STROKE

A new window of opportunity for stroke rehabilitation?

Modulation of neuroplasticity in the region surrounding an infarct could provide the key to functional recovery after stroke, research published in *Nature* reveals. In a mouse stroke model, Tom Carmichael and his colleagues at the University of California, Los Angeles demonstrated increased γ-aminobutyric acid (GABA)-mediated tonic inhibition in the peri-infarct zone, and showed that an inverse agonist of extrasynaptic $GABA_A$ receptors could promote recovery of motor function in the animals.

> “...a window exists for promoting stroke recovery in the first week...”

The investigators used patch-clamp recording to measure the excitability of pyramidal neurons in the motor cortex in mice after stroke. “We know that this area of the brain is adjacent to the stroke but survives; that it normally mediates motor movements of the limbs; and that it is dysfunctional because the mouse cannot control its limbs well after the stroke,” explains Carmichael.

The research team found that tonic (extrasynaptic) GABA inhibition was elevated in the peri-infarct zone for several weeks after stroke. This phenomenon was found to be attributable to accumulation of GABA, which was caused by downregulation of the GABA uptake pump GAT-3 by astrocytes.

Carmichael and colleagues were able to selectively block tonic inhibition without affecting phasic inhibition through *in vivo* administration of L655,708, an agent that targets the α5 subunit of the extrasynaptic $GABA_A$ receptor. In addition to normalizing the excitability of neurons in the motor cortex, this compound produced rapid and dramatic recovery of motor function in the mice.

The timing of drug delivery is vital in this model. As Carmichael points out, “right after the stroke, the increased tonic GABA inhibition promotes neuroprotection—it limits the stroke size. The problem is that this increased inhibition is maintained for weeks, and it limits recovery.” The switch from the neuroprotective to the deleterious effects of tonic GABA inhibition seems to occur in the first 3 days after stroke.

The researchers plan to test their findings in other stroke models, such as subcortical stroke, and they hope that their work will lead to the development of clinically useful drugs that block tonic GABA inhibition.

“Our data indicate that a window exists for promoting stroke recovery in the first week,” says Carmichael. “We should now begin to discuss how we might organize clinical trials, outcome measures and the timeline for both pharmacological and physical rehabilitation treatments that target this early window of neuroplasticity in stroke.”

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Original article Clarkson, A. N. *et al.* Reducing excessive GABA-mediated tonic inhibition promotes functional recovery after stroke. *Nature* **468**, 305–309 (2010)