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Compound shows potential for slowing progression of ALS

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A chemical cousin of a drug currently used to treat sepsis dramatically slows the progression of amyotrophic lateral sclerosis, better known as ALS or Lou Gehrig's disease, in mice. The results offer a bit of good news in efforts to develop a therapy to stop or slow the progression of a disease that generally kills its victims within just a few years.

In a paper published online Oct. 19 in the *Journal of Clinical Investigation*, scientists studied the use of a form of an enzyme known as activated protein C, or APC, to slow the cell death that occurs in ALS. They were able to extend the lifespan of mice with an aggressive form of the disease significantly, by about 25 percent. The compound also extended the length of time that the mice were able to function well despite showing some symptoms of the disease, and it reduced the pace of muscle wasting that is a hallmark of ALS.

While the investigators say that more research must be done before the enzyme is tested in people with the disease, they are encouraged that the work involves a compound that has already been proven to be safe and is currently given to patients via a common injection for another condition. The team hopes to test a treatment in patients within five years.

The work was done by investigators from the University of Rochester Medical Center, the University of California, San Diego School of Medicine, The Scripps Research Institute in La Jolla, University of Notre Dame, and a Rochester-based start-up biotech company, Socratech.

Corresponding author of the study is neuroscientist Berislav Zlokovic, M.D., Ph.D., of the University of Rochester Medical Center, whose group collaborated with laboratories led by Don Cleveland, Ph.D., a widely recognized ALS expert at UC San Diego, and John Griffin, Ph.D., an APC expert at Scripps. First authors of the paper were Instructor Zhihui Zhong of Rochester and post-doctoral associate Hristelina Ilieva of UC San Diego.

The research involved mice with a mutation in a gene known as superoxide dismutase 1 (SOD1), which plays an important role keeping cells safe from damaging molecules known as free radicals. While the cause of most cases of ALS is unknown, scientists do know that SOD1 plays a role in approximately 3 or 4 percent of cases - providing an opportunity to study the disease's initial steps, which occur long before key nerve cells appear sick or die. In addition, recent studies have suggested that the accumulation of mutant forms of SOD1 is linked to most sporadic cases of ALS.

Cell death is central to the symptoms of ALS, a chronic disorder of motor neurons in the brain, brainstem and spinal cord which results in a progressive paralysis that generally kills individuals within five years of onset. Currently there is no cure or even a treatment that can effectively slow disease progression.

In a surprising finding last year, a team led by Zlokovic and Cleveland found that SOD1 mutations weaken the crucial natural barrier between blood and the spinal cord. In effect, blood vessels in the spinal cord become leaky, allowing toxic substances to flood into the spinal cord. Because of the defect, motor neurons are exposed directly to biochemical byproducts of hemoglobin such as iron, which forms reactive oxygen molecules that injure or kill neurons.

Now, the team has shown that APC dramatically lessens the activity of

the SOD1 mutation. This protects neurons that are under assault by blocking the synthesis of aberrant forms of the molecule in motor neurons and other cells in the spinal cord. These include microglia cells, which the Cleveland laboratory has shown play a key role in the inflammatory response and progression of ALS. In addition to reduced SOD1 activity, the flow of dangerous byproducts of hemoglobin into the spinal cord was eliminated by APC, saving neurons.

Currently the group is studying alternate forms of APC, in an effort to create the form that best quells the symptoms of ALS while causing few unwanted side effects, such as bleeding. Zlokovic says the form of APC currently used to treat sepsis carries an increased risk of bleeding and likely will not be appropriate for treating ALS in humans.

While other researchers are exploring the possibility of silencing SOD1 to treat ALS, Zlokovic notes that most approaches would require invasive surgery and delivery by direct infusion into the spinal cord. APC, in contrast, is already approved as an injection.

"The success of this research project has been very gratifying, and we are hopeful that a form of APC will ultimately be useful as a treatment for this disease," said Zlokovic, who is professor of Neurosurgery and Neurology and director of the Center for Neurodegenerative and Vascular Brain Disorders at Rochester.

"I began this line of research at the request of an old friend - a childhood pal with whom I was friends my whole life, until he got ALS and died just a few years later. It was very sad. Clearly, something has to be done - new treatments are needed," added Zlokovic.

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