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Study suggests way to bring stroke treatment in from the cold

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(Medical Xpress) -- Investigating the mechanism behind a common emergency medical procedure known as therapeutic hypothermia, a team of researchers at the University of California, San Francisco (UCSF) and the San Francisco VA Medical Center (SFVAMC) has found a potential new target for drugs that would help protect patients against brain damage after heart attacks or stroke.

When people suffer heart attacks and strokes, depriving their brains of oxygen-rich blood, one way doctors mitigate long-term brain damage is by artificially chilling the head, neck and spine. Doctors have known for years that such therapeutic hypothermia procedures improve outcomes for patients in later recovery – but nobody knew exactly why.

Now the UCSF and SFVAMC team has discovered part of the reason for this protection: cooling the patients shuts down proteins, called "calcium-sensing receptors," on the surfaces of neurons in their brains.

In experiments in mice described at the 63rd Annual Meeting of the American Academy of Neurology in Hawaii last week, the researchers showed that having fewer calcium-sensing receptors helped mice survive with more neurons intact after ischemia.

"This calcium receptor could be an important target to protect the neuron," said UCSF and San Francisco VA Medical Center endocrinologist Wenhan Chang, PhD, a senior author on the study.

From the Ground to the Bones

The work started with a project looking at how the body maintains control over the concentration of blood calcium, one of the most abundant elements in the Earth's crust and a crucial mineral for human health. Calcium is a key constituent of bones, and it also plays a role in cells throughout the body, helping to run the microscopic metabolic machinery that keeps our tissues working.

The body maintains tight control over the levels of calcium in the bloodstream, and losing control over these levels can be dangerous. Too little calcium can deplete the bones of minerals and lead to osteoporosis. Too much, on the other hand, can be toxic to the body's tissues.

Years ago, Chang's mentor, Dolores Shoback, MD, of UCSF and the VA Medical Center discovered that one of the key players in helping maintain the optimal balance is the calcium-sensing receptor – a protein that they found on cells in small bits of hormone-producing tissues in the neck known as the parathyroid glands.

An endocrinologist by training, Chang spent years investigating how these proteins detect minuscule dips in the body's calcium concentration and respond by inducing parathyroid cells to release more of the hormone that releases calcium from bones. It all seemed to make sense.

A few years ago, however, Chang discovered something that did not make sense: these same receptors could also be concentrated in high levels on the surface of neurons in the brain.

Wondering why, Chang formed a collaboration with neurologist Midori Yenari, MD, at UCSF and the San Francisco VA Medical Center. Working with research associates Jong Youl Kim, PhD, and Zhiqiang Cheng, MD, they discovered that the calcium-sensing receptor also plays

an important role in ischemia.

Protecting the Neurons

In their study, Chang and Yenari showed that when mice have ischemia, preventing blood from reaching their brains, the levels of calcium-sensing receptor protein dramatically increase on the surface of neurons in their brains. They also found that these levels correlate directly with whether the neurons are likely to die as a result of the injury.

When the brain is chilled, the cooling reduces the concentration of these calcium-sensing receptors, which protects the neurons. But Chang and Yenari reasoned that they might be able to achieve the same protection without the cooling – by blocking the expression or activity of these receptors in mice brains. Doing so, they found, protected mice against brain damage after ischemic injuries. Conversely, mice with an overabundance of these calcium-sensing receptors on the surfaces of their neurons were more prone to permanent brain damage from ischemia.

Because inhibiting this receptor protects neurons, said Chang, “That provides an opportunity for us to use it as a pharmaceutical target.”

The presentation, “Mild Hypothermia Suppresses Ischemia-Induced Extracellular Calcium-Sensing Receptor (CaSR) Induction: A Possible Therapeutic Target?” was authored by Jong Youl Kim, Nuri Kim, Wenhan Chang, Midori Yenari.

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