Receptor strategy for brain ischemia

By Lev Osherovich, Senior Writer

A U.S. team has devised a way to prevent neurological damage caused by ischemia by agonizing nicotinic acetylcholine receptors.¹ The findings open a new indication for at least two biotech, **Targacept Inc.** and **EnVivo Pharmaceuticals Inc.**, which along with **Roche** have agonists of those receptors in clinical development for cognitive disorders.

Cerebral ischemia typically occurs when cardiac arrest cuts off the blood supply to the brain. Even if the heart is restarted through cardiopulmonary resuscitation or defibrillation, a brief episode of cerebral ischemia “sets off a cascade of proinflammatory markers and cytokines that lead to permanent damage to brain cells,” said Patrick Lippiello, senior principal scientist at Targacept.

Recent studies have suggested that signaling by nicotinic acetylcholine receptor α_7 (CHRNA7) counteracts inflammation in systemic cardiovascular conditions like hypovolemic or septic shock.² Now, researchers at **The Ohio State University** and **The Feinstein Institute for Medical Research** have made a case that the receptor also exerts its effects in the brain, showing that agonizing CHRNA7 protects against ischemia-induced neuronal loss in mice.

A team led by A. Courtney DeVries, associate professor of psychology at Ohio State, suspected that acetylcholine signaling may contribute to brain damage after cardiac arrest. To find out, the researchers looked at gene expression in the brains of mice that had undergone a surgical procedure that temporarily cuts off the brain's blood supply.

“We wanted to see whether cerebral ischemia caused changes in the cholinergic system and what would be the effect of intervention in the cholinergic system,” said Greg Norman, the study's corresponding author. Norman is now a postdoctoral fellow in the Department of Psychology at **The University of Chicago**.

The team found that although levels of inflammatory markers increased in ischemic mice, levels of enzymes involved in cholinergic signaling decreased compared with those in control mice that did not undergo cerebral ischemia. Histological studies showed that the hippocampuses of ischemic mice had fewer neurons than those of controls, presumably as a result of neuronal death.

To demonstrate the beneficial effect of cholinergic signaling, the team gave the mice a CHRNA7 agonist 24 hours after cardiac arrest. Intraperitoneal injections of the agonist led to fewer inflammatory markers and greater neuron survival than injection of vehicle.

Data were published in *The Journal of Neuroscience*.

Calming nerves

Precisely how and where activation of CHRNA7 dampens neuroinflammation remains unclear. Norman told *SciBX* that identifying the specific cells that mediate the receptor's anti-inflammatory effects is the Ohio team's next step.

He suspects that the effects of CHRNA7 agonists are mediated by the interplay between the innate immune response and the autonomic nervous system in the periphery.

Norman cited prior evidence from the laboratory of Kevin Tracey that showed “the autonomic nervous system has a large effect on peripheral immune response.” Tracey, who is president of the Laboratory of Biomedical Sciences at the Feinstein Institute, was part of the study team.

Targacept's Lippiello thinks CHRNA7 agonists likely prevent neuroinflammation by counteracting the downregulation of cholinergic signaling caused by ischemia.

“As a result of this insult, the brain starts shutting down acetylcholine production and you lose the natural ability to intervene against inflammation,” he said.

Targacept's CHRNA7 agonist, TC6987, is in Phase II trials for asthma and type 2 diabetes.

“The news in this paper is that delayed treatment can still yield improvement.”

**—Gerhard Koenig,
EnVivo Pharmaceuticals Inc.**

EnVivo CMO and SVP of clinical development Dana Hilt said CHRNA7 is traditionally considered to be a neuronal target but actually is expressed in a variety of cell types, including microglia in the brain and macrophages in the periphery.

Hilt suspects that in the Ohio team's study, CHRNA7 is acting in the periphery. He said Tracey's group previously used surgical techniques to

demonstrate that the anti-neuroinflammatory effects of CHRNA7 agonists required an intact vagus nerve connected to the spleen, which houses many innate immune cells including macrophages.

“Clipping the vagus nerve branch at the very end near the spleen can abolish the effect” of cholinergic stimulation on neuroinflammation, said Hilt. “This implies that you would have to give a drug to patients that would have some effect in the spleen.”

EnVivo's EVP-6125 CHRNA7 agonist is in Phase II trials for cognitive impairment associated with schizophrenia and for Alzheimer's disease (AD).

Hilt said EVP-6125 acts predominantly in the brain but has not been tested in cerebral ischemia.

“The \$64,000 question is if you're treating someone for ischemia and inflammation, would you want a compound that has more of a peripheral distribution” than centrally acting CHRNA7 agonists like EVP-6125, said Hilt.

In addition to the Targacept and EnVivo compounds, the only other disclosed CHRNA7 agonist in the clinic is Roche's MEM 3454, which is in Phase II trials for AD and schizophrenia.

Window of opportunity

Norman said previous studies have implicated CHRNA7 as a guardian against neuroinflammation in mouse models of acute brain hemorrhage and injury, but the new findings suggest CHRNA7 agonists could be used

for the more global cerebral ischemia that accompanies cardiac arrest.

Preventing brain damage caused by cardiac arrest is a wide-open market without a current standard of care. Previous efforts at neuro-protection have failed because of difficulties in administering brain-penetrant therapies at the right time.

Norman noted that CHRNA7 agonists could be useful during a wide window of time after cardiac arrest and resuscitation. “We didn’t give the drug until 24 hours after the event” and still observed a protective effect, he noted.

According to EnVivo CSO and SVP of research Gerhard Koenig, the peripheral effect and relatively wide time window for agonizing CHRNA7 are potentially game-changing advantages for this target.

“The news in this paper is that delayed treatment can still yield improvement,” said Koenig.

Lippiello suggested the team “should look at even longer windows” to test the time limit for intervention.

Another question is whether dosing animals with CHRNA7 agonists for longer than two days can further improve neuronal survival.

Lippiello and Hilt both said that their respective company’s compounds could in principle be ready for clinical testing to prevent brain damage after cardiac arrest, although the indication is not a primary focus for either biotech.

The Ohio State findings are not patented.

Lippiello did say that Targacept previously licensed IP covering the use of nicotinic acetylcholine receptor agonists for inflammatory indications from Critical Therapeutics, a company cofounded by Tracey that merged with **Cornerstone Therapeutics Inc.** in 2008.

Targacept’s lead candidate is a broad-spectrum nicotinic acetylcholine receptor (nAChR) antagonist, TC-5214, which is in Phase III testing as an adjunct treatment for major depressive disorder (MDD). It is partnered with **AstraZeneca plc**.

Osherovich, L. *SciBX* 4(12); doi:10.1038/scibx.2011.329
Published online March 24, 2011

REFERENCES

1. Norman, G.J. *et al. J. Neurosci.*; published online March 2, 2011; doi:10.1523/JNEUROSCI.4558-10.2011
Contact: Greg J. Norman, The University of Chicago, Chicago, Ill.
e-mail: gnorman@uchicago.edu
2. Tracey, K.J. *Nat. Rev. Immunol.* 9, 418–428 (2009)

COMPANIES AND INSTITUTIONS MENTIONED

AstraZeneca plc (LSE:AZN; NYSE:AZN), London, U.K.

Cornerstone Therapeutics Inc. (NASDAQ:CRTX), Cary, N.C.

EnVivo Pharmaceuticals Inc., Watertown, Mass.

The Feinstein Institute for Medical Research, Manhasset, N.Y.

The Ohio State University, Columbus, Ohio

Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland

Targacept Inc. (NASDAQ:TRGT), Winston-Salem, N.C.

The University of Chicago, Chicago, Ill.