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## The role and mechanism of action of menthol in topical analgesic products

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### Abstract

**What is known and objective:** Menthol has been used as a non-opioid pain reliever since ancient times. A modern understanding of its molecular mechanism of action could form the basis for generating targets for discovery of novel non-opioid analgesic drugs.

**Methods:** The PubMed database was queried using search words related to menthol, pain and analgesia. The results were limited to relevant preclinical studies and clinical trials and reviews published in English during the past 5 years, which yielded 31 reports. The bibliographies of these articles were sources of additional supporting articles.

**Results:** Menthol is a selective activator of transient receptor potential melastatin-8 (TRPM8) channels and is also a vasoactive compound. As a topical agent, it acts as a counter-irritant by imparting a cooling effect and by initially stimulating nociceptors and then desensitizing them. Topically applied menthol may also activate central analgesic pathways. At high concentrations, menthol may generate cold allodynia.

**What is new and conclusions:** Recent elucidation of TRPM8 channels has provided a molecular basis for understanding the molecular action of menthol and its ability to produce both a cooling sensation and reduction in pain associated with a wide variety of pain(ful) conditions. The more modern mechanistic understanding of menthol and its pharmacologic mechanism of action may lead to an expanded role for this substance in the search for replacements for opioid analgesics, particularly those that can be applied topically.

**Keywords:** TRPM8; analgesic; calcium channel; menthol; non-opioid analgesic; topical analgesic.

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