Tulane scientists uncover new pain-signaling switch

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Scientists from Tulane and other universities have discovered a new way that nerve cells communicate — by releasing an enzyme outside the cell that switches on pain signaling after injury. (Image from iStock)

Researchers at Tulane University, with a team of colleagues from eight other universities, have discovered a new nerve cell signaling mechanism that could transform our understanding of pain and lead to safer, more effective treatments.

The study, co-led by Matthew Dalva, the Phyllis M. Taylor Presidential Chair in Brain Science at Tulane, and Ted Price at the University of Texas at Dallas, reveals that neurons can release an enzyme outside the cell that switches on pain signaling after injury. The work, published in *Science*, offers new insight into how brain cells strengthen their connections during learning and memory.

“This finding changes our fundamental understanding of how neurons communicate,” said Dalva, director of the Tulane Brain Institute and professor of cell and molecular biology in the School of Science and Engineering. “We’ve discovered that an enzyme released by neurons can modify proteins on the outside of other cells to turn on pain signaling — without affecting normal movement or sensation.”

Researchers found that nerve cells communicate outside the cell with the enzyme vertebrate lonesome kinase (VLK), which can alter proteins in the space between neurons, affecting how those cells send signals.

“This is one of the first demonstrations that phosphorylation can control how cells interact in the extracellular space,” Dalva said. “It opens up an entirely new way of thinking about how to influence cell behavior and potentially a simpler way to design drugs that act from the outside rather than having to penetrate the cell.”

The team discovered that active neurons release VLK, which then boosts function of a receptor involved in pain, learning and memory. When the scientists removed VLK from pain-sensing neurons in mice, the animals didn’t feel the usual pain after surgery but still moved and sensed normally. Adding extra VLK had the opposite effect, increasing pain responses.

“This study gets to the core of how synaptic plasticity works — how connections between neurons evolve,” said Price, director of the Center for Advanced Pain Studies, professor of neuroscience at the University of Texas at Dallas’ School of Behavioral and Brain Sciences and a co-corresponding author of the study. “It has very broad implications for neuroscience, especially in understanding how pain and learning share similar molecular mechanisms.”

Dalva said the findings point to a safer way to influence pain pathways by targeting enzymes like VLK rather than directly blocking NMDA receptors, which help regulate communication between nerve cells but can cause serious side effects when disrupted.

The finding also provides one of the first examples of how to control interactions between cell-surface proteins outside the cell, which may simplify drug development and reduce off-target effects, since the drug would not enter the cell, he said.

Next steps are to see whether this is a mechanism specific to just a few proteins or part of a broader and underappreciated aspect of biology, and if so, it could reshape

treatment approaches for neurological and other diseases, Dalva said.

The research was conducted in collaboration with Dalva, Price and colleagues at The University of Texas Health Science Center at San Antonio, The University of Texas MD Anderson Cancer Center, the University of Houston, Princeton University, the University of Wisconsin-Madison, New York University Grossman School of Medicine and Thomas Jefferson University.

“Our findings were only possible through this kind of collaboration,” Dalva said. “By combining Tulane’s expertise in synaptic biology with the strengths of our partners, we were able to reveal a mechanism that has implications not just for pain, but for learning and memory across species.”

The research was supported by grants from the National Institute of Neurological Disorders and Stroke, the National Institute on Drug Abuse and the National Center for Research Resources, all part of the National Institutes of Health. Co-first authors of the paper include Kolluru Srikanth, Praveen Chander and Halley Washburn, all members of The Dalva Lab at Tulane.

Matthew Dalva - School of Science and Engineering

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