclofen, a GABA-B receptor agonist that is delivered either systemically or spinally to patients. However, according to Marsala, patients taking this drug often develop tolerance and need increased dosage to achieve the same effect.

"A new therapy to control spasticity is very important," said lead author Michael P. Hefferan, Ph.D., of UCSD's Department of Anesthesiology. "This AMPA receptor blockade offers a novel means of reducing the spasticity and rigidity in muscles because it works through a totally different receptor system than current drugs being used."

Spinal spasticity is the result of increased spinal neuronal excitability. The NGX424 compound - which is delivered via intrathecal catheters that inject the drug into the fluid surrounding the spinal cord - suppresses the AMPA-mediated neuronal excitation, relieving otherwise increased muscle tone.

The authors also demonstrated that intrathecal delivery of GluR1 antisense (a treatment that blocks expression of one of the subunits in the AMPA receptor complex) provides a similar antispasticity effect. This further demonstrates a role for AMPA receptors in spasticity and rigidity, and indicates that blockade of this subunit by NGX424 likely plays a key role in the observed antispasticity effect.

Marsala added that additional large animal safety testing will be required before the researchers can consider clinical trials in humans. However, the rat data from this study indicates no toxicity using infused NGX424. Subcutaneous delivery of the drug is currently being evaluated for treating migraines.

Additional researchers include Karolina Kucharova, Kiyohiko Kinjo, Osamu Kakinohana, Tony L. Yaksh, UCSD Department of Anesthesiology; Gabriella Sekerkova, Feinberg School of Medicine, Northwestern University; Seiya Nakamura and Tatsuya Fuchigami, UCSD Department of Anesthesiology and University of the Ryukyus, Okinawa, Japan; Zoltan Tomori, Institute of Experimental Physics, Slovak Academy of Scineces; and Neil Kurtz, TorreyPines Therapeutics, Inc., La Jolla.

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