Camphor Activates and Sensitizes Transient Receptor Potential Melastatin 8 (TRPM8) to Cooling and Icilin

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Abstract

Camphor is known to potentiate both heat and cold sensations. Although the sensitization to heat could be explained by the activation of heat-sensitive transient receptor potential (TRP) channels TRPV1 and TRPV3, the camphor–induced sensitization to cooling remains unexplained. In this study, we present evidence for the activation of the cold- and menthol–sensitive channel transient receptor potential melastatin 8 (TRPM8) by camphor. Calcium transients evoked by camphor in HEK293 cells expressing human and rat TRPM8 are inhibited by the TRPM8 antagonists 4-(3-chloro-2-pyridinyl)-N-[4-(1,1-dimethylethyl)phenyl]-1-piperazinecarboxamide and 2-aminoethyl diphenylborinate. Camphor also sensitized the cold–induced calcium transients and evoked desensitizing outward-rectifying currents in TRPM8-expressing HEK293 cells. In the presence of ruthenium red (a blocker of TRPV1, TRPV3, and TRPA1), the camphor sensitivity of cultured rat dorsal root ganglion neurons was highest in a subpopulation of cold- and icilin-sensitive neurons, strongly suggesting that camphor activates native TRPM8. Camphor has a dual action on TRPM8: it not only activates the channel but also inhibits its response to menthol. The icilin–insensitive chicken TRPM8 was also camphor insensitive. However, camphor was able to activate an icilin–insensitive human TRPM8 mutant channel. The activation and sensitization to cold of mammalian TRPM8 are likely to be responsible for the psychophysical enhancement of innocuous cold and “stinging/burning” cold sensations by camphor.

Key words

chicken TRPM8  
dorsal root ganglion  
eucalyptol  
human TRPM8  
icilin  
menthol

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