Stroke's 'death signal' discovered; may aid drug development

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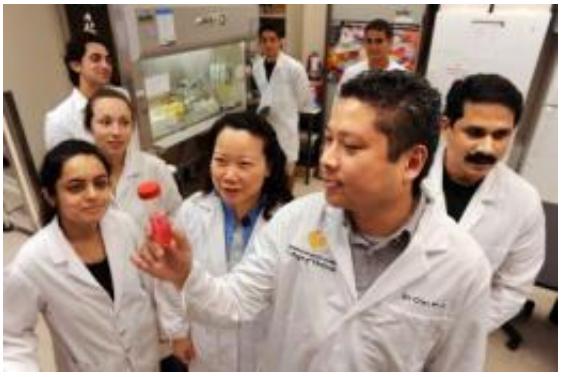

Dr. Sic Chan is an assistant professor at the University of Central Florida in Orlando. Credit: UCF/Jacque Brund

Biomedical scientists from the University of Central Florida and Louisiana State University have identified a way to block a "cell death signal" that they believe triggers brain damage during strokes.

Strokes, also known as cerebral ischemia, are caused by inadequate blood flow to the brain and are the third-leading cause of death in the United States.

The team's work focused on a neurotransmitter that typically plays an important role in communication among nerve cells in the brain and fosters learning and memory. This glutamate neurotransmitter opens the NMDA (N-methyl-D-aspartate) receptors, allowing the entry of calcium

into the nerve cells.

Under normal conditions, the activity of the NMDA receptors is tightly regulated to prevent nerve cells from becoming overloaded with calcium. During a stroke, however, that process of regulation breaks down. The excessive influx of calcium through NMDA receptors kills the nerve cells and can cause severe brain damage.

Striving to prevent such calcium overloads, the research team discovered that an enzyme, DAPK1 (Death-Associated Protein Kinase 1), binds to a portion of the NMDA receptor and acts as a "cell death signal" during strokes.

Researchers hypothesized that by preventing DAPK1 from binding with the NMDA receptors, they could prevent the calcium overloads and cell deaths. They developed a potent compound to test their theory and found that the compound blocked DAPK1, protecting brain cells against stroke injury, and did not affect the beneficial physiological functions of the receptors.

The findings appear in the Jan. 22 issue of *Cell*, one of the leading journals in the field.

"It is conceivable that this study not only provides new insights into the cellular and molecular basis responsible for stroke damage, but also provides a therapeutic target for stroke therapy," said Youming Lu, the LSU professor who led the team of scientists.

The findings also may have significant implications for developing therapeutic drugs to treat other neurodegenerative diseases, said UCF Assistant Professor Sic Chan, a study collaborator who has done extensive research on the role of calcium in neurodegenerative diseases such as Alzheimer's and Parkinson's.

"Anytime we gain an increased understanding of the molecular mechanism of neurodegeneration, that enhances our ability to make better drugs," he said.

To date, all stroke clinical trials targeting glutamate receptors have failed, largely because of their side effects, an inefficient delivery of compounds from the blood to the brain or the length of time it takes for the drugs to work effectively.

Provided by University of Central Florida