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Mice with a migraine show signs of brain damage

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Migraines may be doing more than causing people skull-splitting pain. Scientists have found evidence that the headaches may also be acting like tiny transient strokes, leaving parts of the brain starved for oxygen and altering the brain in significant ways.

A paper describing the work by neuroscientists at the University of Rochester Medical Center appeared online April 29 in *Nature Neuroscience*.

The scientists say the work makes it crucial for migraine sufferers to do everything they can to prevent their headaches. While avoiding severe pain has long been a motivating factor, the scientists say the risk of brain damage makes it imperative to prevent the headaches, by avoiding a person's triggers for the headaches and by using medications prescribed by doctors to prevent them.

"Normally, the focus of migraine treatment is to reduce the pain. We're saying that migraines may be causing brain damage, and that the focus should be on prevention, which will stop not only the pain but also minimize potential damage," said Maiken Nedergaard, M.D., Ph.D., the neuroscientist who led the research team. She is a professor in the Department of Neurosurgery and a member of the Center for Aging and Developmental Biology and worked closely with Takahiro Takano, Ph.D., research assistant professor, who is first author of the paper.

By combining two recently developed imaging technologies, Nedergaard's team was able to get an unprecedented look at the events that happen in the brain of a mouse as a migraine unfolds. The team uncovered a complex, unexpected tale of supply and demand regarding blood flow and oxygen.

In short, the team found that the brain develops a voracious demand for energy as the organ attempts to restore the delicate chemical balance that is lost in the initial throes of a phenomenon known as cortical spreading depression, which is thought to underlie many migraines.

Even though the brain's arteries expand dramatically and make a great deal more oxygen-rich blood available to meet the demand for energy, some parts of the brain still wind up experiencing severe oxygen shortage, or hypoxia. This causes parts of brain cells' sophisticated signaling structures to disintegrate, similar to what occurs when a person has a mini-stroke, or after a severe injury, or when blood flow to the brain is completely stopped, such as during a heart attack.

"In mice, the damage from these episodes looks exactly like the damage that occurs to the brain from repeated TIAs, or transient ischemic attacks," said Takano. "It's long been known that patients having a migraine attack are functionally impaired from the pain. It's also been shown recently that with repeated migraines, a person's cognitive abilities decrease. But actually doing damage to the brain – that is a surprise."

Deborah Friedman, M.D., a neurologist who was not involved in the study, says that a few studies have found that people who get auras with their migraines are at increased risk for vascular problems like heart attack and stroke. The Women's Health Initiative, for instance, found that such women had a 50 to 70 percent higher risk of stroke compared to other women. And a study led by Michel Ferrari of Leiden University in the Netherlands showed that in women under the age of 45, those who suffered from migraines were much more likely to have the type of brain damage done by a stroke, even though they had never reported symptoms of stroke.

Friedman, a member of the board of directors of the American Headache Society who has treated thousands of headache sufferers, echoes Nedergaard's call for a greater emphasis on prevention.

"It's astounding just how many migraine sufferers do not see a doctor and are not on a medication to prevent a recurrence," said Friedman, professor of Ophthalmology and Neurology. "It's estimated that less than 20 percent of people who should be on preventive treatment receive such treatment. Doctors and patients need to be diligent and rigorous about using preventive medications for migraine."

The work puts the visual disturbances known as auras that many migraine sufferers report in a different light. The aura that precedes the headaches for at least one out of four migraine sufferers might involve floating black spots, flashing light, or some other visual changes. Nedergaard says those disturbances might actually be a visual sign that parts of the brain are short of oxygen.

In the work described in Nature Neuroscience, Nedergaard studied a phenomenon known as cortical spreading depression, or CSD. The process is now considered by many scientists as the basis for some migraines, particularly those involving an aura. CSD is an electrical event that initially involves a burst of intense activity among the neurons on the surface of the brain, followed by a gradually spreading wave of suppressed brain cell activity.

Many scientists believe that the phenomenon contributes to injury from stroke and from traumatic brain injury as well as migraine.

While it's been widely recognized that CSD underlies some migraines, Nedergaard's team linked the phenomenon for the first time to both severe hypoxia and to damage to brain cells. As a result of CSD, the team found changes to the synapses, the connections between brain cells known as neurons. The team observed that nerve cells swell and begin to disintegrate, with neurons shedding important connections known as dendritic spines – the tiny extensions of an individual neuron's body that usually number in the thousands within a synapse. Mice in the grasp of a migraine lost up to three-quarters of these important cellular components.

Ironically, the team found that during CSD, even though blood flow in the brain overall increases dramatically, some parts of the brain still suffer from a lack of oxygen.

The problem begins as the brain tries to recover from CSD, which throws the proportion of crucial ions like potassium and sodium out of balance, taking away the brain's ability to function efficiently. This change in the proportion of chemicals gradually sweeps across the brain like a slowly spreading wave.

The brain, in turn, is under tremendous stress, developing a voracious appetite for oxygen as it works frantically to restore the proper chemical balance. Oxygen-rich blood pours into the area to allow brain tissue to work overtime; the team found that the brain's arteries expand by more than 50 percent to keep up with the demand.

It's at this stage that Nedergaard observed the unexpected: While blood flow increased, bringing more oxygen overall to the brain, there were still pockets of severe hypoxia. The brain was working so hard to restore the chemical balance and to resume normal cellular function, using so much oxygen, that the brain simply couldn't keep up with the demand.

"Basically, even though the body has really stepped up the availability of oxygen, the brain's demands for oxygen are suddenly so great that the blood vessels in the brain can't keep up," said Nedergaard. "It's a mismatch between supply and demand."

Brain tissue closest to the oxygen-rich blood vessels soaks up the oxygen as fast as they can, leaving tissues further away with a diminished supply. It's like a pride of lion cubs fighting for their mother's milk – a few may get nudged away, go without, and will eventually die. In a brain in the midst of cortical spreading depression, brain cells closest to oxygen-rich blood vessels survive, while cells further away don't get access to the oxygen and are in jeopardy.

"People have always thought that in order to treat a migraine, you treat the pain. We're going beyond that. Migraines could be dangerous. The focus should be on prevention," said Nedergaard, who notes that by the time a person feels pain or notices a visual disturbance, the changes to the brain are already well underway.

To make the finding, the team used a sophisticated laser system known as two-photon imaging to look at the activity of live cells in the intact brain of a mouse. They combined that with a new technique to precisely measure how brain cells allocate and use energy.

Source: University of Rochester Medical Center

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