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Therapeutic opportunities for targeting cold pain pathways

Kathleen Yin [a,b], Katharina Zimmermann [c], Irina Vetter [a,b], Richard J. Lewis [a,*]

[a] Institute for Molecular Biosciences, The University of Queensland, St Lucia, Queensland 4072, Australia
[b] School of Pharmacy, The University of Queensland, Woolloongabba, Queensland 4102, Australia
[c] Department of Physiology and Pathophysiology and Department of Anesthesiology, Friedrich-Alexander University Erlangen-Nürnberg, 91054 Erlangen, Germany

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ABSTRACT

Cold pain is a frequent symptom in neuropathic pain. Compared to other pain modalities, such as heat pain, the mechanisms behind physiological and pathological cold pain remain elusive. Moreover, it is becoming increasingly evident that cold pain pharmacology differs between various neuropathic pain conditions, making mechanism-directed treatment based on an understanding of the underlying pathophysiological mechanisms imperative to achieving clinical success. Here we review the processes of physiological and abnormal cold sensing, the pharmacology of cold nociception, cold hyperalgesia and cold allodynia, and provide an overview of cold pain syndromes and their current and potential treatments.

1. Introduction

The perception of temperature is vital for human survival. As homoeothermic animals, humans rely on temperature regulation mechanisms to maintain a constant body temperature of ~37 °C irrespective of activity or the external environment. However, while innocuous hot or cold is considered harmless and often pleasurable, temperature extremes are painful and interpreted as signs of impeding tissue damage. The sensation of pleasant cool is usually elicited at temperatures just below normal skin temperature (32 °C), with temperatures approaching 10–15 °C and below gradually eliciting burning, aching and pricking pain [1–3]. Indeed, many of us are familiar with the excruciating pain that follows consumption of cold beverages or food, resulting in a cold-induced headache also known as "brain freeze". Similarly, immersion in ice-cold water is a commonly used nociceptive assessment in sensory testing to quantify an individual's pain threshold [4]. In this review, we describe the different cold pain pathways, ion channels involved in cold pain signalling, their involvement in pathological cold pain, and discuss mechanisms of current and potential new treatments for cold pain that might alleviate chronic cold pain sensitisation.

2. Cold pain pathways

Specific peripheral nerves activated by innocuous cold were discovered almost a century ago, first in the cat [5] and later in primates, where *in vivo* studies in anesthetised animals identified peripheral nerve fibres that discharged action potentials in response to cold stimulation of their receptive fields [6,7]. Initially, these studies identified afferent fibres that only responded to innocuous temperatures (below 27 °C) and not to heat or mechanical stimuli. The firing frequency of these cold-sensitive neurons, later regarded as 'classic' innocuous cold thermosensors, is inversely proportional to temperature, with peak discharge rates occurring on cooling between 30 and 25 °C [7]. Since this early discovery, other cold-sensitive sensory fibre subtypes were characterised in primates and in other species, as shown in Table 1 [6–13]. Subsets of slowly conducting (typically < 1 m/s) C-fibres are monomodal and sense innocuous and noxious cold or are multimodal mechanothermal nociceptors, with the remaining cold-sensitive neurons classified as fast-conducting (up to 16 m/s) Aδ-fibres [3,13–15]. Given that C-fibres sensitive to noxious cold are mostly polymodal nociceptors that respond to other stimuli, including mechanical stimulation, it appears likely that C-fibres conduct pain signals without discriminating the nature of the stimuli, while Aδ-fibres code that discomfort is caused specifically by cold [7,16]. It is thus very likely that the full sensation of cold pain requires the presence of both C- and Aδ-fibres.

* Corresponding author.
E-mail address: r.lewis@imb.uq.edu.au (R.J. Lewis).

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Table 1
Peripheral nerve subtypes involved in sensing innocuous and noxious cold.

Fibre type	Fibre subtype	Sensitivity	References
C-fibres	CC (C-cold)	Only respond to cold, menthol-sensitive	[3,6,15,102,158]
	CMHC (C-mechano-heat-cold)	Polymodal nociceptors, respond to noxious mechanical, heat and cold	[14,60,159]
	CMC (C-mechano-cold)	Polymodal nociceptors, respond to noxious mechanical and cold	[13,60,158,159]
	High-threshold cold-sensitive fibres	Only respond to noxious cold (<20 °C)	[7]
Aδ-fibres	Low-threshold cold-sensitive fibres	Respond to innocuous cold	[160]
	AδMHC (Aδ-mechano-heat-cold)	Polymodal nociceptors, respond to noxious mechanical, heat and cold	[13,159]
	AδMC (Aδ-mechano-cold) fibres	Polymodal nociceptors, respond to noxious mechanical and cold	[159]
	Mechano-insensitive cold-sensitive fibres	Respond to innocuous or noxious cold	[6,160]

In humans, the physiological cold pain threshold is significantly more variable than the heat pain threshold, with temperatures below approximately 15 °C eliciting pain. Broadly, the intensity of cold pain increases rapidly between approximately 20 and 0 °C [1,2,17]. In rodents, frank nocifensive behaviour on contact exposure to cold surfaces is usually only elicited at temperatures below 5 °C [18,19], which may reflect the relative insensitivity of these behavioural assays to detect mild to moderate pain-related behaviours in rodents.

Centrally, temperature signals reach the brain via the lateral spinothalamic tract, whereas pain signals are additionally carried via the spinoreticular and spinothalamic tracts, which terminate in the thalamus and the frontal cortices, respectively [20–23]. In healthy humans, stimulation of the forearm skin with innocuous cold leads to activation of the contra- and ipsilateral-posterior insular cortices as the primary somatosensory area [24]. In contrast, noxious cold stimuli activate the contra- and ipsilateral-insular cortices and secondary somatosensory cortices and the cingulate cortex, as revealed by magnetoencephalography [24]. Functional magnetic resonance imaging has been employed to investigate brain areas activated during menthol-induced cold allodynia, identifying increased activation within the ipsilateral dorsolateral prefrontal cortices and the brainstem (ipsilateral parabrachial nucleus) [25]. These observations illustrate some of the differences between the brain regions responsible for innocuous cold, cold pain, and pathological cold pain. In contrast, the molecular mechanisms underlying central cold pain processing are less clear. Studies to date have revealed that the beneficial effects of spinal cord stimulation were abolished by serotonin receptor antagonists in a murine spinal nerve ligation model [26], and that ablating neuropeptide Y receptors in the superficial spinal dorsal horn reduced cold allodynia in Freund's Adjuvant (CFA)-induced inflammation in rats [27]. Interestingly, μ-opioid receptor binding potential in the striatum predicted the cold pressor test threshold in humans, but not cold tolerance, possibly correlating peripheral cold pain threshold with central opioid-dependent inhibition [28].

3. Pathological cold pain conditions

Pathological cold pain is a frequent symptom in a range of neuropathic pain syndromes, including those of peripheral and central origin, and usually presents as cold allodynia or hyperalgesia [29]. While many conditions, including diabetic neuropathy, peripheral nerve injury, chemotherapy-induced neuropathy, post-stroke central pain and ciguatera (see Table 2) can present with the symptom of pathological cold pain, the mechanisms by which cold pain arises are still poorly understood and can vary significantly between diseases [30–35].

A condition that is defined by cold allodynia is ciguatera, a form of marine food poisoning arising from the consumption of tropical and subtropical fish contaminated with ciguatoxins. Ciguatoxins originate from dinoflagellates of the *Gambierdiscus* family and accumulate in reef fish through the marine food chain [36]. Symptoms of ciguatera include dysaesthesias, headache, dental pain, and myalgia, with cold allodynia occurring in almost all ciguatera patients (for review see [36]). Experiments with human volunteers showed that intracutaneous injection of ciguatoxin induced local cold allodynia which faded after a few hours, suggesting ciguatoxin acts acutely and peripherally to cause cold pain [37]. Similarly, mice of the C57BL/6 strain develop cold, but not mechanical or heat allodynia, within one hour after intraplantar ciguatoxin injection, an effect that is mediated predominantly through peripheral sensory neurons expressing the transient receptor potential (TRP) cold sensor TRPA1 [38].

In contrast, cold allodynia elicited after intraplantar injection of the chemotherapeutic agent oxaliplatin involved sensory neurons expressing voltage-gated sodium channel (Na_v) subtype 1.6 and voltage-gated potassium channels (K_v), and developed independent of cold-sensitive TRP channels [39]. While oxaliplatin is administered intravenously in humans, intraplantar injection of oxaliplatin in mice recapitulated the immediate-onset cold-induced dysaesthesias that often occur in humans undergoing therapy with the platinum-derived anti-tumour agent. The immediate occurrence of painful symptoms after subcutaneous oxaliplatin exposure in mice implies that primary sensory effects are sufficient to elicit cold allodynia. However, the long-lasting progression of the disease in humans after intravenous infusion does not exclude an altered expression of cold-sensing TRP channels contributing or aggravating the disease at a later stage, as found for TRPA1 or TRPM8 in mouse models of chronic oxaliplatin-induced neuropathy [40–43].

Treatment with paclitaxel, a chemotherapy agent used in the management of solid tumours such as breast cancer, is also associated with a high incidence of cold allodynia. Paclitaxel-induced cold allodynia commences in the hands and feet and gradually progresses centrally. Cold allodynia appears to parallel the development of paclitaxel-induced neuropathy with signs such as demyelination, accumulation of abnormal mitochondria in sensory nerves, and fibre loss in severe cases [44,45]. Subcutaneous injection of tetrodotoxin (TTX) reduced paclitaxel-induced mechanical, heat and cold allodynia [46], suggesting the involvement of TTX-sensitive Na_v isoforms as observed for oxaliplatin-induced cold allodynia.

Interestingly, diabetic animals with pre-existing peripheral neuropathy are more susceptible to develop cold allodynia when

Table 2
Common neuropathic pain conditions exhibiting symptoms of cold allodynia.

Conditions associated with pathological cold pain	Cold pain prevalence
Ciguatera	71–88% [161–163]
Oxaliplatin-induced neuropathy	81–98% [164]
Paclitaxel-induced neuropathy	84% [165]
Diabetic neuropathy	Uncertain
Central post-stroke pain (CPSP)	17–70% [166–168]
Post-traumatic cold intolerance following upper limb injury	38–82% [52,54,55]