

NEWS RELEASE

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New understanding of why brain cells die after stroke will lead to development of new treatments

(Toronto – December 24, 2003) – Scientists at Toronto Western Hospital and the University of Toronto have found a major mechanism that causes brain cells to die from stroke. They discovered that when brain cells are deprived of oxygen and vital nutrients, as happens to parts of the brain affected by a stroke, a special channel on the surface of those brain cells is activated, triggering a lethal chain reaction. The channel, called TRPM7, when activated causes brain cells to produce large quantities of free radicals – toxic molecules that break down the cell's DNA, proteins, and other components. Free radicals also cause TRPM7 to become even more active, causing massive overproduction of free radicals, resulting in death of the brain cell.

In a study published in the December 26 issue of *Cell*, an international science journal, the scientists also report that they have found a way to interfere with this lethal chain reaction. While brain cells can only survive for a few minutes without oxygen, interfering with the activity of TRPM7 allows brain cells to survive for more than three hours without oxygen and vital nutrients.

With this new understanding, there is now an opportunity to develop new medications that prevent activation of the TRPM7 channel. It will take approximately three years to develop a medication.

“This is a quantum leap forward in understanding how stroke causes brain damage,” says Dr. Michael Tymianski, neurosurgeon at the Krembil Neuroscience Centre at Toronto Western Hospital and associate professor of surgery and physiology at the University of Toronto. “Now we can see the bigger picture of why brain cells die from stroke.”

“This project is a primary example of how basic and clinical scientists can come together as an effective research team to tackle the major health problem of stroke,” says Dr. John MacDonald, Chair of the Department of Physiology, Faculty of Medicine at the University of Toronto. “We are also very excited to explore the many potential functions of TRPM7 channels in the brain.”

Until now, scientists thought they understood why brain cells die when deprived of oxygen and essential nutrients. Past research suggested that the major culprit was glutamate, an amino acid normally used by brain cells to communicate by carrying signals from one brain cell to the next. Dying brain cells release glutamate, which attaches to a special channel called the NMDA receptor located on the surface of the neighbouring brain cells. This causes the NMDA channel to open and allows an influx of calcium ions into the brain cell. For years, it was thought that this sequence of events caused brain cells to die from stroke.

For this reason, many experimental medications for treating strokes were aimed at blocking the effects of glutamate on NMDA receptors. Although it worked in the lab, the medications failed to reduce brain damage in humans. Despite three decades of research that pointed to glutamate as the culprit in cell death, the failure of these medications remained a mystery. To solve this mystery, Drs. Tymianski and MacDonald went back to the drawing board and discovered that glutamate was only one part of the reason why brain cells die from stroke.

“We have significant experience in translating such basic discoveries into drugs that might help patients. With this new knowledge, we will now focus on developing medications that we can inject into stroke patients up to several hours after a stroke. These medications will prevent the consequences of activating TRPM7, extend the life of brain cells after a stroke, and help improve the outcome of patients suffering from a stroke.”

As the fourth most common cause of death in Canada, and the second leading cause of death in the world, stroke kills about 16,000 Canadians every year. Stroke is a major cause of disability, as people who survive strokes suffer irreparable damage to their brain cells. These effects can include partial paralysis, problems with thinking, problems with language, and difficulty with movement. Approximately 300,000 Canadians live with the effects of stroke. The warning signs of a stroke include sudden weakness, trouble speaking, vision problems, headache, and dizziness.

This research was funded by grants from the Canadian Institutes of Health Research, the Ontario Heart and Stroke Foundation, and the National Institutes of Health of the United States of America.

Toronto Western Hospital has been serving the health care needs of its culturally diverse community for more than 100 years. Today, the hospital provides highly specialized tertiary care to people from surrounding areas and across Canada. Home to the Krembil Neuroscience Centre, one of the largest combined clinical and research neurological facilities in North America, the hospital also offers a community and population health program and expertise in musculoskeletal health and arthritis. Toronto Western Hospital is one of three hospitals – including Toronto General Hospital and Princess Margaret Hospital – that make up University Health Network, a teaching hospital of the University of Toronto.

The University of Toronto (U of T), Canada's leading research university with over 60,000 students, was founded in 1827 by British royal charter. For the tenth consecutive year, U of T has taken the top spot among medical/doctoral universities in the annual Maclean's magazine university ranking. The university now comprises 31 divisions, colleges and faculties on three campuses, including 14 professional faculties, numerous research centres and Canada's largest library system – one of the top research libraries in North America. U of T's Department of Physiology is the largest and most research-intensive university physiology department in Canada and has research and training partnerships with numerous hospital-based research institutes.

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Diagram and flow chart are available.

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A stroke is a "brain attack" that blocks blood flow to the brain or causes bleeding in the brain. Symptoms include paralysis, dizziness, difficulty speaking, or difficulty with movement.

The lack of blood flow to the brain deprives brain cells of oxygen and glucose. Brain cell A is deprived of oxygen and glucose, and it releases glutamate, an amino acid normally used for cell communication.

Glutamate binds to the neighbouring brain cell B at a channel called NMDA, located on the surface of the cell.

NMDA opens and allows calcium ions (Ca^{2+}) to enter brain cell B.

The influx of calcium ions causes free radicals, called NO (nitric oxide), to be released inside cell B.

NO activates another channel on the cell's surface, called TRPM7, which opens and allows more calcium to enter the cell.

This sets off a toxic cycle, which continues until the cell dies:

additional calcium through TRPM7 causes more free radicals to be released;

more free radicals causes additional calcium to enter the cell through TRPM7.

Free radicals destroy the brain cell by causing the breakdown of proteins, DNA, and other parts of the cell.



