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## The menthol receptor TRPM8 is the principal detector of environmental cold

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### Abstract

Sensory nerve fibres can detect changes in temperature over a remarkably wide range, a process that has been proposed to involve direct activation of thermosensitive excitatory transient receptor potential (TRP) ion channels. One such channel--TRP melastatin 8 (TRPM8) or cold and menthol receptor 1 (CMR1)--is activated by chemical cooling agents (such as menthol) or when ambient temperatures drop below approximately 26 degrees C, suggesting that it mediates the detection of cold thermal stimuli by primary afferent sensory neurons. However, some studies have questioned the contribution of TRPM8 to cold detection or proposed that other excitatory or inhibitory channels are more critical to this sensory modality in vivo. Here we show that cultured sensory neurons and intact sensory nerve fibres from TRPM8-deficient mice exhibit profoundly diminished responses to cold. These animals also show clear behavioural deficits in their ability to discriminate between cold and warm surfaces, or to respond to evaporative cooling. At the same time, TRPM8 mutant mice are not completely insensitive to cold as they avoid contact with surfaces below 10 degrees C, albeit with reduced efficiency. Thus, our findings demonstrate an essential and predominant role for TRPM8 in thermosensation over a wide range of cold temperatures, validating the hypothesis that TRP channels are the principal sensors of thermal stimuli in the peripheral nervous system.

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