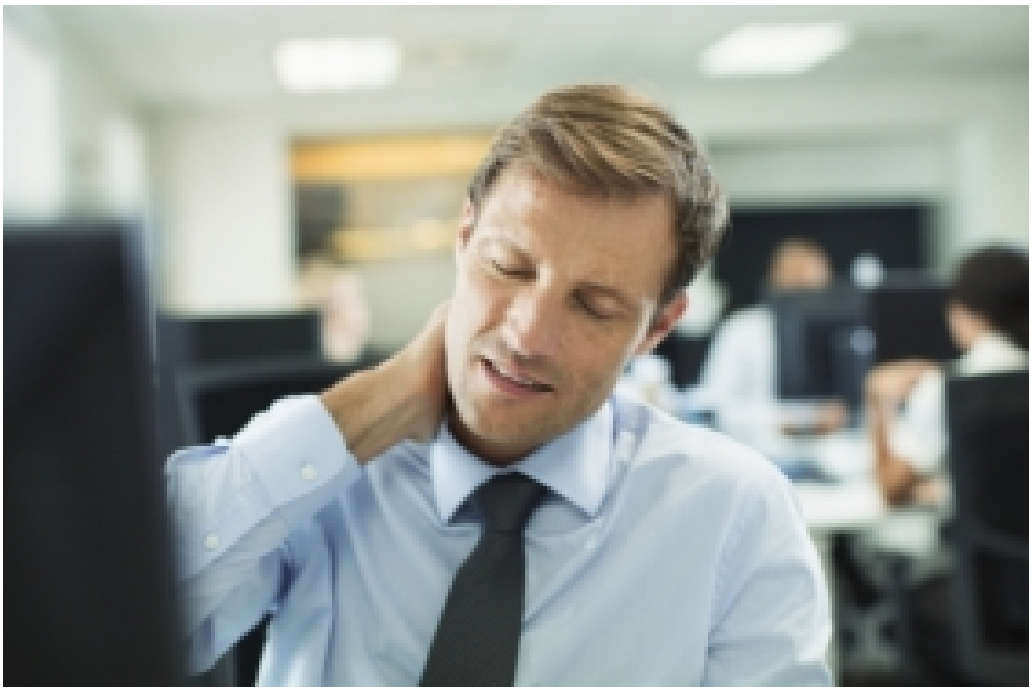
Brain's Support Cells Could Explain Mysterious "Spreading Pain"

Scientists uncover how non-neuronal cells induce synaptic plasticity in pain circuits, potentially across long distances

By Diana Kwon on November 11, 2016



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In people who suffer from pain disorders, painful feelings can severely worsen and spread to other regions of the body. Patients who develop chronic pain after surgery, for example, will often feel it coming from the area surrounding the initial injury and even in some parts of the body far from where it originates. New evidence suggests glia, non-neuronal cells in the brain, may be the culprits behind this effect.

Glia were once thought to simply be passive, supporting cells for neurons. But scientists now know they are involved in everything from metabolism to neurodegeneration. A growing body of evidence points to their key role in pain. In a study published today in *Science,* researchers at the Medical University of Vienna report that glia are involved in long-term

potentiation (LTP), or the strengthening of synapses, in pain pathways in the spinal cord.

Neuroscientists Timothy Bliss and Terje Lømo first described LTP in the hippocampus, a brain area involved in memory, in the 1970s. Since then scientists have been meticulously studying the role this type of synaptic plasticity—the ability of synapses to change in strength—plays in learning and memory. More recently, researchers discovered that LTP could also amplify pain in areas where injuries or inflammation occur. “We sometimes call this a ‘memory trace of pain’ because the painful insult may lead to subsequent hypersensitivity to painful stimuli, and it was clear that synaptic plasticity can play a role here,” says study co-author Jürgen Sandkühler, a neuroscientist also at the Medical University of Vienna. But current models of how LTP works could not explain why discomfort sometimes becomes widespread or experienced in areas a person has never felt it before, he adds.

There are two forms of LTP. In one, synapses strengthen when two neurons transmit signals or “fire” closely in time. The other form, which has long been thought to be dependent on the first, occurs when activity in one circuit reinforces connections in nearby, inactive neural pathways. In their latest study Sandkühler and colleagues show that these two forms of potentiation can, with the help of glial cells, happen independently of each other.

To test the role of glia in pain circuits, the researchers conducted a series of experiments in rat spinal cord slices and live rats and found that they could induce both types of LTP between two pain-related neurons—even in the absence of each other—by activating two types of glia, microglia and astrocytes. In a key experiment they induced LTP in one rat and transferred its spinal fluid to another rat; they found that this could induce LTP in the new animal. These results were evidence that the molecules released from glial cells were capable of strengthening synapses between pain-related neurons on their own. Ru-Rong Ji, a neurobiologist studying pain at Duke University who was not involved in the study, praises the work, but adds, “It would be nice to correlate this measurement with behavioral changes—if you see that the animal not only shows LTP but also shows enhanced or prolonged pain behavior.”

The Sandkühler group’s study is the most recent addition to a growing body of evidence that glia—and the molecules they release—are involved in long-term potentiation in the spinal cord. This is, however, one of the first studies to provide evidence this effect could be transferable across long distances, although more studies are needed to confirm this. For example, an experiment should be able to demonstrate LTP can, with the help of glia, spread throughout the spinal cord of a single animal. This is something Sandkühler and his colleagues are working on now. “The paper is very provocative because it competes with the idea that LTP is really a single synapse thing [and suggests] a more global process,” says Yves De Koninck, a neuroscientist studying synaptic transmission at Laval University in Quebec. He wonders, however, whether the spreading effect is dependent on the level of neural activation, pointing out that the researchers used a strong electrical stimulus to trigger pain-related neurons and activate glial cells in this study. It is possible, he notes, a small amount of activation could lead to strengthening of specific synapses and that the effect starts to spread as activation increases.

The biggest implications of these findings is that molecules released from glial cells in response to a painful stimulus could travel away from the injury site, increasing sensitivity to pain in other parts of the body. Sandkühler also believes glia might be involved in similar mechanisms in the brain, which may explain why physical sickness also has cognitive effects.

“I think that the significance of this work is that it will open up the new thinking,” says Min Zhou, a pain neuroscientist at the University of Toronto who did not take part in the work. “Now we [will start] to look if any additional mechanisms may contribute to pain-related emotional changes in the brain.”

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Diana Kwon is a freelance science writer with a master's degree in neuroscience from McGill University. More of her pieces can be found at www.dianakwon.com.

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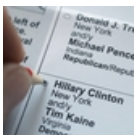

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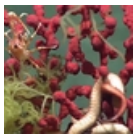

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