MedicalXpress

Study reveals why brain has limited capacity for repair after stroke, IDs new drug target

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Stroke is the leading cause of adult disability, due to the brain's limited capacity for recovery. Physical rehabilitation is the only current treatment following a stroke, and there are no medications available to help promote neurological recovery.

Now, a new UCLA study published in the Nov. 11 issue of the journal *Nature* offers insights into a major limitation in the brain's ability to recover function after a stroke and identifies a promising medical therapy to help overcome this limitation.

Researchers interested in how the brain repairs itself already know that when the brain suffers a stroke, it becomes excitable, firing off an excessive amount of brain cells, which die off. The UCLA researchers found that a rise in a chemical system known as "tonic inhibition" immediately after a stroke causes a reduction in this level of excitability.

But while this "damping down" initially helps limit the spread of stroke damage, the increased tonic inhibition level and reduced brain excitability persists for weeks, eventually becoming detrimental to the brain's recovery.

Based on this finding, the researchers identified a new way to "turn off" this inhibitory response in order to promote stroke recovery and determined the window of time in which this and other brain-repair therapies after stroke should be administered. These findings offer new targets for drug development to promote stroke recovery.

"It was surprising to find that the level of tonic inhibition was increased for so long after stroke and that there was an inflection point where the increased level eventually hindered the brain from recovering," said Dr. Tom Carmichael, associate professor of neurology at the David Geffen School of Medicine at UCLA and a member of the UCLA Stroke Center. "It was also surprising that we could easily manipulate tonic inhibition in the brain after stroke to restore it back to a normal, 'non-stroke' level and, in doing this, enhance behavioral recovery."

Other studies have looked in general terms at excitatory signaling or at a type of inhibitory signaling after stroke known as "phasic inhibition." However, this previous work focused on the direct connections between brain cells.

The UCLA research is the first to examine tonic inhibition in stroke, focusing on the chemical system, which does not directly link brain cells together but instead senses the overall activity level in the brain and sets the thresholds for when brain cells will fire off new signals.

By studying stroke and stroke recovery in mice, the researchers found that since stroke causes a reduction in the normal clearance of an inhibitory brain chemical, it causes neurons in the tissue that borders the stroke to be less excitable. They found that by applying specific blockers of this inhibitory brain chemical, they could then "turn off the switch."

The resulting enhanced brain excitability immediately improved behavioral recovery after stroke. As a result, these findings identified the potential for a new target in the brain for effective stroke recovery treatments.

"An important element in stroke treatment is the timing of drug delivery," added Carmichael. "We found that blocking tonic inhibition too early could produce cell death, but by delaying treatment to three

days after stroke, it promoted functional recovery without altering the stroke size."

The next stage of research will be to validate the findings in other pre-clinical models of stroke, and then to design clinical trials for humans. Pharmaceutical companies have been active in this region of neuroscience and there are some promising candidate drugs for human use that exist.

Provided by University of California - Los Angeles