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The brain's forgotten glial cells

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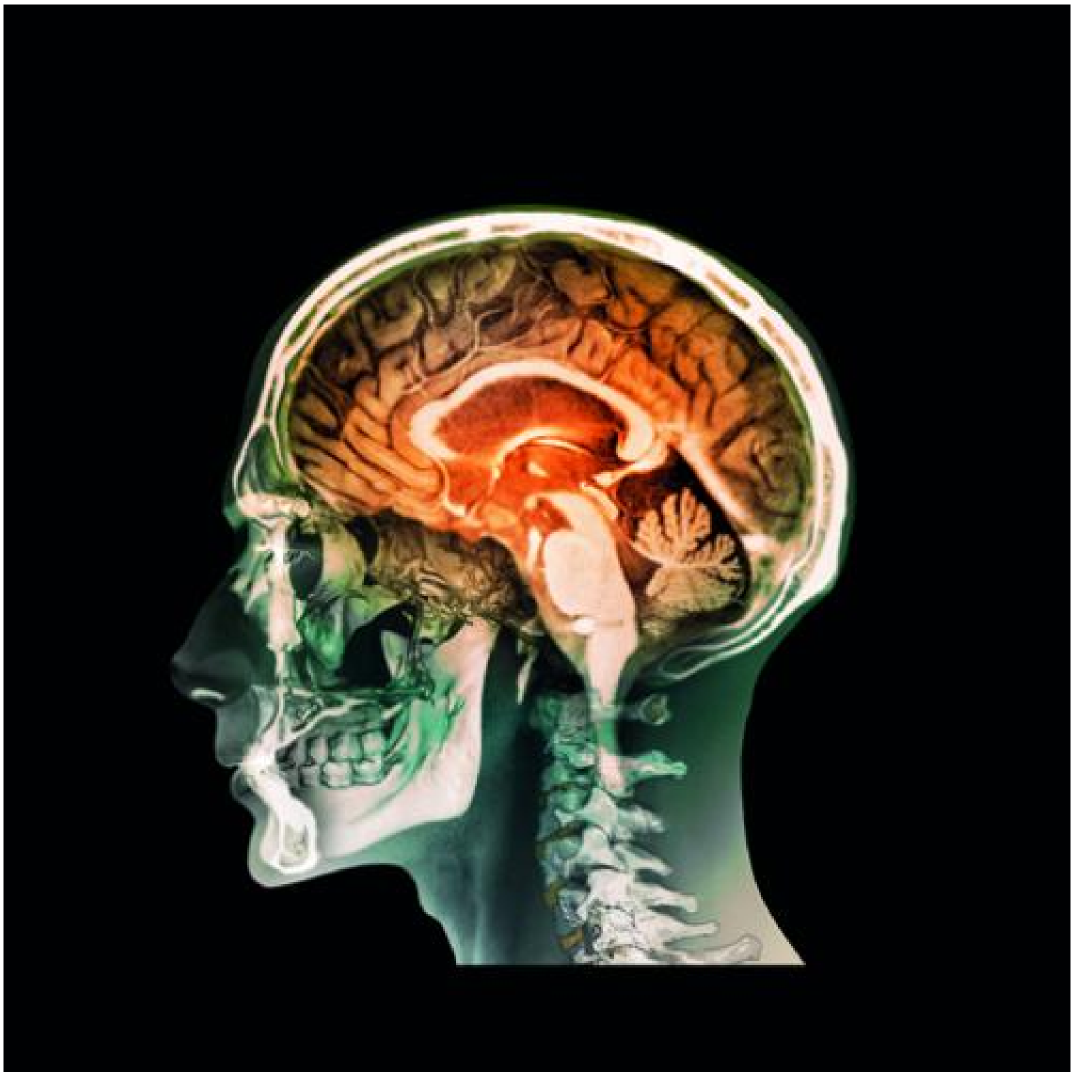

In the post-war period, the most internationally recognized research group at the Faculty of Medicine was located at the Institute of Anatomy. This brain research group, which gradually became known as “The Oslo School of Neuroanatomy”, was world famous for its studies of the cerebellum. The brain research community at the University of Oslo is still considered a world leader to this day.

For a long time, researchers have neglected the 100 million glial cells found in our brains, but that is no longer the case. Now they have discovered that the glial cells cleanse the brain of waste.

New laser technology has enabled us to take a deeper look into the mysteries of the brain, showing that the glial cells are extremely important for its proper function. In the long term, better knowledge about these cells can help improve the treatment of a number of brain diseases, such as epilepsy, migraine, stroke and dementia.

"The glial cells lie between the nerve cells and encircle the blood vessels. There are at least as many glial cells as there are nerve cells in the brain. Because we didn't have the technology to discover their activity, the glial cells were previously regarded as passive support cells. Now we know that the glial cells can communicate with each other and with other brain cells. They just use another language than the nerve cells, which communicate by electrical impulses. The glial cells, on the other hand, use calcium ions and probably play a far more active role in the brain than was previously assumed," says Erlend A. Nagelhus, professor at the Institute of Basic Medical Sciences, University of Oslo.

The brain's washing machine

Nagelhus is head of the Letten Centre and GliaLab, whose objective is to identify the functions of the glial cells, especially the astrocytes – the star-shaped brain cells. One reason why the astrocytes are so crucial is that the water channels are located within these cells.

"These water channels are tiny pores in the astrocytes' cell membrane. The pores are so narrow that only water molecules can pass through them. Many years ago, we discovered that there is a particularly high number of water channels along the brain's surface and around the blood vessels. The function of the water channels long remained a mystery.

Now we know a little more. In contrast to other organs in the body, the brain has no lymphatic vessels. Therefore, we have been unable to understand how it disposes of waste material and excess tissue fluids. In collaboration with researchers in the US we have now shown that the water channels in the glial cells are important for cleansing the brain. The water channels function like a washing machine and help rinse out waste material. At the same time, the water channels may exacerbate other damage, for example in the case of a stroke or a head injury. In conditions like these they can transport too much water into the brain, causing a life-threatening increase in pressure," Nagelhus informs us.

If a sudden brain injury occurs, it will normally be advantageous to stop the flow of water through the channels. Efforts are therefore underway to develop drugs that can block the water channels.

"Sufficiently effective drugs have not yet been developed. Nor is blocking the water channels beneficial for all types of illnesses. Sometimes the water channels will help transport excess fluids and waste products, including in case of illness. These are complex issues that we need to investigate further," PhD scholar Gry Fluge Vindedal adds.

A window to the mysteries of the brain

Many of the projects undertaken by the Nagelhus group seek to find out what happens to the brain's signalling system as we grow older and when the brain is affected by disease.

"To see what happens inside the brain, both how the cells communicate with each other and how the brain rids itself of waste products, we use highly sophisticated laser microscopy. By drilling a hole in the cranium of anaesthetized mice and mounting a small glass pane over the hole, we obtain a kind of window to the mysteries of the brain. We inject fluorescent dyes into the brain, and the laser beams make the cells and matter in the cerebral fluid light up while we take photos. In other words, we can see the disease processes as they unfold, and inject drugs to test their effect," Vindedal explains.

This sophisticated laser technique has enabled the researchers to show that the astrocytes are not silent, and that brain cells can communicate in other ways than by electrical impulses.

"The astrocytes are extremely active, and they also react to the electrical impulses emitted by the nerve cells. A new fluorescent substance that we inject into the mice's brains lights up when the calcium level in the astrocytes increases. This substance permits us to see when the astrocytes communicate with each other and with other brain cells. We seek to understand the interplay between nerve cells, astrocytes and blood vessels. This may help us understand what goes wrong in many different brain disorders," says Nagelhus.

Simulation of a migraine attack

The type of laser microscope used by the group was developed back in the 1990s. However, a long time passed before Norwegian researchers could put this technology to use. Nagelhus himself went to the USA to learn the method. When he returned in 2009, the Letter Centre was established, thanks to a generous donation from the Letten Fund to the University of Oslo. The two laser microscopes at the centre come at a cost of NOK 15 million and provide unique opportunities, since the researchers can look deeply into living tissue without the laser beams causing damage.

"We are also now in the process of studying the aura stage of a migraine attack. In cooperation with Rune Enger, PhD scholar, Vindedal attempts to show what is actually going on in the cerebral cortex during such attacks. Extreme changes occur. A calcium wave sweeps through the cerebral cortex, almost like a tsunami, accompanied by major changes in blood flow," Nagelhus explains.

"We have also established mouse models for epilepsy, stroke and head trauma. It's extremely exciting to look down into the cerebral cortex and follow events from one second to the next," Vindedal adds.

Some researchers believe that the glial cells are also important for our memory.

"We wish to find out more about this. We are in the process of establishing methods for brain imaging on awake laboratory mice. The mice can be trained to run on a treadmill or a polystyrene ball while under the microscope. At the same time, they can be trained to perform simple tasks. Such trials can provide us with knowledge about the importance of glial cells for learning, memory and behaviour," Nagelhus concludes.

Provided by University of Oslo