Non-neuronal Cells Make "Painful" Contributions

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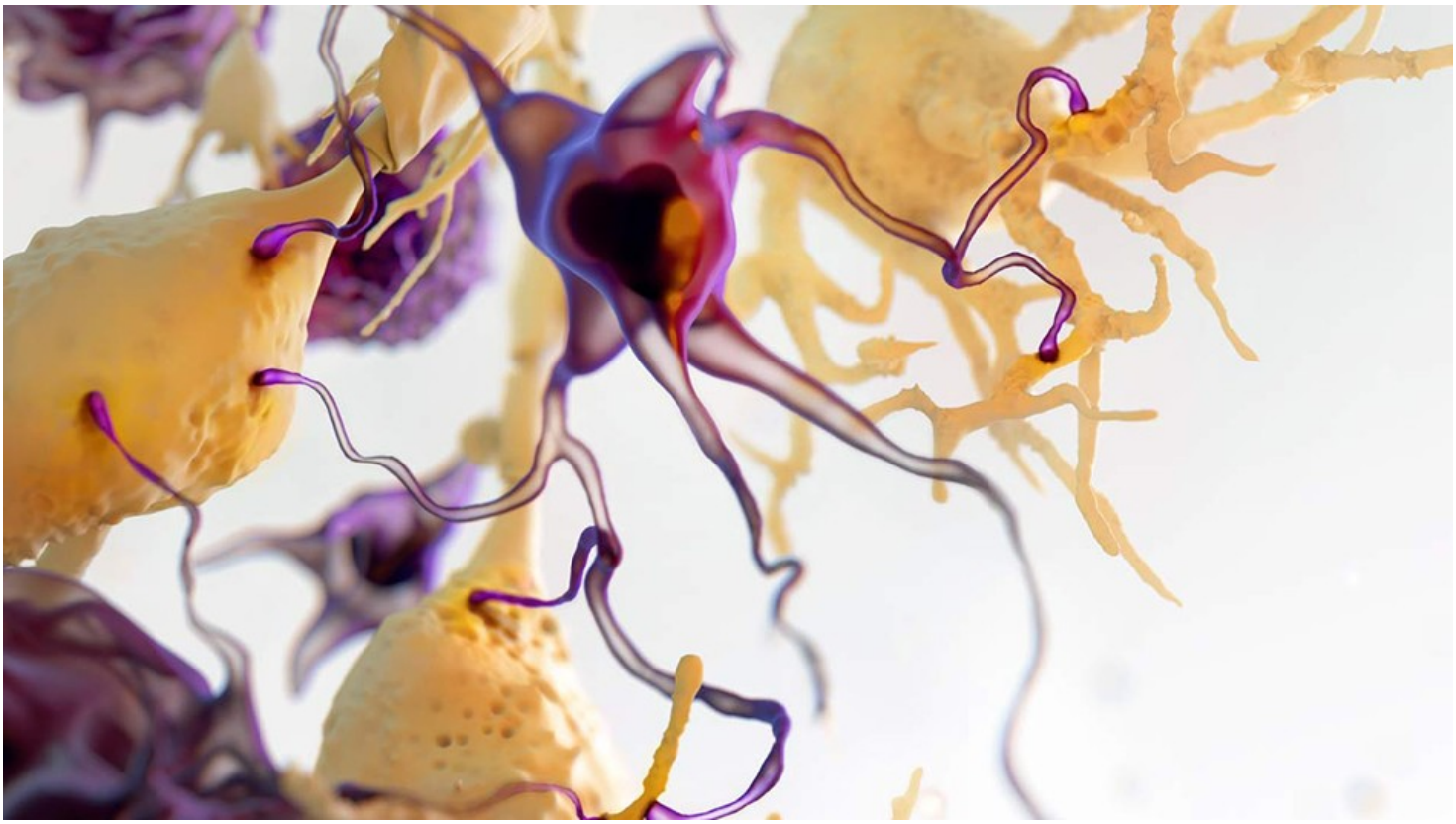

GLIAL CELLS, WHICH PROTECT NEURONS, ALSO PARTICIPATE IN A KEY SIGNALING PATHWAY THAT CAN LEAD TO PAIN HYPERSENSITIVITY. | VAL ALTOUNIAN/ *SCIENCE*

Scientists have discovered that a fundamental nerve pathway associated with memory, learning and pain can be activated and regulated by non-neuronal cells called glia.

This surprising result, reported in a study published in the 10 November issue of *Science,* may help pave the way for new pain therapies, especially those that treat pain hypersensitivity, said Jürgen Sandkühler, professor at the department of neurophysiology at Medical University of Vienna, Austria, and co-author of the paper.

Although it may initially serve as a protective mechanism to prevent further injury or inflammation, pain hypersensitivity

can be especially debilitating when it gets out of hand, quickly spreading to regions of the body that are unaffected by and are far from the site of injury. "There are estimates that 15 to 45% of the adult population in developed countries have suffered from some type of pain hypersensitivity," said Sandkühler.

"We need to more deeply understand the complex and dynamic processes involved with neuroinflammation in order to better treat not only chronic pain, but also diseases often related to pain such as depression, anxiety disorders, chronic stress, diabetes and obesity," he added.

Neural pathways leading to pain hypersensitivity involve a process called long-term potentiation (LTP), in which signals between nerve cell connections called synapses are repeatedly and methodically strengthened in order to establish more long-term neural functions, like memory or learning. Though a boost in LTP activity is known to contribute to pain amplification at the site of an injury, it is still a mystery how the pain can sometimes spread, even impacting parts of the body unrelated to the damaged region.

In the past, it was widely believed that glial cells, which reside in the brain alongside neurons, do not contribute to synaptic transmission, instead mainly providing structural support and protection for their signal-producing neural neighbors.

Recently, scientists have presented evidence to the contrary, revealing that these elusive non-neuronal cells are players in inflammatory reactions of the brain and the spinal cord. Glial cells have even been found to release their own "gliotransmitters" — chemicals that help influence synaptic functions.

Until now, any glial associations with pain-causing LTP pathways were thought to be nonexistent or confined to small spaces, unable to account for far-reaching pain. But Sandkühler and his colleagues found evidence for this association in their experiments with rats.

"It was a major challenge to unravel the extreme complexity of interacting cell types and molecules including those that mediate neuroinflammation," notes Sandkühler.

The researchers compared the effects of a pain-instigating protein on glial and neuronal cells in the spinal dorsal horn, an internal segment of the spinal cord removed from rats.

The protein activated the glial cells, which in turn induced LTP in more than half of the nerve fiber sections studied. LTP activity was regulated by gliotransmitters that diffused widely throughout the neural network. By contrast, synaptic signaling from neuronal cells was unaffected.

Remarkably, the researchers were able to trigger strong LTP in laboratory rats that were not exposed to any pain stimulation, just by transferring the gliotransmitters produced in anesthetized, pain-stimulated rats to the pain-free rats. This demonstrates the ability of glial LTP to disperse over significant distances, even to uninjured areas.

"Our findings now provide a model that can explain the spreading of pain hypersensitivity," said Sandkühler. "Glial cells are interconnected to each other and when activated, such as by a pain condition, they produce and release pro-inflammatory substances that can spread quite some distances within the spinal cord — sufficient to turn on spinal pain

amplifiers at multiple sites."

While their findings have a long way to go before reaching the clinic, Sandkühler suggested that there are personal therapeutic steps pain sufferers can take in the meantime. "Though there are drugs available that dampen glial cell activation, every one of us can combat neuroinflammation in a drug-less way with moderate exercise for 30 minutes three to four times a week, balanced nutrition and a closely-monitored body mass index."