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New understanding about mechanism for cell death after stroke leads to possible therapy

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Scientists at the Brain Research Centre, a partnership of the University of British Columbia Faculty of Medicine and Vancouver Coastal Health Research Institute, have uncovered new information about the mechanism by which brain cells die following a stroke, as well as a possible way to mitigate that damage. The results of the study were recently published online in *Nature Medicine*.

Following a stroke, many brain cells continue to die even after blood flow has been restored. Researchers have long known this is due to a complicated cascade of cellular messages that lead to the "self-destruction" and death of brain cells.

The team of Brain Research Centre scientists discovered that, in animal models, the over-activation of NMDA receptors—special receptors on the surface of brain cells—activates another protein, called SREBP-1, which subsequently causes cell death. SREBP-1 is found naturally in cells throughout the body and is involved with cholesterol and other fat production.

NMDA receptors control the movement of calcium in and out of brain cells, which is necessary for normal brain function. However, following a stroke, levels of glutamate—the most abundant chemical messenger in the brain—rise rapidly in cells, leading to over-activation of NMDA receptors, an excess of calcium entering cells, and the onset of cell death.

The researchers found that under normal conditions, SREBP-1 is largely

kept in an inactive form by a protein known as Insig-1. After a stroke, over-activation of NMDA receptors leads to a rapid degradation of Insig-1, which increases the level of active form of SREBP-1.

"How over-activation of NMDA receptors caused cell death after a stroke has been a mystery," says Dr. Yu Tian Wang, co-lead on the study, a Professor in the UBC Division of Neurology, and the Heart and Stroke Foundation of BC & Yukon Chair in Stroke Research. "We found that SREBP-1 was one of the missing key players in that process."

While the detailed mechanisms by which activation of SREBP-1 leads to brain cell death remain to be established, the researchers discovered a way to inhibit SREBP-1 and thereby significantly reduce cell death.

"We developed a drug that can stabilize Insig-1, which in turn inhibits the activity of SREBP-1," says Dr. Max Cynader, co-lead on the study, a Canada Research Chair in Brain Development, and the Director of the Brain Research Centre. "By doing so, we were able to prevent cell death."

The researchers also found that the drug works post-stroke in animal models. "When we administered it post-stroke, there was less brain cell damage 30 days later than compared to controls," says Dr. Wang. "This is important because previous studies focused on blocking the NMDA receptors in order to prevent cell death, but this approach didn't work because it affected normal cell function and had a relatively short therapeutic window. The drug we studied works downstream of NMDA receptors and appears to have less detrimental side effects with a much improved therapeutic window."

Further investigations will help researchers understand how SREBP-1 causes cell death and to further determine efficacy of the drug. As well, because of the protein's connection to cholesterol synthesis and other

cellular functions, further investigations may reveal if it has a role in other neurological disorders, such as ALS, and whether the drug might be effective for those conditions as well.

Source: University of British Columbia (news : web)