NEUROSCIENCE TODAY, NEUROLOGY TOMORROW

Synthetic Drug May Find Niche in Poststroke Recovery

BY JEFF EVANS

FROM THE INTERNATIONAL STROKE CONFERENCE

LOS ANGELES – Efforts to develop a drug to enhance poststroke recovery yielded promising results in a recent study in mice.

Dr. Marion Buckwalter of Stanford (Calif.) University and her colleagues found that a synthetic compound that mimics the positive effects of brain-derived neurotrophic factor (BDNF) significantly improved motor function and increased neurogenesis in mice when given 3 days after a stroke.

"An ideal pro-recovery agent would be something that didn't need to be given within the first 3 or 4.5 or 6 hours but could be given days after a stroke," Dr. Buckwalter said at the conference, sponsored by the American Heart Association.

Although little is known about how the brain recovers from stroke at cellular and molecular levels, Dr. Buckwalter said the process "might include neurogenesis, the formation of new connections between neurons, and the strengthening of existing, useful synapses."

BDNF is critical for synaptic plasticity and learning, especially motor learning and memory. It has been shown to be involved in the enlargement of motor maps during learning, in the promotion of neurogenesis, and in axonal and dendritic sprouting.

BDNF binds to two different receptors, TrkB and p75. Activation of TrkB is neuroprotective, promotes neurogenesis and axonal and dendritic sprouting, and is essential for learning and synaptic plasticity; p75 activation is known to increase neuropathic pain.

One of Dr. Buckwalter's coauthors at Stanford, Dr. Frank M. Longo, worked around the problem of p75 activation in an earlier study by designing a compound that would activate only TrkB. Dr. Longo and his associate, Dr. Stephen M. Massa, wrote a computer program that sifted through a library of compounds that might theoretically bind and activate TrkB. They found that one of the compounds in the library, called LM22A-4, activated TrkB without activating other Trk receptors or p75.

In subsequent experiments, Dr. Buckwalter and her associates randomized mice to 10 weeks of daily intranasal administration of LM22A-4 or placebo, beginning 3 days after stroke. They found that after 3 weeks, the compound significantly improved gait accuracy and increased the speed of their use of the contralateral paw, based on ladder and catwalk testing, in comparison with saline-treated mice. These results were comparable to those obtained with sham-treated mice given saline. The rate of neurogenesis of both mature and immature neurons more than doubled in regions near the stroke in mice treated with LM22A-4, compared with saline-treated mice after stroke.

The study was funded by the National Institute for Neurological Disorders and Stroke and the Stanford Stroke Center. Dr. Buckwalter had no relevant financial disclosures. Dr. Longo is the founder of PharmatrophiX, a company focused on the development of small-molecule ligands for neurotrophin receptors. ■

ADVISERS' VIEWPOINT

Unique Targeted Approach

Endogenous growth factor ligands and their receptors have a lot to teach us about physiology, development, and repair mechanisms. Much research has shown that BDNF exerts effects that could be beneficial in a variety of neurologic disease categories, including degenerative, ischemic, and traumatic conditions.

BDNF itself has been an impractical and ineffective agent in the few trials that have utilized it, because of both its inability to cross the blood-brain barrier and its short half life.

The exciting study by Dr. Buckwalter and her colleagues was made possible by Dr. Stephen Massa and his associates' groundbreaking discovery of LM22A-4. They showed that TrkB activation with LM22A-4 resulted in protection against neurodegeneration in in vitro models and against traumatic brain injury in an in vivo model (J. Clin. Invest. 2010;120:1774-85).

Just as Dr. Massa and his colleagues considered what properties a BDNF-like ligand required to achieve practical utility, so too did Dr. Buckwalter and her coauthors consider what clinical parameters would be useful to show that a neurotrophic strategy could enhance clinical outcomes after stroke. The administration of LM22A-4 on day 3 following ischemic injury was one such consideration, although it is premature to extrapolate from mouse models to humans based on that.

While TrkB activation may prevent neurodegeneration and promote neurogenesis, it also appears to be oncogenic (Blood 2009;113:2028-37). Therefore, oncologists are not in search of TrkB activators but rather TrkB inhibitors (Mol. Cancer Ther. 2009;8:1818-27).

Dr. Buckwalter and her coauthors found no evidence of angiogenesis, glial scar formation, or contralateral neurogenesis, which provides some reassurance, but clearly more work is needed.

How soon we might see clinical trials is not clear. To date, there are no drugs with an indication for poststroke recovery that have been approved by the Food and Drug Administration. An agent that promotes recovery on a cellular level but also results in clinical improvement would be a milestone.

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Cerebral Microbleeds Increase With Age, Rarely Disappear

BY SHERRY BOSCHERT

FROM THE INTERNATIONAL STROKE CONFERENCE

LOS ANGELES – The prevalence of cerebral microbleeds increased from 24% to 28%, and microbleeds rarely disappeared over a mean of 3 years, in a study of 831 older adults in the general Dutch population.

A subset of nondemented adults aged 60 years or older in the Rotterdam Study underwent brain MRI scans and other examinations in 2005-2006 and again in 2008-2010. Independent raters looked for microbleeds in side-by-side comparisons of the baseline and follow-up scans without knowing which was which and without access to other imaging or test results. The mean time between scans was 3.4 years.

People with microbleeds at baseline were five times more likely to develop new microbleeds. Among 203 people with microbleeds on the first scan, 25% had new microbleeds on the second scan compared with 5% of 628 people without microbleeds at baseline, Dr. Mariëlle M.F. Poels said at the conference.

The risk was even higher in people who had multiple cerebral microbleeds at baseline, who were seven times more likely to develop new microbleeds compared with people with no microbleeds on the initial scan, said Dr. Poels of Erasmus University, Rotterdam, the Netherlands.

While 258 new microbleeds developed between the first and second scans, only 18 seemed to disappear.

DR. POELS

The incidence of microbleeds increased with age, from 8% in people aged 60-69 years to 19% in people older than 80 years (Stroke 2011;42:656-61).

Previous longitudinal studies of cerebral microbleeds were smaller and focused on patients seen at memory clinics or patients with cerebral amyloid angiopathy instead of the general population.

VITALS

Major Finding: Cerebral microbleeds were present in 24% of elderly people in the general population, increased in number with age, and rarely disappeared over time.

Data Source: Repeat brain MRI scans a mean of 3 years apart in 831 elderly nondemented adults within the longitudinal Rotterdam Study.

Disclosures: Dr. Poels and her associates said they had no relevant financial disclosures.

The study used a three-dimensional T2*-weighted gradient-recalled echo sequence to detect microbleeds, defined as focal areas of very low signal intensity. The investigators used other MRI sequences to rate infarcts and used a validated tissue classification technique to assess white matter lesion volume. They collected DNA samples for apolipoprotein E genotyping.

Only six people (3%) had fewer microbleeds at follow-up compared with baseline. Four of these six had one microbleed on the initial scan and none at follow-up. The fifth person had two microbleeds at baseline and one at follow-up. The number of microbleeds in the sixth person decreased from 11 at baseline to 6 at follow-up, Dr. Poels said at the conference, sponsored by the American Heart Association.

In addition, another six people had some microbleeds on the initial scan that had disappeared at follow-up, but they also had new microbleeds, so their total number of microbleeds did not decrease over time. All but one of these six had more than five microbleeds at baseline and a higher number at follow-up.

In the entire cohort, 258 new microbleeds developed between the first and second scans, and only 18 microbleeds seemed to disappear. "Microbleeds rarely disappear," she said.

The location of microbleeds at baseline strongly predicted the location of

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