$GABA_A$: better late

By Michael J. Haas, Senior Writer

The vast majority of ischemic stroke patients are unable to receive treatment with tissue plasminogen activator (tPA) within the drug's three-hour efficacy window, and there are no approved therapies that promote recovery of motor function after the damage is done. Researchers at the **University of California, Los Angeles** think they have a solution to the latter problem after having shown that inhibitors of $GABA_A$ receptor increase functional recovery in mice when given several days post-stroke.[1]

A key next step will be honing the therapeutic window for $GABA_A$ receptor blockers, as the molecules have negative effects when given immediately following a stroke.

The brain houses two types of $GABA_A$ receptors with differing functions and structures. The synaptic (phasic) type regulates signaling between neurons. The extrasynaptic (tonic) type inhibits neuronal excitability and contains α5 and δ subunits that the phasic type lacks.

Over the past eight years, multiple studies have shown that γ-aminobutyric acid (GABA) signaling plays a role in both early cortical development in humans[2] and cortical remapping after motor nerve damage in rats.[3] Additional studies have shown that blocking tonic $GABA_A$ receptors improved learning and memory in mice, thereby suggesting a role for that subtype in brain plasticity.[4,5]

Collectively, these findings led the UCLA team to hypothesize that signaling between GABA and tonic $GABA_A$ receptors plays a role in the brain's response to loss of motor function and thus might be targeted therapeutically to recover that function after stroke.

The group's electrophysiological studies showed that wild-type mouse models of cortical stroke had higher levels of tonic $Gaba_A$ receptor activity than normal controls. In contrast, mice with tonic $Gaba_A$ receptors that lacked α5 and δ subunits showed greater motor recovery after stroke than wild-type controls.

Next, the researchers treated wild-type mice with a selective inhibitor of tonic $Gaba_A$ receptors beginning three days after cortical stroke. The animals had better motor function than vehicle-treated controls.

The timing of treatment turned out to be critical, as giving the inhibitor right after stroke actually increased infarct size and stroke damage.

The findings indicate that tonic $GABA_A$ receptor signaling initially is neuroprotective after stroke, team leader S. Thomas Carmichael told *SciBX*. "But there is an inflection point somewhere between one and three days after stroke" when that signaling blocks recovery in mice and thus could be targeted with an inhibitor to promote recovery.

Carmichael is associate professor of neurology at UCLA's David Geffen School of Medicine. Data were reported in *Nature*.[1]

"The study presents a means of promoting recovery without requiring immediate treatment and so nicely addresses a major challenge in stroke treatment," said Anthony Caggiano, vice president of preclinical development at **Acorda Therapeutics Inc.** "There's nothing in the study to suggest the findings should not be pursued further as a stroke treatment."

He added: "It would also be much easier to standardize a trial design and enroll patients" to test this kind of treatment compared with a therapy that requires identifying and treating stroke patients right away.

Acorda's glial growth factor 2 (GGF2), which stimulates the production of myelin, is in preclinical development to treat stroke and heart failure. The company plans to run a Phase I trial in the latter indication but has not announced a timeline.

The UCLA study "looks at treating cortical stroke with a drug in an elegant way: by turning off neurotransmitter signaling to promote recovery," said Paul Stroemer, head of preclinical research at **ReNeuron Group plc**. "It is a pragmatic approach to the problem of treating stroke patients in whom the damage is already done. I will be interested to see the rest of this story and how it turns out."

> **"The study presents a means of promoting recovery without requiring immediate treatment and so nicely addresses a major challenge in stroke treatment."**
>
> *—Anthony Caggiano, Acorda Therapeutics Inc.*

ReNeuron's ReN001, neural stem cells derived from the company's c-mycER technology, is in Phase I testing to treat stroke.

Different strokes

Both Caggiano and Stroemer said it would be crucial to determine when post-stroke treatment with a $GABA_A$ receptor inhibitor could safely begin and how long treatment should continue to induce permanent recovery in humans.

"If you have a negative effect with early treatment and a positive effect with delayed treatment, you'd better have a good way to define the transition," Caggiano said.

Additionally, the transition between those two states would have to be relatively consistent across all patients, he said.

Stroemer cautioned that "stroke patients are all different and have a heterogeneous presentation in terms of the location and extent of stroke damage," making it unlikely that single time points for beginning and ending treatment with a $GABA_A$ receptor inhibitor would apply to every patient.

Caggiano said monitoring cortical activity could be one way to define the transition. "But what is more likely to happen is that animal studies will help determine when the risk of increasing stroke damage by blocking $GABA_A$ receptor is gone—at, say, 24 hours—and treatment in humans could begin well after that—at, say, 48 hours"—to set a wide safety margin.

Conversely, he said, "you don't want to be on a $GABA_A$ receptor inhibitor for the rest your life—not when this signaling pathway affects brain plasticity." Thus, additional studies also need to determine how long a patient requires the inhibitor to achieve lasting functional recovery.

Stroemer said the findings demonstrate the need for closer investigation of post-stroke brain biology. "We don't fully understand what happens neurochemically in the weeks and months after stroke and what factors influence recovery," he said. "What we really need are biomarkers or high-end imaging to diagnose how much damage there is and thus begin to understand the degree to which a medication would help promote recovery."

He also wanted to know whether inhibiting tonic $GABA_A$ receptors would promote functional recovery in animal models of striatal stroke. "It's my understanding that most stroke patients present with some combination of cortical and striatal damage. What helps for one type of stroke damage may be an impediment in another type," he said.

Carmichael said his team's ongoing work includes testing $GABA_A$ receptor inhibitors in aging mouse models of stroke and an undisclosed model "to capture a type of infarct we did not monitor in the *Nature* paper."

He said his team also is investigating the optimal time frame for starting and ending such treatment in mice and how that might translate to humans.

Meanwhile, another Carmichael-led team that included researchers from the **National Cancer Institute**, **Drexel University** and the **University of Michigan** is investigating the biological mechanisms that control the regrowth of axons in the infarct zone after stroke.

In a study published this month in *Nature Neuroscience*, that team identified multiple transcription factors—including α-thalassemia/mental retardation syndrome X-linked (ATRX; RAD54), insulin-like growth factor-1 (IGF-1) and reticulon 4 receptor-like 2 (RTN4RL2; NgR2)—that were up- or downregulated in sprouting axons of mouse models of stroke compared with in axons from controls.[6]

Carmichael said it is too early to say whether any of the identified transcription factors could be therapeutic targets to promote recovery after stroke.

UCLA has filed a patent on the findings reported in *Nature* and the IP is available for licensing or partnering, Carmichael said.

Haas, M.J. *SciBX* 3(45); doi:10.1038/scibx.2010.1343
Published online Nov. 18, 2010

REFERENCES

1. Clarkson, A.N. *et al. Nature*; published online Nov. 4, 2010; doi:10.1038/nature09511
   Contact: S. Thomas Carmichael, University of California, Los Angeles, Calif.
   e-mail: scarmichael@mednet.ucla.edu
2. Hensch, T.K. *Nat. Rev. Neurosci.* **6**, 877–888 (2005)
3. Foeller, E. *et al. J. Neurophysiol.* **94**, 4387–4400 (2005)
4. Collinson, N. *et al. J. Neurosci.* **22**, 5572–5580 (2002)
5. Atack, J.R. *et al. Neuropharmacology* **51**, 1023–1029 (2006)
6. Li, S. *et al. Nat. Neurosci.*; published online Nov. 7, 2010; doi:10.1038/nn.2674
   Contact: S. Thomas Carmichael, University of California, Los Angeles, Calif.
   e-mail: scarmichael@mednet.ucla.edu

COMPANIES AND INSTITUTIONS MENTIONED

Acorda Therapeutics Inc. (NASDAQ:ACOR), Hawthorne, N.Y.
Drexel University, Philadelphia, Pa.
National Cancer Institute, Bethesda, Md.
ReNeuron Group plc (LSE:RENE), Guildford, U.K.
University of California, Los Angeles, Calif.
University of Michigan, Ann Arbor, Mich.