New mechanism for stroke treatment shows successful proof-of-concept

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Many people who suffer a stroke are permanently disabled. Stroke remains the leading cause of long-term disability in the United States. Paralysis of one side of the body, speech and language problems, vision problems and memory loss are some of the major consequences of stroke injury.

Every year, nearly 800,000 people in the United States have a stroke. Even with recent advances in treatments to reduce damage and enhance recovery after stroke, solutions are significantly lacking.

Recently, UConn School of Medicine researchers published a paper in *Experimental Neurology* showing how they successfully inhibited an important receptor implicated in post-stroke damage and recovery.

The researchers specifically looked at ischemic stroke, which comprises 87% of strokes. Ischemic stroke occurs when there is a blockage in an artery leading to the brain. This reduces the amount of blood and oxygen getting to the brain, causing damage or death of brain cells.

Damaged or dying brain cells release excessive amounts of stored adenosine triphosphate (ATP), a molecule that carries energy within cells, leading to over-stimulation of its receptor P2X4 (P2X4R). When P2X4R is over-active, it causes a cascade of detrimental effects in brain cells, leading to ischemic brain injury.

In this study, the researchers found inhibition of P2X4R can regulate the activation of a kind of immune cell that plays a large role in post-stroke inflammation.

By partially short-term blocking this receptor, the researchers limited the over-stimulated immune response to improve both acute and chronic stroke recovery.

The method presented in this paper is particularly attractive as it only operates during this period of over-activation and does not inhibit normal functions of P2X4R during long-term recovery.

"Short-term P2X4R inhibition works perfectly to prevent brain damage immediately after stroke as well as during long-term recovery," author

Rajkumar Verma, assistant professor of neuroscience at the UConn School of Medicine and the Pat and Jim Calhoun Cardiology Center at UConn Health, says.

Using mouse models, the researchers observed improved balance and coordination, as well as reduced anxiety after their intervention.

The P2X4R inhibitor treatment decreased the total number of infiltrated leukocytes, which are white blood cells that promote ischemic injury when over abundant.

This treatment effectively reduced the cell surface expression and activation of P2X4R without reducing its total protein level in brain tissue after stroke injury.

One challenge many experimental drugs, including commercially available P2X4R inhibitors, face is insolubility, meaning they cannot enter the body in order to deliver the treatment. The researchers are currently working with team members Dr. Bruce Liang, Dean of the UConn School of Medicine, and Kenneth Jacobson from the National Institutes of Health to develop more soluble and potent novel P2X4R inhibitors.

This technology would have a major impact as there is currently no effective drug to target stroke damage on the market aside from a few narrowly applicable treatment to dissolve blood clot or device to remove it.

"From a drug perspective, we don't have anything for neuroprotection," Verma says. "It's a very big and open market."

With this successful demonstration of their proof of concept, the researchers will continue to refine this method to find the most effective

inhibitors.

More information: Pranay Srivastava et al. Neuroprotective and neuro-rehabilitative effects of acute purinergic receptor P2X4 (P2X4R) blockade after ischemic stroke, *Experimental Neurology* (2020). DOI: 10.1016/j.expneurol.2020.113308

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