A protein that detects cold and menthol may also be key to migraine headaches

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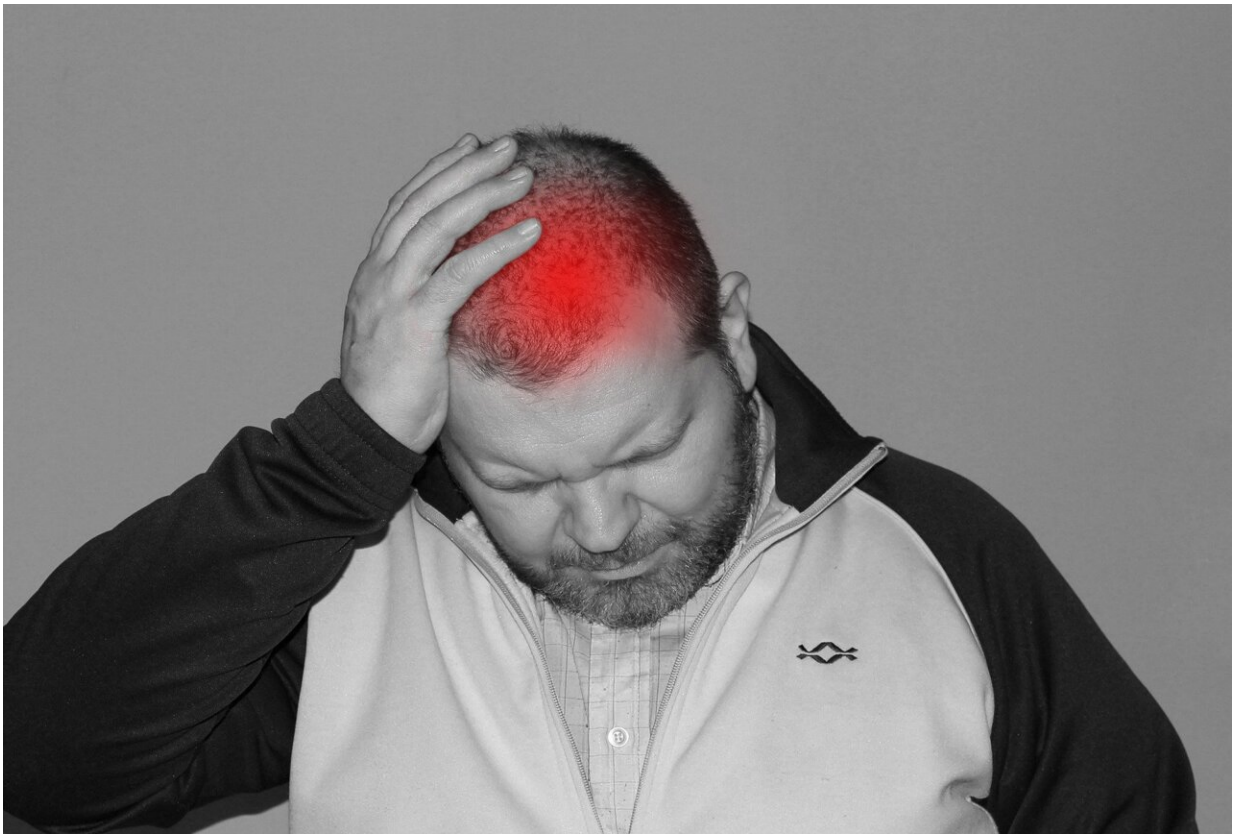

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Scientists have provided the strongest evidence yet that a protein that enables us to detect the sensation of cold may also be responsible for migraines. The findings appear in the journal *Pain*.

The findings move TRPM8 into the light as a potential target for new drugs aimed at relieving migraine.

"Our results confirm the importance of TRPM8 in migraines that was suggested by human genome-wide association studies and implicate the protein as a potentially important component of the pathology that leads to migraine. Thus, other scientists or clinicians can now add TRPM8 to their models of migraine and potential targets for treatment," says David McKemy, professor of biological sciences at USC Dornsife and corresponding author on the study.

- About 10% of all humans suffer from migraine—nearly 800 million people globally.
- Those who experience migraine are known as migraineurs.
- Symptoms include painful headaches as well as nausea, sensitivity to light, sound and sometimes touch and smell.
- Migraine may also cause aura, including visual effects (shapes, flashes or vision loss), weakness or numbness in the face or body, prickly sensations in an arm or leg, or trouble speaking.

To understand TRPM8's role in migraine, McKemy and his team studied mice that were genetically engineered to lack TRPM8. They gave the mice either nitroglycerin or a peptide known as CGRP, both of which can induce migraine-like symptoms including spontaneous pain and evoked pain.

- Spontaneous pain includes the headache arising during a migraine episode.
- Evoked pain comes from increased sensitivity during migraine, such as when touched or exposed to light.

"We showed that both spontaneous pain and evoked pain that is induced in mice by treatments with nitroglycerin and CGRP was absent in mice

genetically modified to not make the TRPM8 protein or lack the nerves that normally contain TRPM8," McKemy said. "The results show that TRPM8 is necessary for migraine-like pain in mice."

McKemy and his team also took a pharmacological approach, studying normal mice that had TRPM8 to understand how they react when given nitroglycerin or CGRP.

"We showed that we could treat mice with a drug that blocks TRPM8 function and prevent migraine-like pain," he said, giving further evidence that TRPM8 is a strong candidate target for new anti-migraine drugs.

The researchers now aim to answer new questions arising from their work, including:

- How does TRPM8 mediate migraine-like pain at the molecular and cellular level?
- Are migraineurs predisposed to headaches due to mutations in TRPM8 or is it something in the cellular processes that alter TRPM8 function?
- Can blocking TRPM8 function in humans with medicines be a method of treatment?

More information: Chao Wei et al, Transient receptor potential melastatin 8 (TRPM8) is required for nitroglycerin and calcitonin gene-related peptide induced migraine-like pain behaviors in mice, *Pain* (2022). DOI: 10.1097/j.pain.0000000000002635

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