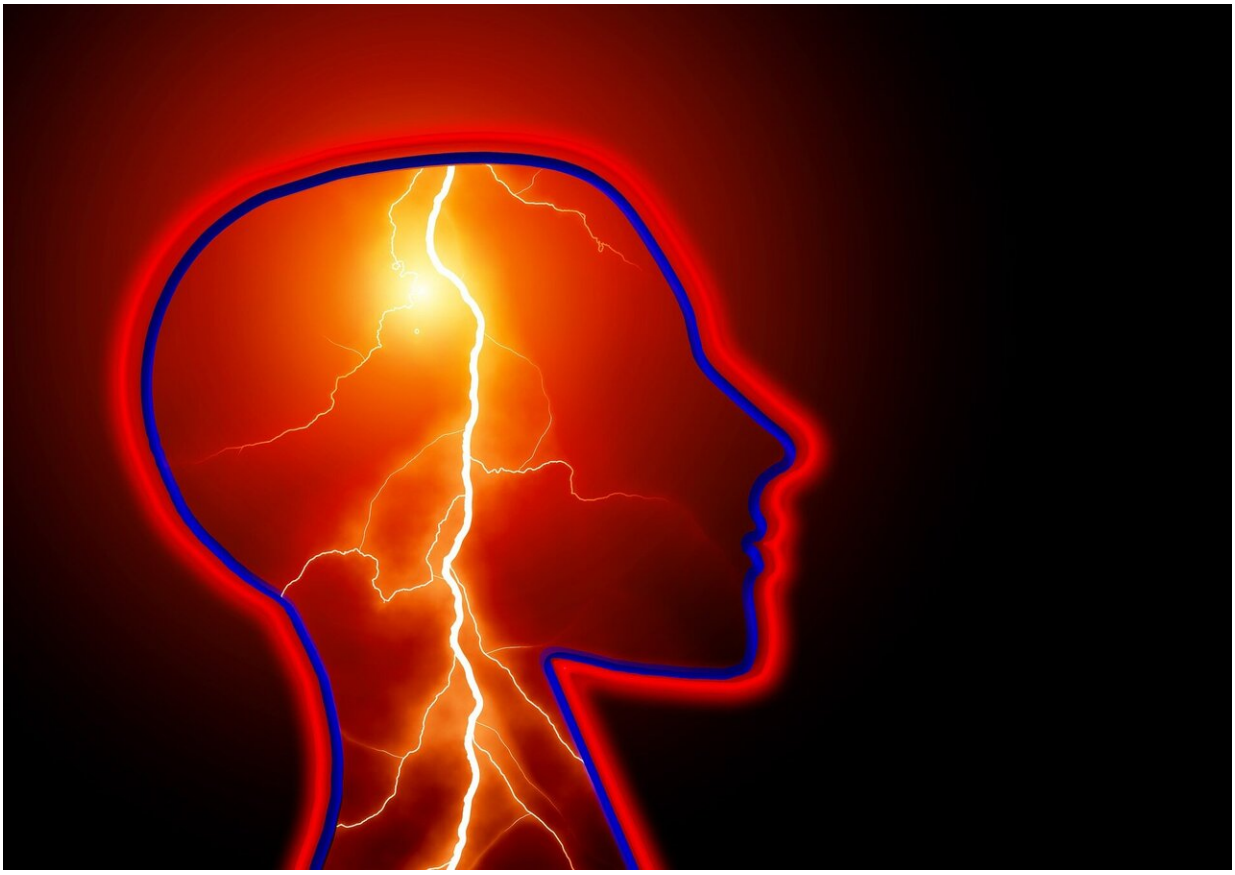
Family of proteins offers promise as ischemic stroke treatment, preclinical trial finds

September 1 2021



Credit: CC0 Public Domain

Boosting a family of naturally occurring proteins that dampens inflammation in the body has been shown to be effective in reducing

damage from an ischemic stroke, according to preclinical researchers at The University of Texas Health Science Center at Houston (UTHealth).

Called inter-alpha inhibitor proteins (IAIP), the family of structurally related proteins—produced largely in the liver and found in high concentrations in the plasma—has broad anti-inflammatory activity. The study was published today in *The Journal of Clinical Investigation*.

"By extensively testing for neuroprotective role of IAIPs in stroke, we found that IAIPs offer remarkable neuroprotection and could potentially represent an important, novel treatment for ischemic stroke," said Venugopal Reddy Venna, Ph.D., senior author of the report and an assistant professor in the Department of Neurology at McGovern Medical School at UTHealth. "To test the clinical relevance of these proteins, we first studied for changes of IAIP using blood and brain samples from stroke patients. Next, to study the role of these IAIPs, we performed experiments in mice, using clinically relevant stroke models to mimic the most common strokes seen in patients. Finally, we used genetically engineered mice in which a receptor for complement activation is deleted to identify the mechanism of action of this family of blood-derived proteins."

Stroke is the primary cause of long-term adult disability and fifth-leading cause of mortality in the U.S. Ischemic strokes, which account for 80% to 85% of all strokes, are caused by a blockage in an artery that supplies blood to the brain. The blockage reduces the blood flow and oxygen to the brain, leading to damage or death of brain cells.

The researchers discovered that naturally occurring levels of IAIP dropped in mice and humans after stroke. They also found that administering supplemental purified IAIP in mice immediately after ischemic stroke reduced the size of the damaged area and limited brain swelling.

Importantly, even delayed administration of IAIP reduced the size of the damaged area and improved functional recovery even when the therapy was administered 4.5 hours after ischemic stroke onset. Moreover, treating the mice anywhere from six hours to nine days after stroke (known as "extended delayed treatment") also showed benefit, with reduced brain atrophy and improved long-term recovery.

IAIP was also most effective in mice when used in combination with tissue plasminogen activator (t-PA), which is currently the only Food and Drug Administration-approved pharmacotherapy for the treatment of acute ischemic strokes. The combination significantly reduced the size of the damaged area in the brain compared to t-PA alone, and reduced bleeding in the brain. These proteins may be a viable treatment for stroke patients, the authors wrote.

More information: Louise D. McCullough et al, Exogenous inter-α inhibitor proteins prevent cell death and improve ischemic stroke outcomes in mice, *Journal of Clinical Investigation* (2021). DOI: 10.1172/JCI144898

Provided by University of Texas Health Science Center at Houston