International study uncovers a molecule that could alleviate stroke-related brain injury

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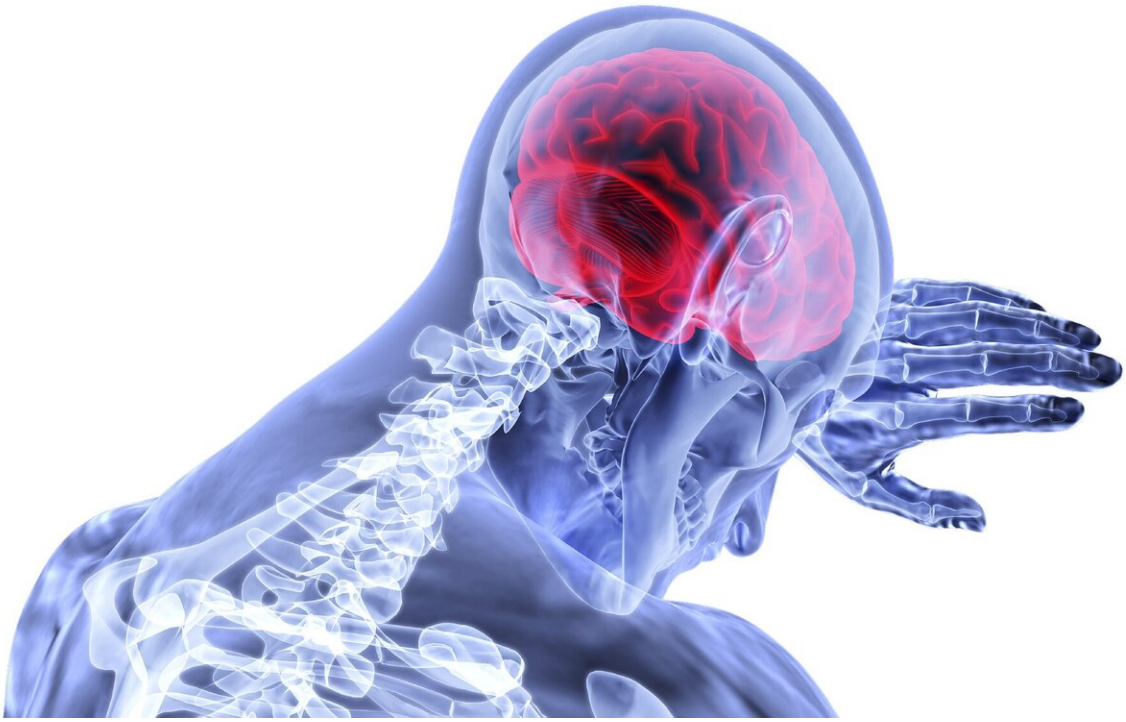

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A newly developed molecule, LK-2, could inform new therapies for stroke-related brain injury, find scientists at The Hospital for Sick Children (SickKids).

An ischemic stroke occurs when blood flow to a part of the brain is

interrupted, depriving the brain cells of oxygen and nutrients. Without timely treatment, brain cells can die, resulting in permanent damage to the brain and its functions. Stroke is one of the leading causes of death and disability worldwide, affecting millions every year.

An international study published in Nature co-led by Dr. Lu-Yang Wang, a Senior Scientist in the Neurosciences & Mental Health program at SickKids, and clinician scientists at the Shanghai Jiao Tong University School of Medicine, has uncovered a molecule that holds the potential to protect neurons during stroke and prevent stroke-related brain damage.

"Our findings provide an entirely new way to think about saving cells while minimizing the adverse neural side effects of conventional stroke therapy," says Wang, who holds a Tier 1 Canada Research Chair in Brain Development and Disorders. "The LK-2 molecule could be the key to unlocking successful therapeutics for stroke patients."

How one neurotransmitter is contributing to stroke-related brain damage

One of the main culprits behind stroke-induced brain damage is a neurotransmitter called glutamate. When the brain is starved of oxygen and sugar, glutamate levels rise dramatically, overstimulating N-methyl-Daspartate receptors (NMDARs) on the membrane of brain cells. This causes a surge of calcium to enter cells, triggering a cascade of events that ultimately leads to cell death.

For decades, researchers have tried to develop drugs that can block NMDARs and prevent the neurotoxicity that comes with elevated levels of glutamate.

However, previous drugs targeting NMDARs have been ineffective and

failed to move beyond clinical trials because NMDARs play important roles in regular brain functions, such as learning and memory. In addition, blocking NMDARs completely can cause serious side effects, such as psychosis and cognitive impairment.

The team found that glutamate can also bind to and activate a type of acidosis sensor called acid-sensing ion channels (ASICs), which are normally activated by acids. ASICs are present in the membrane of brain cells—like NMDARs—and can allow calcium ions to enter the cells when stimulated.

"We have shown that glutamate can supercharge the activity of ASICs, especially under the acidic conditions that occur during stroke," explains Wang. "This means that glutamate is attacking brain cells through both NMDARs and ASICs—something we did not know before now."

A new way to block excess glutamate

By identifying the specific site in ASICs where glutamate binds, the team was able to develop a new molecule, called LK-2, that can selectively block the glutamate binding site in ASICs, but leave NMDARs intact.

In preclinical models, the team found that LK-2 effectively prevented glutamate from overstimulating ASICs to reduce the flow of calcium and cell death. Furthermore, LK-2 did not affect NMDARs or other regular neural transmissions, which suggests its potential as the next generation of stroke therapeutics.

"Our research has revealed a new way to protect the brain from glutamate toxicity without interfering with NMDARs," Wang says.

Wang's research will continue to explore the function and mechanisms

of LK-2, in the hopes of developing future clinical trials.

The research team wants to thank Dr. Julie Forman-Kay, a Senior Scientist and Program Head of the Molecular Medicine program, and Dr. Iva Pritišanac, a postdoctoral fellow in Forman-Kay's lab, who assisted Wang in locating the binding sites for glutamate on ASICs.

More information: Lu-Yang Wang, Glutamate acts on acid-sensing ion channels to worsen ischaemic brain injury, *Nature* (2024). DOI: 10.1038/s41586-024-07684-7.
www.nature.com/articles/s41586-024-07684-7

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