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Blocking key enzyme minimizes stroke injury, study finds

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Dr. James Bibb is an associate professor of Neurology and Neurotherapeutics at UT Southwestern and senior author of the study. Credit: UT Southwestern Medical Center

A drug that blocks the action of the enzyme Cdk5 could substantially

reduce brain damage if administered shortly after a stroke, UT Southwestern Medical Center research suggests.

The findings, reported in the June 11 issue of the *Journal of Neuroscience*, determined in rodent models that aberrant Cdk5 activity causes nerve cell death during stroke.

"If you inhibit Cdk5, then the vast majority of brain tissue stays alive without oxygen for up to one hour," said Dr. James Bibb, Associate Professor of Neurology and Neurotherapeutics at UT Southwestern and senior author of the study. "This result tells us that Cdk5 is a central player in nerve cell death."

More importantly, development of a Cdk5 inhibitor as an acute neuroprotective therapy has the potential to reduce stroke injury.

"If we could block Cdk5 in patients who have just suffered a stroke, we may be able to reduce the number of patients in our hospitals who become disabled or die from stroke. Doing so would have a major impact on health care," Dr. Bibb said.

While several pharmaceutical companies worked to develop Cdk5 inhibitors years ago, these efforts were largely abandoned since research indicated blocking Cdk5 long-term could have detrimental effects. At the time, many scientists thought aberrant Cdk5 activity played a major role in the development of Alzheimer's disease and that Cdk5 inhibition might be beneficial as a treatment.

Based on Dr. Bibb's research and that of others, Cdk5 has both good and bad effects. When working normally, Cdk5 adds phosphates to other proteins that are important to healthy brain function. On the flip side, researchers have found that aberrant Cdk5 activity contributes to nerve cell death following brain injury and can lead to cancer.

"Cdk5 regulates communication between nerve cells and is essential for proper brain function. Therefore, blocking Cdk5 long-term may not be beneficial," Dr. Bibb said. "Until now, the connection between Cdk5 and stroke injury was unknown, as was the potential benefit of acute Cdk5 inhibition as a therapy."

In this study, researchers administered a Cdk5 inhibitor directly into dissected brain slices after adult rodents suffered a stroke, in addition to measuring the post-stroke effects in Cdk5 knockout mice.

"We are not yet at a point where this new treatment can be given for stroke. Nevertheless, this research brings us a step closer to developing the right kinds of drugs," Dr. Bibb said. "We first need to know what mechanisms underlie the disease before targeted treatments can be developed that will be effective. As no Cdk5 blocker exists that works in a pill form, the next step will be to develop a systemic drug that could be used to confirm the study's results and lead to a clinical trial at later stages."

Currently, there is only one FDA-approved drug for acute treatment of stroke, the clot-busting drug tPA. Other treatment options include neurosurgical procedures to help minimize brain damage.

Provided by UT Southwestern Medical Center

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