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NEUROPLASTICITY

Functional recovery after stroke

There is no pharmacological therapy available to promote recovery after stroke. The brain region next to that suffering stroke damage — the peri-infarct zone — has some capacity for increased neuroplasticity that can aid functional recovery. Carmichael and colleagues now show that manipulation of the GABA (γ-aminobutyric acid) signalling pathway that constrains this plasticity can promote recovery after stroke.

The authors examined the neuronal excitability of the peri-infarct cortex in a photothrombotic mouse model of focal stroke. They measured an increase in the GABA type A ($GABA_A$) receptor-mediated tonic inhibition in these mice after stroke compared with sham controls, and the inhibition remained raised for 3–14 days. As GABAergic signalling is crucial in regulating normal cortical plasticity, it might have a similar role after stroke.

So, if excessive tonic inhibition constrains neuronal plasticity in the peri-infarct zone, does reducing this inhibition improve functional recovery? To address this question, the authors used L655,708 — a specific inverse agonist of α5-containing $GABA_A$ receptors that, together with δ-containing $GABA_A$ receptors, mediates tonic inhibition. Administration of this drug to the mice 3 days after stroke led to decreased tonic inhibition in post-stroke neurons compared with control neurons at day 7, which translated into improved forelimb motor control. Recovery from stroke was also tested in transgenic mice lacking either α5-$GABA_A$ or δ-$GABA_A$ receptors. The *Gabra5*$^{-/-}$ mice showed better motor recovery from stroke than control wild-type mice, a similar recovery to that seen in the drug-treated wild-type animals. *Gabrad*$^{-/-}$ mice also showed improvement in motor function, but less so than the *Gabra5*$^{-/-}$ mice. When L655,708 was administered to the *Gabrad*$^{-/-}$ mice, an even greater recovery was observed.

One note of caution is that dampening tonic inhibition too early might actually increase cell death, as $GABA_A$ receptor agonists given at the time of stroke are known to decrease the size of stroke. Indeed, when L655,708 was given from stroke onset, stroke volume was significantly increased compared with that measured in mice given L655,708 from day 3 after stroke or in mice treated with vehicle only.

Therefore, extrasynaptic GABA receptors are promising new targets for developing therapy to aid stroke recovery, but there is a critical time frame for dampening tonic inhibition after stroke to promote recovery rather than exacerbating stroke damage.

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ORIGINAL RESEARCH PAPER Clarkson *et al.* Reducing excessive GABA-mediated tonic inhibition promotes functional recovery after stroke. *Nature* **468**, 305–309 (2010)