

# Why does mint give a cooling sensation? Scientists reveal the mechanism behind it.

Scientists have for the first time observed the mechanism by which the protein TRPM8 helps the body sense cold and menthol. This discovery opens up avenues for treating chronic pain, dry eyes, and many other conditions.

When you step outside into the cold or put a mint candy in your mouth, your body activates a specialized 'sensor' that sends signals to the brain that you are feeling 'cool'. Recently, researchers have obtained the first detailed images showing the mechanism of this sensor, explaining how it reacts to low temperatures as well as menthol – the cooling compound found in mint.

The focus of the research is TRPM8 – a protein channel responsible for detecting cool temperatures. According to Hyuk-Joon Lee, a doctoral student at Duke University's lab, TRPM8 can be envisioned as a 'micro-thermometer' inside the body. It's the primary sensor that helps the brain recognize when it's cold. While this mechanism has been known for a long time, scientists previously didn't fully understand how it operates at the structural level. Now, they can 'see' that process.

TRPM8 is located in the membranes of sensory nerve cells in the skin, mouth, and eyes. When the temperature drops to around 8–28°C (46–82°F), this channel opens, allowing charged particles called ions to enter the cell. The movement of ions creates an electrical signal that travels to the brain, where it is interpreted as a sensation of coolness. The same mechanism explains why menthol, eucalyptus oil, or similar substances can create a cooling sensation even when the actual temperature remains unchanged.

Lee explained that menthol acts like a "trick" on the body. It binds to a specific location on the TRPM8 channel and triggers the channel to open, similar to the effect of cold. While menthol doesn't actually freeze anything, the body still receives a signal similar to touching ice.

To understand how TRPM8 changes structure when activated, the research team used cryo-electron microscopy (cryo-EM). This method allows for the imaging of proteins that are rapidly frozen by an electron beam, thereby capturing the different structural states as the channel transitions from closed to open.

The results showed that cold temperature and menthol activate TRPM8 through intrinsic pathways that overlap but are not entirely identical. Cold primarily affects the 'pore' region – the opening that allows ions to pass through. Meanwhile, menthol binds to a different site on the protein, subsequently causing structural changes that propagate throughout the molecule until the pore opens.

When cold is combined with menthol, the reaction is enhanced via a resonance mechanism. The research team leveraged this combination to record the fully open state of the channel – something previously impossible with

cold temperatures alone.



## Medical significance and the special 'cold spot'

Understanding how TRPM8 works could be of great value in medicine. Disorders related to this channel have been documented in conditions such as chronic pain, migraines, dry eyes, and some types of cancer. One drug targeting TRPM8, acoltremon, has now been approved by the U.S. Food and Drug Administration (FDA) as an eye drop for the treatment of dry eyes. As a menthol analog, it activates the cooling pathway to stimulate tear production and reduce irritation.

Additionally, scientists have identified an area called the 'cold spot' on the protein – a region central to temperature sensing. This area appears to help the channel maintain its responsiveness during prolonged cold exposure, preventing desensitization.

Previously, researchers were unclear how cold activates this channel at the structural level. Now, they have demonstrated that low temperatures produce specific changes in the channel's pore region. This finding lays the groundwork for the development of new therapies that precisely target the cold perception pathway.

By elucidating how temperature and cooling compounds converge on a single molecular sensor, the research has provided the first detailed explanation of the body's mechanism for recognizing the sensation of coolness. This is a significant advance in sensory biology and paves the way for more precise and effective treatments in the future.

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