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Mini-review

Unmyelinated afferents in human skin and their responsiveness to low temperature

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ABSTRACT

In humans, there are different types of cutaneous cold-sensitive afferents responsible for cold sensation and cold pain. Innocuous cold is primarily mediated by a population of slow A delta afferents, based on psychophysical and neurophysiological studies. Noxious cold (usually below 15 °C) is mediated, at least in part, by polymodal nociceptors. There is also a population of unmyelinated afferents responsive to innocuous low temperature, some of which also respond to heat, whose sensory function has not been completely defined. A paradoxical hot/burning evoked by cooling is unmasked by A-fibre block, and similar sensations are evoked by applying simultaneous cool and warm stimuli to adjacent skin areas. These unmyelinated fibres activated by innocuous cooling (and heating) may contribute to this hot/burning sensation, along with other thermoregulatory functions.

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Lowering skin temperature normally evokes sensations of 'cool' that merge into 'cold' or 'icy' as the temperature is lowered further. When it falls below 15–20 °C, low temperature can also evoke pain, which is typically described as 'cold pricking pain', 'deep cold pain', or sometimes even 'burning'. Like other sensory modalities, cold sensation is mediated by a peripheral system of cutaneous receptors and afferent nerve fibres projecting into the spinal cord and on to the brain, where the cognitive process of cold recognition takes place. Under certain experimental or pathological conditions, cooling the skin can evoke a paradoxical burning sensation (cold allodynia) at a temperature that normally evokes innocuous cold. This disturbed sensation has been postulated to emerge from the removal of an inhibitory effect of cold-specific afferents, which normally prevent the input from low temperature-activated nociceptors to reach consciousness.

The function of thermosensitive nerve endings has been studied by different approaches: (a) observing the specific temperature sensations in human subjects; (b) studying thermoregulatory reflexes and behaviours at different temperatures; (c) by recording afferent impulses from specific sensory units activated by different thermal stimuli. Albeit important, the two initial methods are indirect, whereas recording afferent activity from thermosensitive units provides some direct evidence for the neural mechanisms behind the thermal sensations. In this paper this latter approach will be discussed.

It has been generally accepted that innocuous low temperature is conveyed from the skin by small myelinated (Aδ) fibres [6]. The most direct evidence for this comes from a microneurographic study in humans, in which pressure was used to selectively block myelinated before unmyelinated fibres [30]. The presence of cold discrimination appeared to correlate with the conduction of fibres in the Aδ velocity range (5–15 m s^{-1}). In monkeys, Darian-Smith et al. [7] recorded from many cold-specific afferents in the Aδ range (5–30 m s^{-1}, average 14.5 m s^{-1}), and those recorded by Long [29] conducted in the range 2.2–22.5 m s^{-1}. However, evidence from reaction times of cold sensation in humans has indicated that the fastest fibres responsible for signaling cold conduct not faster than 8 m s^{-1} [42], while other estimates put them at the very slowest end of the Aδ velocity range, near 2.5 m s^{-1} [10,11,53]. The fibres that signal cold threshold are not necessarily the only type of afferent that may contribute to cold sensation, and in addition to the small myelinated fibres responding to innocuous low temperature, there is also abundant evidence for a significant contingent of unmyelinated fibres responsive to this thermal energy in different animal species, including rat [14,34,43], and cats [21].

Following the original reports of Raymond et al. [34], Thalhammer et al. [43] and Gee et al. [14] that specific patterns of activity-dependent slowing of conduction velocity predict the functional sub-classes of C fibres in animals, it has become much easier to identify sub-classes of unmyelinated fibres in humans [36,37,51] through microneurography. Among the different patterns of activity-dependent slowing, those afferent C fibres slowing

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by ~5% during an electrical tetanus (2 imp s^{-1}) were also distinguished from the others by their selective response to small changes in the temperature of the cutaneous receptive field [2]. They increased their firing rate upon cooling, stopped their ongoing firing on sudden warming, and were unresponsive to mechanical stimulation, thus, fulfilling the definition of a cold fibre. We described [2] 18 units from the superficial peroneal nerve which were responsive to innocuous low temperature. Among these fibres, only one had a conduction velocity in the low Aδ range (3 m s^{-1}), while the remainder were presumed to be unmyelinated at that level of the nerve. However, we also recorded 4 other fibres conducting between 2 and 4 m s^{-1} with the same pattern of activity-dependent slowing, which were probably also cold-sensitive. Very few other cold fibres have been described in humans. Hensel and Boman [20] described one cold fibre from the exposed superficial radial nerve in a human subject, without specifying the conduction velocity; Konietzny [28] described 13 cold-specific afferents in human subjects, and the 3 units in which conduction velocity was measured, fell in the unmyelinated category.

The typical receptor response feature of a C cold afferent from the superficial peroneal nerve from a human volunteer is illustrated in Fig. 1. At a skin temperature of 34 °C the fibre displays an ongoing, regular discharge, around 7 imp s^{-1}. This firing rate is suddenly increased when skin temperature is lowered from 34 to 33 °C displaying an initial dynamic response adapting into a lower frequency discharge when skin temperature has reached a new steady state. On rewarming, the unit stops firing, later resuming a lower frequency regular discharge. In our sample of cold-specific afferents [2], the mean cold threshold was 29.4 °C (±2.0 °C). All units displayed a dynamic discharge pattern that increased according to the target temperature, from a mean of 16 imp s^{-1} achieved at 30 °C, to 34 imp s^{-1} when the temperature was lowered from 35 to 15 °C. During the tonic firing state, the mean impulse frequency varied from 5 to 23 imp s^{-1}, when temperatures of 30 and 15 °C were reached (see Fig. 5, in Ref. [2]).

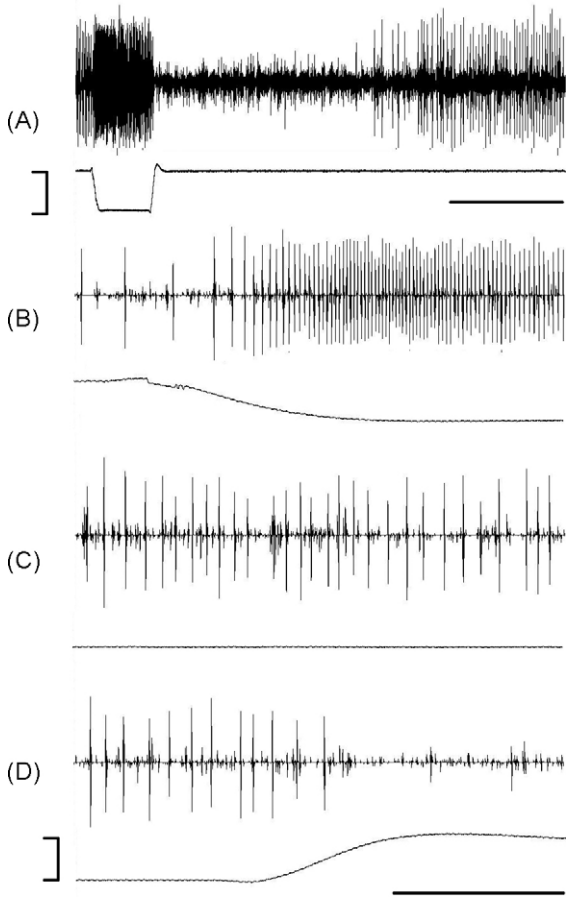

Fig. 1. Single recording of a C cold afferent (conduction velocity 1.31 m s^{-1}) from the superficial peroneal nerve on a healthy volunteer. (A) At baseline temperature (34 °C) the unit displayed a spontaneous regular firing ~7 imp s^{-1}. On sudden cooling to 30 °C for 5 s, the unit had an abrupt increase in firing rate (B) to ~30 imp s^{-1}. After this dynamic phase, the fibre adapted to a more stable firing of 15 imp s^{-1} (C), becoming silent for several seconds (D) after returning to baseline temperature. After some seconds the C cold fibre resumed its baseline spontaneous firing (A). Horizontal bar in A, 10 s; B–D, 1 s. Vertical bar 4 °C.

Although the Aδ cold fibres described in animals fire in bursts [35] there is evidence that cold-specific afferents with unmyelinated fibres have a rather regular discharge pattern [21]. This was also the case for cold fibres recorded in humans [20,28], where dynamic and static discharges with regular firing rates were recorded. We also described a regular firing rate for C cold fibres from the superficial peroneal nerve in human volunteers [2]. A bursting pattern was only observed in some of the fibres during the paradoxical excitation with heat (see below).

Early and more recent psychophysical studies on cold sensation [15,47] have found cold sensation to be confined to rather small cold spots on the skin. This feature of cold sensation is in line with the punctiform receptive fields of cold afferents described in animals [19,23,24] and humans [2].

Dodt et al. [9] and later Kenshalo and Duclaux [26] and Long [29] described a population of cold-specific afferents that displayed an additional 'paradoxical' response to warming the cutaneous receptive field. This phenomenon provided an explanation for the paradoxical cold sensation described by von Frey [47] when stimulating previously identified "cold" spots with heat. Paradoxical firing of cold afferents in humans has also been reported [25]. This feature of cold afferents is illustrated in Fig. 2. In this example a cold fibre with a steady discharge at 35 °C, upon sudden heating, had a transient arrest in the ongoing discharge, and then discharged regularly during a 48 °C 5-s pulse.

Its has been generally agreed that temperature below 20 °C may evoke pain [4,18,33], with cold pain threshold being around 10–20 °C, depending on the size and territory stimulated. Cold pain occurs with intact afferent nerve fibres and also during selective block of myelinated fibres [12,52]. Therefore, unmyelinated afferents seem to be responsible for conveying the cold pain signal from the skin. Low temperature activates polymodal nociceptors in a number of animal species [39]. In humans, low temperature below 20 °C activates a fraction of polymodal nociceptors with C fibres. In experimental animals, noxious low temperature also activates a population of small myelinated afferents [40]. For humans there have been some isolated reports on the sensitivity of C nociceptor to low temperature [44,45]. We described [3] in more detail the response characteristics of C polymodal nociceptors to cold.

The firing rate of polymodal nociceptors on activation by noxious low temperature is very low, in general, only a few action potentials in several seconds. In fact, the highest instantaneous firing rate we recorded in a human CMH on cold activation was 3 imp s^{-1} [3], but the typical response profile is that no more than 4–6 action potentials occur over a 30-s period of low temperature stimulation (see Fig. 3 in Ref. [3]). The marking technique [46], used to recognize activity in C fibres by identifying the slowing of conduction velocity during simultaneous electrical and natural stimulation, is useless during noxious cold stimulation, because activity-dependent slowing is masked by the dramatic slowing due to the temperature-dependent kinetics of sodium channels in cutaneous nerve fibres. Only when the signal-to-noise ratio allows clear identification of action potentials in a single unit, does it become possible to count the spikes during low temperature stimulation. This was the case for the recording in Fig. 3. In this subject lowering the temperature from 32 to 6 and 2 °C evoked only 4 and 7 action

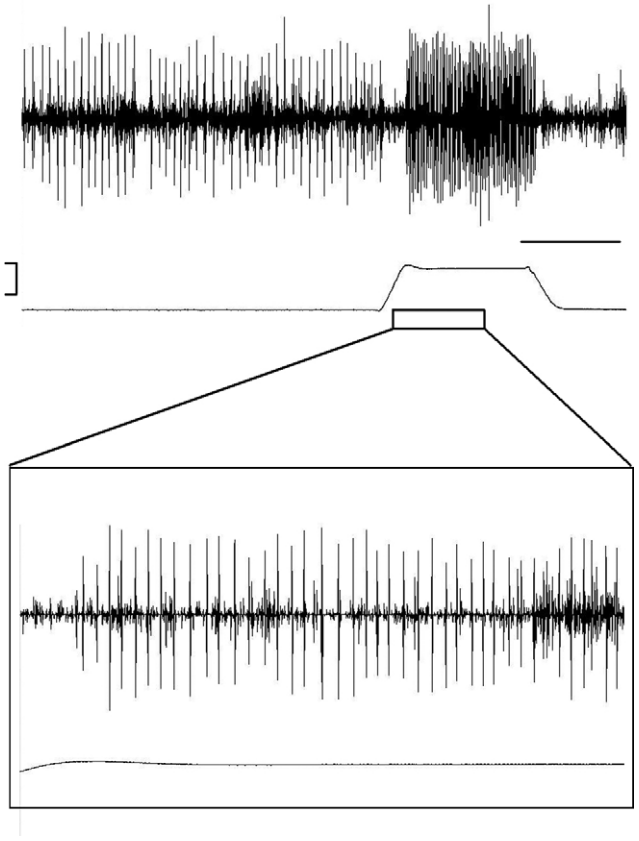

Fig. 2. Same unit as in Fig. 1. This cold unit was excited by heating as well as by cooling. The unit responded to a ramp of 14 °C above the resting temperature, with a brief period in which the unit stopped firing with the sudden temperature raise, but resumed rapidly a faster firing rate during heating the receptive field at 48 °C for 5 s. The initial response of the unit to the heat pulse is displayed in the inset, with a firing rate of ~20 imp s^{-1}. Horizontal bar = 5 s; vertical bar 14 °C.

potentials respectively, during the 30 s period. Heat evoked a much more vigorous response, with up to 8 action potentials per 850 ms (9.4 imp s^{-1}).

Until recently, the transducer for innocuous low temperature was unknown, although the vanilloid receptor sensitive to heat and capsaicin (TRPV1) had already been described in nociceptors, as part of the family of transient receptor potential (TRP) ionic channels. McKemy et al. [31] described in trigeminal neurons an ionic channel (TRPM8) of the same TRP family, which was sensitive to innocuous low temperature and to menthol. For centuries menthol, which occurs naturally in peppermint and other mint oils, has been used topically to alleviate pain. Psychophysical studies have shown that menthol applied topically to the skin causes a perception of cold and enhances the cold sensation evoked by innocuous low temperature [15]. There is agreement that menthol also lowers the threshold for cold-induced burning sensation (less cold is required to evoke burning) and this effect has been proposed as a model for cold hyperalgesia [49,50]. However, there is controversy on whether menthol induces cutaneous flare and mechanical hyperalgesia [18,33,50].

In addition to the TRPM8, another cold-sensitive receptor from the TRP family has been described (TRPA1, [41]), which is only activated in the noxious temperature range (<17 °C). Cinnamaldehyde is a powerful agonist of this TRP channel. TRPA1 is not expressed in cold afferents, but is co-expressed with the capsaicin receptor TRPV1 in nociceptors [27]. Thus, TRPA1 has been implicated as one possible transducer for cold pain.

The effect of menthol on cold receptors has been studied for a long time [22], and the results have been very consistent. Menthol causes sensitization of cold afferents (both with Aδ and C fibres), raising the temperature at which they are silenced to near 40 °C. Menthol also causes an increase in firing rates compared to fibres not exposed to the TRPM8 agonist. The effect of cinnamaldehyde is very different from menthol: it induces spontaneous burning pain, a large flare reaction and mechanical and heat hyperalgesias, but no cold hypersensitivity. In fact, cinnamaldehyde may cause, if anything, cold hypoalgesia [32].

A preliminary report on the effect of menthol on cold afferents in humans [1] indicates that it produces a similar sensitizing effect as in animals [22]. Whether human Aδ cold afferents respond similarly to menthol exposure is likely, but remains speculative.

Some questions have emerged on the role of TRPM8 in cold nociceptors. Wasner et al. [50] argued that mechanical hyperalgesia induced by menthol in normal volunteers was probably due to the expression of TRPM8 in C nociceptors. Nevertheless there is also psychophysical data suggesting that menthol-induced burning sensation is mediated neither by C mechano-sensitive nor mechano-insensitive nociceptors [32]. Although C nociceptors in

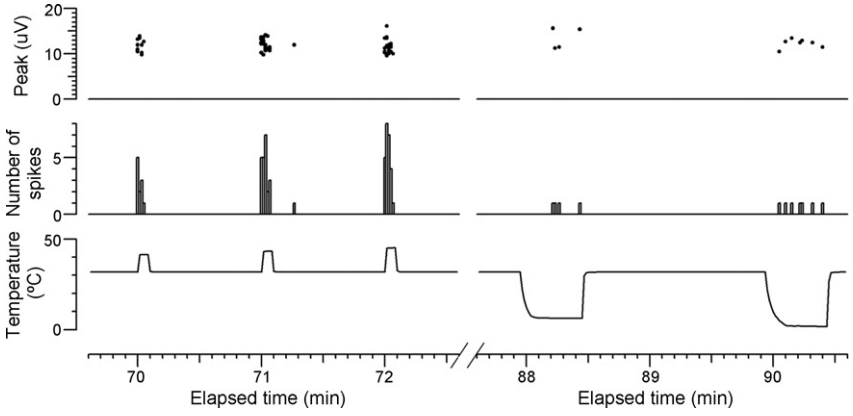

Fig. 3. One C mechano-heat sensitive nociceptor recorded from the superficial peroneal nerve from a normal subject with a conduction velocity of 0.54 m s^{-1}. In the upper panel the peak amplitudes of each action potential corresponding with that of the identified polymodal nociceptor is displayed as a filled circle. The number of action potentials per 850 ms time interval is represented as bar in the middle panel. In the lower panel the temperature of the thermal stimulator is displayed in °C. The left panel displays the response to three successive pulses of 5 s heat, from a baseline temperature of 32–44, 46 and 48 °C (left to right). On the right panel is shown a similar display of pulses of 30 s duration of low temperature from 32 to 6 and 2 °C applied to the receptive field. The response to heat peaks at 8 impulses every 850 ms (9.4 imp s^{-1}) at 48 °C, whereas the response to noxious cold (2 °C) comprised 7 action potentials in 30 s (0.27 imp s^{-1}).

humans respond to low temperature, there is some preliminary evidence that they are not activated by menthol [1]. Their response to cinnamaldehyde has not been reported.

The term 'cold allodynia' describes a common symptom in neuropathic pain patients, which is an unpleasant sensation – usually 'burning' – evoked by innocuous cooling of the skin. In spite of its clinical importance, the mechanisms of cold allodynia are not fully understood.

Besides menthol (see above), another two experimental models have been proposed to explain pathological cold pain and cold hyperalgesia. One model is based on the lowering of the threshold for cold-induced burning sensation that occurs during ischemic or compression A-fibre block. The second model is based on the 'synthetic heat', or the 'thermal grill illusion' in which simultaneous application of innocuous cold and warmth results in a hot or burning sensation.

During the selective block of myelinated fibres by compression or ischemia, most subjects experience a change in the quality of the sensations evoked by lowering skin temperature. The 'cold' sensation is replaced by a dysesthetic sensation, described as 'hot', 'burning', or 'icy' [12,48,52]. Nevertheless, a proportion of subjects having a 'complete' A-fibre block, never loses the sensation of cold (unpublished observations; see [12,48,52]). It has been proposed [48,52] that blocking the input from Aδ cold afferents releases a gate in the central nervous system, and allows the activity of polymodal nociceptors to reach the conscious brain. However, we have shown that C polymodal nociceptors are not activated at temperatures above 15–20 °C [3], so that the 'nociceptive' activity must arrive from a different set of cold-sensitive nerve fibres. The explanation suggested by Fruhstorfer [12] fits better the psychophysical results. Although they had not yet been demonstrated in humans, he proposed that there were low-threshold cold-sensitive C afferents which contribute to cold sensations, and that these C cold fibres were responsible for the icy, burning, dysesthetic sensation evoked by innocuous low temperature during A-fibre block. It seems possibly that these unmyelinated afferents are responsible for the burning, C-fibre-mediated sensation that can be evoked by innocuous cold stimulation in normal subjects, especially when the stimulated area is small and after preheating the skin [42]. Similarly, these fibres could be involved in the 'synthetic heat', or 'thermal grill' illusion. However, there is controversy whether the sensation evoked by chequered innocuous cold and warmth is painful or not [5,8,13].

Very recently, however, Serra et al. [38] have reported a patient with cold allodynia in whom a proportion of C nociceptors were sensitized to low temperature. These fibres were also activated by topical menthol, suggesting that abnormal TRPM8 expression was responsible. The cold pain was described as aching, and it is possible that the aching element may help distinguish this type of cold allodynia from others.

In summary, in humans, a population of unmyelinated fibres responsive to innocuous cold has been described, with a small proportion conducting in the low end of the Aδ range. This is in line with psychophysical studies suggesting that cold is transmitted by small myelinated fibres, but unmyelinated cold afferents may also contribute to cold sensation. When A fibres are blocked, cold evokes a sensation of hot/burning, which has been interpreted as nociceptive [5,8,17] or innocuous [13,16] by different groups. When cold sensation is blocked by compression or ischemia, cold induces a sensation of hot/burning at temperatures above the threshold reported to activate C polymodal nociceptors. Thus, hot/burning could be mediated, at least in part, by C cold afferents. It is as yet unclear whether this sensation is more appropriately classified as nociceptive or thermoreceptive. In some patients, cold hyperalgesia may be mediated by sensitized nociceptors.

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