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Review

Thermoreceptors and thermosensitive afferents[☆]

Raf J. Schepers, Matthias Ringkamp[*]

Dept of Neurosurgery, School of Medicine, Johns Hopkins University, Baltimore, MD 21218, USA

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ABSTRACT

Cutaneous thermosensation plays an important role in thermal regulation and detection of potentially harmful thermal stimuli. Multiple classes of primary afferents are responsive to thermal stimuli. Afferent nerve fibers mediating the sensation of non-painful warmth or cold seem adapted to convey thermal information over a particular temperature range. In contrast, nociceptive afferents are often activated by both, painful cold and heat stimuli. The transduction mechanisms engaged by thermal stimuli have only recently been discovered. Transient receptor potential (TRP) ion channels that can be activated by temperatures over specific ranges potentially provide the molecular basis for thermosensation. However, non-TRP mechanisms are also likely to contribute to the transduction of thermal stimuli. This review summarizes findings regarding the transduction proteins and the primary afferents activated by innocuous and noxious cold and heat.

Contents

1. Introduction

The skin forms a protective layer around the body against physical, chemical and thermal environmental challenges. In addition to providing a physical barrier, the skin serves as a sensory organ that enables the body to detect stimuli of the outside world so that an appropriate behavior can be initiated. Thermosensation is one of the sensory modalities of the skin. It provides (1) a thermoregulatory afferent signal for homeostatic mechanisms which keep the body at an optimal working temperature, (2) the capability to detect potentially noxious thermal stimuli that pose an immediate threat to the integrity of the integument (i.e. noxious

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[*] Corresponding author at: Dept of Neurosurgery, School of Medicine, Johns Hopkins University, 600 N Wolfe St, Meyer 5-109, Baltimore, MD 21287, USA. Tel.: +1 410 614 1998; fax: +1 410 955 1032.

E-mail address: platelet@jhmi.edu (M. Ringkamp).

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cold and heat stimuli) (3) afferent signals which contribute to the identification of objects and materials through touch, e.g. metals are easily discriminated from wood because metals feel colder than wood.

Thermal stimuli applied to the skin induce distinct sensations. Small changes in skin temperature are perceived as warm or cool, but these sensations adapt quickly. Adaptation of thermal sensation can be observed over a relatively wide temperature range. Thermal stimuli that lead to skin temperatures outside this range lead to non-adapting thermal sensations. With decreasing stimulus temperatures the quality of sensation may change from cool, cold, icy to painful. Similarly, stimuli of increasing temperature cause sensations of warmth, heat and pain. The reported temperatures that cause these different sensations vary considerably. This variability can be explained by differences in the characteristics of the stimulus used (temperature ramp rate, duration and area of thermal stimulus, stimulus history), experimental conditions employed (site of testing, skin condition and properties, day time of measurement), and individual differences (previous pain experiences, ethnicity, sex) (Chery-Croze, 1983a).

Cutaneous thermosensation is mediated by a variety of primary afferent nerve fibers that transduce, encode and transmit thermal information. Over the last decade, a number of transient receptor potential (TRP) ion channels have been identified whose activity depends on the temperature of their environment (Voets et al., 2004). Each of these receptors operates over a specific temperature range, thereby providing a potential molecular basis for thermosensation. These specialized thermal receptors are embedded in the terminals of afferent fibers which end as free nerve endings in the skin. In humans, 28 different TRP channels have been identified and these can be grouped into 6 families (Pedersen et al., 2005). Of these, members of 3 families, i.e. the vanilloid TRP channels (TRPV), the melastatin or long TRP channels (TRPM), and the ankyrin transmembrane protein channels (TRPA) are of particular interest as thermoreceptors. This review summarizes findings regarding the different classes of primary afferents involved in innocuous and noxious thermal sensation and their thermosensors.

2. Innocuous temperatures

2.1. Cold

2.1.1. Afferent nerve fibers

In vivo electrophysiology studies have long demonstrated the existence of a class of afferent fibers in the skin of various mammals and frogs which are exclusively activated by cool stimuli. These so-called 'cold' fibers often exhibit ongoing action potential activity at normal skin temperatures. The cutaneous receptive fields of cold fibers consist of a single or multiple cold sensitive spots and they are unresponsive to mechanical stimulation (Darian-Smith et al., 1973; Dubner et al., 1975; Kenshalo and Gallegos, 1967). Previous studies in cat located cold receptors at a depth of 100–150 μm (Hensel et al., 1951) or at the dermal–epidermal border (Hensel et al., 1974). Results from more recent studies in rat suggest that cold fibers project into the epidermis (Dhaka et al., 2008). At steady state temperatures cold fibers have a characteristic stimulus response function which is bell-shaped, with a maximal steady state activity between 20 and 30 °C and lower activity at lower and higher temperatures (Darian-Smith et al., 1973; Dubner et al., 1975; Kenshalo and Duclaux, 1977). The reported temperature range over which cold fibers are active varies (Hensel, 1973b). At maintained temperatures above 40 °C or below 17 °C, cold fibers maintain a very low frequency discharge or become silent. However, some cold fibers can also be activated by high temperatures in the noxious range (Campero et al., 2001; Dubner et al., 1975; Kenshalo and Duclaux, 1977; Long, 1977), and this activation may be the basis for the paradoxical cold sensation that can be elicited by stimulation of cold spots with noxious heat stimuli. Cold afferents respond vigorously when the skin is actively cooled; conversely, when the skin is warmed, activity is inhibited. These dynamic responses are transient (Darian-Smith et al., 1973; Dubner et al., 1975; Kenshalo and Duclaux, 1977), i.e. the activity of the neuron decreases to a steady level shortly after reaching a discharge rate appropriate for the steady state temperature (Hensel and Zotterman, 1951c).

Cold fibers are activated by menthol (Hensel and Zotterman, 1951a). At temperatures when cold fibers are already active, menthol increases the stationary discharge rate drastically, i.e. it sensitizes cold fibers. Upon repetitive stimulus presentation at short intervals (<30–50 s) the responses in cold fibers undergo fatigue (Darian-Smith et al., 1973; Dubner et al., 1975). The average conduction velocity of cold fibers in monkey is between 9.0 and 15 m/s, suggesting that they are thinly myelinated (Aδ) afferents (Darian-Smith et al., 1973; Dubner et al., 1975).

Using microneurography, C fibers responding to innocuous cold temperatures have been found in human skin (Campero et al., 2001; Konietzny, 1984). Similar to the cold fibers described above, these afferents have ongoing activity at resting temperature, are readily activated by a cold probe and are insensitive to mechanical stimuli. In addition to the 'C cold' fibers, so-called 'high threshold' cold receptors (HCRs) have previously been identified in monkey skin (LaMotte and Thalhammer, 1982). These afferents are sensitive to cold temperatures below 27 °C but do not respond to mechanical or heat stimuli and have conduction velocities in the low A to C fiber range (Duclaux et al., 1980; LaMotte and Thalhammer, 1982). Compared to 'classical' cold fibers, HCR do not have ongoing activity at neutral temperatures, adapt quickly and cease responding to steady state temperatures in the range of 20–30 °C (i.e. where the response of classical cold fibers is maximal and maintained). Upon cold stimulation, HCRs have response latencies longer than cold fibers. Since HCRs start to respond within a second after application of non-painful cold stimuli, it has been suggested that these fibers contribute to the sense of innocuous cold at temperatures at the lower end of the working range of cold fibers (LaMotte and Thalhammer, 1982). Rapid cooling of the skin is also able to activate unmyelinated, low-threshold mechanoreceptors (CLTMs). These C fibers are non-responsive to intense heat stimuli and respond vigorously to gentle touch (Kumazawa and Perl, 1977). Their response to cooling is only transient, and a relatively rapid decrease in temperature is required for their effective activation (>2 °C/s); static temperatures do not induce activity. Since their response to cold stimuli is small compared to that induced by mechanical stimuli, their role in the percept of cold is questionable. The above studies demonstrate that C fibers respond to innocuous cold stimuli. Yet, a role of C fiber afferents in the sensation of innocuous cold is unlikely, since psychophysical experiments in humans employing differential nerve fiber blocks indicate that cold sensation is mediated by small myelinated (Aδ) afferents (Mackenzie et al., 1975).

Cold sensitivity can also be found in large myelinated afferents which respond vigorously to mechanical stimuli. Thus, about half of the slowly adapting mechanoreceptors (SA fibers), i.e. the Merkel discs in superficial skin layers and the Rufini endings in deeper skin layers, respond to cooling thermal gradients from normal skin temperature to 14.5 °C (Cahusac and Noyce, 2007; Duclaux and Kenshalo, 1972; Hensel and Zotterman, 1951b; Iggo and Muir, 1969; Tapper, 1965). The sensitivity of these mechanoreceptors to cold stimulation provides an explanation for Weber's deception or the silver Thaler (a coin used in Europe in the 18–19th century) illusion, i.e. the perception that cold objects appear heavier than warm objects. Nevertheless, it is rather unlikely that activity in large myelinated afferents actively contributes to the