New study shows a role for cholesterol in pain perception

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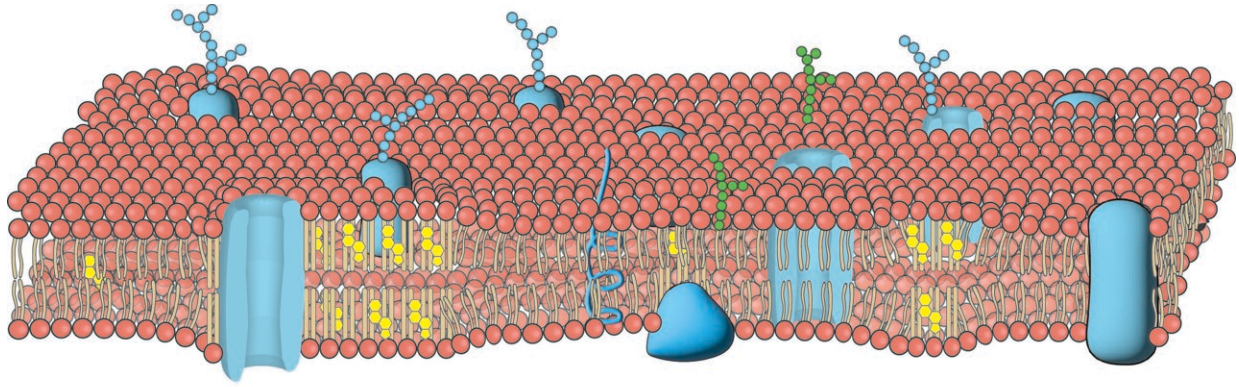

A cell membrane is illustrated to show the surface in red. Blue objects are proteins, including ion channels, which can send electrical impulses into cells. Lipids, or fats, are in yellow. In this cross section, an ion channel associates with a lipid raft. The function of the lipid structures is regulated by cholesterol. Mechanical force can deplete the cholesterol and release the ion channel, changing activity within the cell. Credit: Scott Hansen, Ph.D., The Wertheim UF Scripps Institute

When you stub your toe or bump your head, you know that rubbing the injury can lessen the ouch. But how? New research from the lab of Scott B. Hansen, Ph.D., shows how physical pressure on cells can reduce pain signals, while excessive cholesterol clumps in cell membranes can interfere with that process.

The research carried out at The Herbert Wertheim UF Scripps Institute for Biomedical Innovation & Technology appears in the journal *eLife*.

Hansen and his colleagues' discoveries are important for several reasons. They show for the first time that cell membrane lipids, or fats, help send an electrical pulse into cells after experiencing pressure and force. The research illuminates the path that pain signals take from an injury site to the brain and connects the many biological players involved. Importantly, the research shows how excess cholesterol in cell membranes may interfere with pain control.

"Excess cholesterol is a feature in many diseases and disorders, including diabetes and diseases of aging," said Hansen, an associate professor of molecular medicine at The Wertheim UF Scripps Institute. "This could be one explanation for why we see more chronic pain in these groups."

The study also adds to mounting evidence that the fatty molecules that make up cell membranes require structure to perform their many duties, he added.

"Originally, science thought only proteins had structures with function," said Hansen. "It looks like the lipids can be added to that list."

A cell is made of a fatty exterior membrane encasing a water-based interior. Advanced microscopes and other new technologies are revealing that the cell membrane isn't simply a fatty sac, though. Rather, it's a sophisticated collection of sensors, pores, channels, receptors, and cholesterol clumps held in place by precisely arranged fat molecules.

"There are two types of fats in the membrane: one is fluid, like olive oil and a second contains cholesterol and is found as tiny, rigid clumps, more like lard," Hansen said. "It wasn't known that those fats might play a role in pain signaling."

To feel pain, first, the injury must be sensed. Second, that injury message must convert to a signal that can travel rapidly through the body and be interpreted by the brain. The lipid structure appears to sense the force and convert it into a signal. The signal can then help activate the body's own pain-relieving responses—so long as there's no interference—lessening the pain's severity.

Scientists have previously documented the role of a mechanical force-sensing enzyme called PLD2 in these steps and its ability to activate a pain-relief-providing potassium channel called TREK-1. Missing was an understanding of how PLD2 and TREK-1 could be activated by the membrane. PLD2 lacked the ability to sense tension, the typical way that mechanosensors are engaged. Membrane lipids weren't considered, perhaps because they were poorly understood due to technical limitations.

"Until recently, the study of these cholesterol-containing lipid clumps, also called lipid rafts, has been difficult because they are too small to be seen by a regular light microscope," Hansen said.

Using a special microscope, Hansen and colleagues documented in several cell types that pressure and stretching, or "shear," caused changes to those fat molecules that temporarily altered the cell's ability to activate pain relief. Studies in mice and fruit flies also underscored their findings.

The research raises interesting questions and opportunities for more study, Hansen said. Many proteins associate with this lipid structure, including the proteins involved in Alzheimer's disease and inflammation. Understanding whether inflammation affects membrane cholesterol structure, especially in brain cells, may also prove important to understanding the pain-inflammation link.

"New types of non-opioid pain therapeutics are urgently needed for people who live with chronic pain," Hansen said. "Understanding what factors set the threshold for pain is an important step toward that goal."

More information: E Nicholas Petersen et al, Mechanical activation of TWIK-related potassium channel by nanoscopic movement and rapid second messenger signaling, *eLife* (2024). DOI: 10.7554/eLife.89465.3

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