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Editorial comment

It's not cool to reduce the skin temperature and activate the TRPM8 ion channel after spinal injury

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Sensory signals eliciting perceptions of pain, warmth and cool are mediated by thin myelinated or unmyelinated primary afferent nerve fibers. In the skin, these nerve fibers appear in light microscopy as free nerve endings. To be able to detect and discriminate sensory stimuli, the cell membrane of the free nerve endings expresses various types of receptors that are specialized for transducing mechanical, thermal and/or chemical stimuli into electrical signals. The transduction of external stimuli to action potentials is required for eliciting sensations resulting from peripheral stimulation, since the sensory signal to the brain is carried by action potentials in the primary afferent nerve fibers. Among the receptors contributing to the transduction process on free nerve endings are those belonging to the transient receptor potential (TRP) family of ion channels [1]. TRP channels, when activated by sensory stimuli, allow inflow of cations (Na^+ and Ca^{2+}) and thereby they cause depolarization that may induce action potentials. Of the TRP family members expressed on nociceptive primary afferent nerve fibers, the transient receptor potential vanilloid 1 (TRPV1) and transient receptor potential ankyrin 1 (TRPA1) are so far the best-known ion channel receptors involved in the transduction of potential tissue-damaging stimuli. TRPV1 is activated by painful heat and also by some pain-inducing chemicals, such as capsaicin, while TRPA1 is activated by various irritant compounds, such as those resulting in oxidative stress, some spices (e.g., mustard oil, cinnamaldehyde and wasabi) and directly or indirectly also by noxious mechanical stimulation. TRPA1 was originally considered to be involved in transduction of painful cold to electrical signals (see for references [1]), while later studies indicate that it plays a role in pathophysiological cold pain hypersensitivity rather than physiological detection of cold pain [2].

Transient receptor potential melastatin 8 (TRPM8), unlike TRPV1 and TRPA1, is expressed on both non-nociceptive and nociceptive nerve fibers [3,4]. In physiological conditions, TRPM8 is considered to have an important role in transduction of innocuous cool stimuli. TRPM8 can also be activated by chemical compounds, such as menthol or icilin, which elicit a cool sensation. Concerning potential contribution of TRPM8 to pain, previous neurophysiological findings are diverse and allow speculating that TRPM8 might aggravate as well as suppress pain. On one hand, it may be argued that since TRPM8 is expressed by a subset of nociceptive primary afferent nerve fibers [3] and since stimulation of the cool sensing TRPM8 receptor in the skin activates a subpopulation of the presumed spinal pain-relay neurons [5], it might be expected that TRPM8 activation induces pain as well as non-painful cool sensations even under physiological conditions. In the skin of healthy subjects, however, activation of TRPM8 by mild cooling or chemically with menthol has failed to induce pain or a cutaneous axon reflex that typically results in activation of nociceptive nerve fibers [6]. In addition to the sensation of non-painful cooling, the only finding in healthy subjects treated with topical menthol was the reduced cold pain threshold [6]. On the other hand, there are neurophysiological findings suggesting that TRPM8 might have analgesic properties. The TRPM8 agonist menthol has been shown to have a bimodal action on the pain-inducing TRPA1 channel that varies from activation at low doses to inactivation at high doses [7]. This finding suggests that inactivation of TRPA1 by a high dose of menthol might explain its local analgesic effect. Results of a recent patch clamp study indicate that menthol may induce local analgesia also due to inactivation of voltage-gated sodium channels [8]. Additionally, there is previous evidence indicating that the activation of ascending pathways mediating the innocuous cool sensation may suppress pain signaling at central levels (see for references [9]). In line with these findings, there are reports that menthol may in some conditions have an analgesic action [10], although overall the results on the effect of menthol on pain in patients have been variable [11,12].

Taking into account that the role of the TRPM8 in pain is still quite unclear, the study by Gao et al. [13] in this issue of Scandinavian Journal of Pain provides some valuable data that help in understanding mechanisms of allodynia in neuropathic conditions. Using an experimental model of spinal cord injury, Gao et al. show that innocuous cooling of the skin or cutaneous administration of TRPM8 agonists (menthol or icilin) elicited pain-like behavior that was associated with aggravation of mechanical hypersensitivity [13]. This result in spinally injured animals is in line with the attenuation of hypersensitivity by an inhibitor of TRPM8 in a peripheral nerve injury model of neuropathy in the study of Knowlton et al. [14]. While there is recent evidence indicating that TRPA1 may also be involved in cold hypersensitivity [2], the results of Gao et al. [13]

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indicate that at least in the spinal injury model TRPM8 rather than TRPA1 in the distal endings of primary afferent nerve fibers contributes both to cold and mechanical hypersensitivity. In contrast, cutaneous TRPA1 [15] rather than TRPM8 [14] appears to be critical in the cold hypersensitivity induced by a chemotherapeutic compound oxaliplatin.

Since TRP channels are also expressed on central terminals of primary afferent nerve fibers where they regulate transmission [16], the results by Gao et al. [13] still leave open whether the spinal regulation of transmission by TRPM8, TRPA1 or both [17] exerts a role in pain-like behavior evoked by mild cooling or low-intensity mechanical stimulation of the skin in spinally injured animals. Independent of the potential role of spinal TRP channels, the study of Gao et al. [13] suggests that blocking the TRPM8 on the cutaneous nerve endings might provide a useful method for attenuating tactile and cool allodynia in patients with a spinal injury.

References

[1] Patapoutian A, Tate S, Woolf CJ. Transient receptor potential channels: targeting pain at the source. Nat Rev Drug Discov 2009;8:55–60.
[2] del Camino D, Murphy S, Heiry M, Barrett LB, Earley TJ, Cook CA, Petrus MJ, Zhao M, D'Amours M, Deering N, Brenner GJ, Costigan M, Hayward NJ, Chong JA, Fanger CM, Woolf CJ, Patapoutian A, Moran MM. TRPA1 contributes to cold hypersensitivity. J Neurosci 2010;30:15165–74.
[3] McKemy DD, Neuhausser WM, Julius D. Identification of a cold receptor reveals a general role for TRP channels in thermosensation. Nature 2002;416:52–60.
[4] Peier AM, Moqrich A, Hergarden AC, Reeve AJ, Andersson DA, Story GM, Earley TJ, Dragoni I, McIntyre P, Bevan S, Patapoutian A. A TRP channel that senses cold stimuli and menthol. Cell 2002;108:705–15.
[5] Zanotto KL, Merrill AW, Carstens MI, Carstens E. Neurons in superficial trigeminal subnucleus caudalis responsive to oral cooling, menthol, and other irritant stimuli. J Neurophysiol 2007;97:966–78.
[6] Namer B, Seifert F, Handwerker HO, Maihöfner C. TRPA1 and TRPM8 activation in humans: effects of cinnamaldehyde and menthol. Neuroreport 2005;16:955–9.
[7] Karashima Y, Damann N, Prenen J, Talavera K, Segal A, Voets T, Nilius B. Bimodal action of menthol on the transient receptor potential channel TRPA1. J Neurosci 2007;27:9874–84.
[8] Gaudioso C, Hao J, Martin-Eauclaire MF, Gabriac M, Delmas P. Menthol pain relief through cumulative inactivation of voltage-gated sodium channels. Pain 2012;153:473–84.
[9] Craig AD, Bushnell MC. The thermal grill illusion: unmasking the burn of cold pain. Science 1994;265:252–5.
[10] Proudfoot CJ, Garry EM, Cottrell DF, Rosie R, Anderson H, Robertson DC, Fleetwood-Walker SM, Mitchell R. Analgesia mediated by the TRPM8 cold receptor in chronic neuropathic pain. Curr Biol 2006;16:1591–605.
[11] Namer B, Kleggetveit IP, Handwerker H, Schmelz M, Jørum E. Role of TRPM8 and TRPA1 for cold allodynia in patients with cold injury. Pain 2008;139:63–70.
[12] Baron R. Neuropathic pain: a clinical perspective. Handb Exp Pharmacol 2009;194:3–30.
[13] Gao T, Hao J, Wiesenfeld-Hallin Z, Xu XJ. Activation of TRPM8 cold receptor triggers allodynia-like behavior in spinally injured rats. Scand J Pain 2013;4:33–7.
[14] Knowlton WM, Daniels RL, Palkar R, McCoy DD, McKemy DD. Pharmacological blockade of TRPM8 ion channels alters cold and cold pain responses in mice. PLoS ONE 2011;6:e25894.
[15] Nassini R, Gees M, Harrison S, De Siena G, Materazzi S, Moretto N, Failli P, Preti D, Marchetti N, Cavazzini A, Mancini F, Pedretti P, Nilius B, Patacchini R, Geppetti P. Oxaliplatin elicits mechanical and cold allodynia in rodents via TRPA1 receptor stimulation. Pain 2011;152:1621–31.
[16] Pertovaara A, Koivisto A. TRPA1 ion channel in the spinal dorsal horn as a therapeutic target in central pain hypersensitivity and cutaneous neurogenic inflammation. Eur J Pharmacol 2011;666:1–4.
[17] Wrigley PJ, Jeong HJ, Vaughan CW. Primary afferents with TRPM8 and TRPA1 profiles target distinct subpopulations of rat superficial dorsal horn neurones. Br J Pharmacol 2009;157:371–80.