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Brain cells potentiate harmful electrical discharges during stroke

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In the aftermath of stroke, brain damage is exacerbated by electrical discharges. Researchers at the German Center for Neurodegenerative Diseases (DZNE) have investigated the mechanisms of these "spreading depolarizations" in mice, and found that astrocytes potentiate the fatal discharges. The study highlights potential counter-measures—a signaling pathway that acts upon the calcium concentration in astrocytes may be a potential starting point for treating stroke in humans. Dr. Cordula Rakers and Prof. Gabor Petzold report on these findings in *The Journal of Clinical Investigation*.

The brain depends on a constant supply of oxygen. This is why a stroke can have fatal consequences. Whether caused by cerebral hemorrhage or a blocked artery, the oxygen deficit triggers a rapid loss of nerve cells. Stroke is, therefore, one of the most common causes of death, and even if the patient survives, paralysis, speech difficulties or other disabilities may occur depending on which part of the brain was injured.

The damaged area can even expand, to some extent. This is due to "spreading depolarizations," which can occur minutes after a stroke and may recur over the following days. They start at the infarct core and engulf the surrounding tissue like an avalanche. These electrical discharges put the cells under severe stress. "The spreading depolarizations radiate into the healthy tissue. Each wave can increase the volume of the brain affected by stroke," says Petzold. "Incidentally, these depolarizations do not occur only in stroke but also in other severe brain injuries. Therapy might therefore be relevant for many

neurological diseases."

Favourable opportunities for treatment might arise from the fact that the discharges spread over several days. Petzold notes, "Each wave is potentially harmful. However, the damage occurs gradually as there is a cumulative effect. Treatment could therefore have a positive impact, even if it is given days after the stroke. The time window for treating spreading depolarizations might therefore be larger than in established therapies against stroke."

Harmful interaction between nerve cells and astrocytes

DZNE researchers have now discovered how various events and cell types interact during spreading depolarizations, thereby intensifying the discharge. Cells known as astrocytes play a key role. These cells form a dense network with the brain's nerve cells and are involved in various metabolic processes.

"When nerve cells depolarize, they release large quantities of the neurotransmitter glutamate. Glutamate then diffuses to other cells, in particular to neighboring astrocytes," explains Petzold. "This was known before. However, we have now been able to show what follows this event. The glutamate causes calcium levels in the astrocytes to soar. As a result, the astrocytes release glutamate as well. This in turn can act on nerve cells. A vicious circle emerges that potentiates the spreading depolarizations. This process is amplified by the astrocytes."

The neuroscientists were also able to show that certain drugs can interrupt this chain of events. Ultimately, these drugs reduce the abnormally elevated calcium levels in astrocytes. "At present, there is no established treatment that directly affects spreading depolarizations. Our

results show that it is possible to reduce the frequency and severity of these discharges by modulating the astrocytes' calcium metabolism. In theory, this could also be possible in humans. This could lead to a new approach to treating stroke," says Petzold.

More information: Cordula Rakers et al, Astrocytic calcium release mediates peri-infarct depolarizations in a rodent stroke model, *Journal of Clinical Investigation* (2016). DOI: 10.1172/JCI89354

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