Decoy pill saves brain cells

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Tricking a key enzyme can soothe over-excited receptors in the brain, say neuroscientists, calling this a possible strategy against stroke, Alzheimer's and other neurodegenerative diseases.

Lead author Michel Baudry of the University of Southern California, his graduate student Wei Xu and collaborators from the University of British Columbia outline their technique in the Feb. 1 issue of *Neuron*.

The researchers injected laboratory mice with a decoy peptide containing a snippet of a receptor that facilitates cell death in neurodegenerative diseases.

They hoped the toxic enzyme calpain would latch on to the decoy instead of the actual receptor, averting brain damage.

As a test, the researchers then injected the mice with kainic acid, a chemical known to cause seizures and neuron death.

While seizures still occurred, as in control mice, no brain lesions were observed in the subjects.

"We eliminate a big chunk of neuronal death," Baudry said. "I was surprised that this works. It looks like the peptide is almost completely neuroprotective."

Baudry, one of USC's most frequently cited researchers, has been studying calpain and other chemicals in the brain for more than 20 years.

Scientists have known for decades that the neurotransmitter glutamate, which tells neurons to fire, can also destroy them. If over-activated, glutamate receptors start a chain reaction that raises the concentration of calcium and activates calpain, among other toxic enzymes.

But Baudry and Xu observed that in one receptor, mGluR1?, the situation is even worse. Under normal conditions, this receptor is neuroprotective. However, calpain truncates it and makes it neurodegenerative in such a way as to start a positive feedback loop that leads to ever-higher levels of calcium and continuous calpain activation.

In addition, by cutting mGluR1?, calpain eliminates its neuroprotective function.

The decoy, developed by Xu, reversed the outcomes. By tricking calpain, it prevented damage to the receptor and allowed the beneficial reaction to continue. In addition, it interrupted the feedback loop that stoked calpain activation.

"This is potentially a treatment for any conditions that involve this kind of excitotoxicity," Baudry said, and especially, he added, for the "window of opportunity" in the few hours after a stroke.

While a stroke kills some brain cells right away, others take much longer to die. If the stroke triggered a calcium-calpain feedback loop, treatment with decoy peptides might save some cells, Baudry said.

His group plans to test the treatment in a stroke model in mice.

Source: University of Southern California