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Spinal cord thermosensitivity: An afferent phenomenon?

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ABSTRACT

We review the evidence for thermoregulatory temperature sensors in the mammalian spinal cord and reach the following conclusions. 1) Spinal cord temperature contributes physiologically to temperature regulation. 2) Parallel anterolateral ascending pathways transmit signals from spinal cooling and spinal warming: they overlap with the respective axon pathways of the dorsal horn neurons that are driven by peripheral cold- and warm-sensitive afferents. 3) We hypothesize that these 'cold' and 'warm' ascending pathways transmit all extracranial thermosensory information to the brain. 4) Cutaneous cold afferents can be activated not only by cooling the skin but also by cooling sites along their axons: we consider that this is functionally insignificant *in vivo*. 5) By a presynaptic action on their central terminals, local spinal cooling enhances neurotransmission from incoming 'cold' afferent action potentials to second order neurons in the dorsal horn; this effect disappears when the spinal cord is warm. 6) Spinal warm sensitivity is due to warm-sensitive miniature vesicular transmitter release from afferent terminals in the dorsal horn: this effect is powerful enough to excite second order neurons in the 'warm' pathway independently of any incoming sensory traffic. 7) Distinct but related presynaptic mechanisms at cold- and warm-sensitive afferent terminals can thus account for the thermoregulatory actions of spinal cord temperature.

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Introduction

Thermosensitivity of the spinal cord in mammals is a topic that has been neglected in recent years. In the 40 y since Simon's landmark review,[38] some key experiments have been performed and we have learned more about the nature of thermo-afferents and their pathways. Here we revisit this topic in the light of current information. Coming from outside this specialist area, we set out by asking 2 sceptical questions:

1) *Can the phenomenon of spinal cord thermosensitivity be attributed to activating the central terminals of incoming thermosensory afferent fibers ?*
2) *If so, is this an experimental artifact without a physiological counterpart in real life?*

Background – thermoregulatory context

Traditionally, temperature regulation by mammals has been described in terms of a control system, or set of control systems, that defend body core temperature. For this purpose, the central nervous system drives homeostatic responses that are informed by temperature signals from the body surface and from deep body structures, including the brain.[15,19,25,41] Temperature signals from the skin are relayed by 2 main classes of afferent fiber, referred to as warm and cold receptors. They are used for both thermoregulation and conscious thermal sensation. Skin cold receptors drive cold-defense responses and express the cold-sensitive transient receptor potential (TRP) ion channel TRPM8; they respond to non-noxious skin cooling below about 35°C. Skin warm receptors that drive heat loss responses are progressively activated at temperatures above 35°C.[9,16,18] They are believed to possess warm-sensitive TRP channels that have not yet been defined.[7] Warm receptors have been much less studied than cold receptors, at least partly because they are rare in the furry skin of the commonly used laboratory animals.[9] Warm and cold skin signals for thermoregulation follow separate but parallel pathways in the central nervous system. They synapse with

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and excite secondary neurons in the superficial spinal dorsal horn.[4,8] These in turn send excitatory ascending connections, via the contralateral anterolateral tract, to the parabrachial nuclei (dorsal subnucleus – warm skin; external lateral subnucleus - cold skin). Neurons of both parabrachial subnuclei then relay those signals to the preoptic area, where they interact with thermoregulatory control circuits.[28,29]

Our knowledge of the core temperature signal for thermoregulation is incomplete. Part, but only part, resides in the anterior hypothalamus/preoptic area (AH/PO). In goats, Claus Jessen and colleagues clamped AH/PO temperature with a bank of implanted thermodes. When they selectively cooled the AH/PO by up to 3°C, they found that this caused only about 30% of the metabolic response that was observed when the whole body core was cooled by a similar extent.[14,27] In other experiments, they clamped both AH/PO temperature and spinal cord temperature together (spinal temperature was manipulated by a perfused U tube over its dorsal surface). The combined effect of cooling AH/PO and spinal cord temperatures together had a metabolic action equal to that of the rest of the body core – i.e. 50% of the core response.[23] The gradient of the response to spinal temperature was approximately linear between 32 and 40°C[14,23] - covering the physiological range - and the effects of spinal and AH/PO temperatures added linearly.[23] We can therefore infer that, at least in goats under these conditions, temperature sensors in the spinal cord drive ~20% of the body's response to core cooling. Comparable quantitative measurements of spinal temperature (rather than thermode temperature) are not available for warming or for other species, though generally stronger responses are reported for spinal warming than cooling.[19,24,38] But it is clear that also in other species such as the pig,[6] rat[5] and rabbit,[24] thermoregulatory responses are a continuous function of spinal thermode temperature across the physiological range. Outside the AH/PO and spinal cord, the remainder of the body core temperature signal (50% in the goat) remains largely undefined, although part is attributable to warm-sensitive intra-abdominal afferents that travel via the splanchnic nerves.[1,32,34,35]). It worth noting here, however, that the relative importance of thermoregulatory signals from different sites may vary with body size and species.[19,24]

The above information thus answers our second initial question in the negative. It is clear that spinal temperature sensors play a functional role at physiological temperatures.

Spinal temperature detection and transmission

Present evidence indicates all neurons that are activated in response to spinal heating or cooling, and that send ascending axons in the contralateral anterolateral (spinothalamic) tracts, are located in the superficial dorsal horn.[4,8] The key evidence is that in cats the signals generated when the lumbar spinal cord is cooled or warmed are carried by axons in the anterolateral tract of the cervical spinal cord.[40] The anterolateral tract is known to carry crossed ascending axons from superficial (laminae I and outer II) dorsal horn neurons that receive inputs from cutaneous thermoreceptor afferents. Importantly for our title and first question, the majority of axons in anterolateral tract whose activity was modulated by cooling and/or heating the spinal cord were also affected by thermal stimulation of skin.[39] Notably, axons in the anterolateral tract that were activated by cooling the spinal cord were also activated by cooling the skin. By contrast, the axons in the anterolateral tract that were activated by warming the spinal cord could be either inhibited or excited by warming the skin, although most of them responded to some type of cutaneous thermal stimulus.[39] In this context, there is a paradox. Simon and colleagues reported finding similar numbers of spinal warm-sensitive and spinal cooling-sensitive anterolateral axons in cats;[39,40] but this balance contrasts strikingly with the paucity of superficial dorsal horn neurons (in the spinal cord or in the homologous trigeminal region) found to be activated by skin warming. In the cat and other species *in vivo*, the reported numbers dorsal horn cells responding to cold skin outnumber those responding to warm skin by at least 10:1.[4,8,10,11] It therefore seems evident that spinal warm detection involves not only neurons in the cutaneous warm afferent pathway, but also other neurons that send their axons into the anterolateral tract. Some of these 'missing' neurons could be those receiving warm signals from visceral afferents in the splanchnic nerves.[32,33,35] Visceral afferents also terminate in the same superficial spinal laminae,[30] but would most likely not have responded to the search stimuli used in the hunt for cells responding to skin warming.[4,10,11]

The above findings are thus compatible with the hypothesis that spinal cold sensitivity feeds into the neural pathway from cutaneous cold receptors. But the

neural pathway from cutaneous warm receptors seems to comprise too few neurons to account for spinal warm sensitivity.

Given the concordance between the ascending afferent pathways for cutaneous and spinal temperatures, we further hypothesize that ***all*** extracranial temperature signals for thermoregulation follow the same ascending neural pathways. We predict that those influencing thermoregulatory reflexes would do so by relaying at glutamatergic synapses in (respectively) the dorsal and external lateral parabrachial nuclei, as established for cutaneous warm and cold signals by Nakamura and Morrison.[28,29] Besides cutaneous and spinal temperatures, these would include signals from deep body regions such as the abdomen, which are known to travel via the splanchnic nerves and spinal cord.[32,35] We do not yet know whether these spino-parabrachial projections are collateral branches of the spinothalamic neurons that underlie thermal perception,[4,8] though this would be the simplest possibility. How, and via which neural connections, spinal temperature might influence behavioral thermoregulation remain open questions.

Thermally induced behavior of thermoresponsive neurons in the spinal cord is similar to that of cutaneous thermoreceptors

Recordings from the axons of the ascending anterolateral tract demonstrate that many of the neurons that are activated by heating or cooling in the cat spinal cord have similar response characteristics to those of cutaneous warm and cold receptors respectively.[40] The spinal cord cold-sensing neurons have a peak level of activity at a static temperature around 28°C, whereas the activity of spinal cord warm-sensing neurons rises steeply with static temperatures between 35 and about 43°C and then declines at higher temperatures. This thermosensitivity is virtually identical to that described for cutaneous cold and warm receptors in primates[9] and cutaneous cold receptors in cats.[17] The warm receptors in the abdominal wall of rabbits recorded in the splanchnic nerve also have similar thermosensitivity to cutaneous warm receptors and spinal warm-sensitive neurons in other species.[34] Some of the cold- or warm-sensing spinal cord neurons displayed peak levels of nerve activity during cooling or heating, respectively. This dynamic response to changes in temperature is a commonly reported feature of both cold and warm receptors in skin,[9,17] but not of reflex responses to core temperature.[36] In the study of Simon and Iriki,[40] the activity of some cold-sensing spinal cord neurons increased steeply at temperatures above 41°C (44 and 47°C). This so called paradoxical response to noxious heating has also been described in primate cutaneous cold receptors.[9] Taken together, these findings strongly suggest that similar mechanisms in the spinal cord and in the periphery transduce thermal stimuli into neural activity.

Mechanisms of spinal cold sensitivity

In cutaneous sensory receptors responding to innocuous cooling, it has been firmly established that TRPM8 plays a primary role in transducing thermal stimuli.[2,3] In these cold sensitive primary afferent neurons, functional studies have indicated that membrane expression of TRPM8 is not confined to sensory nerve endings in skin, but is present over other parts of the neuron including the presynaptic endings in the superficial dorsal horn.[21,44,45,47] Importantly, studies using TRPM8 reporter mice have identified axon terminals of TRPM8 expressing dorsal root ganglion neurons in the superficial dorsal horn, but have not identified TRPM8 expressing neurons within this region of the spinal cord.[42,43]

Consistent with the presence of TRPM8 in the presynaptic-terminals of the cutaneous cold receptor, in rat spinal cord slices both the TRPM8 agonist menthol and cooling increase the frequency of spontaneous miniature excitatory postsynaptic synaptic currents (mEPSCs) in a subpopulation of neurons in lamina I and II of the dorsal horn.[47] Similar findings have been observed in co-cultures of dorsal root ganglion neurons and dorsal horn neurons, where menthol increased both the frequency of mEPSCs and the amplitude of action potential-evoked excitatory post-synaptic synaptic currents in dorsal horn neurons.[46] These findings indicate that cold and menthol have a presynaptic action that would enhance action potential-evoked neurotransmitter release at the first synapse in the cold afferent pathway. The idea is illustrated in Figure 1.

If this explanation is correct, the cold afferent pathway would need to have ongoing activity for the mechanism to work, or there would be no incoming synaptic signals to enhance. The prediction would

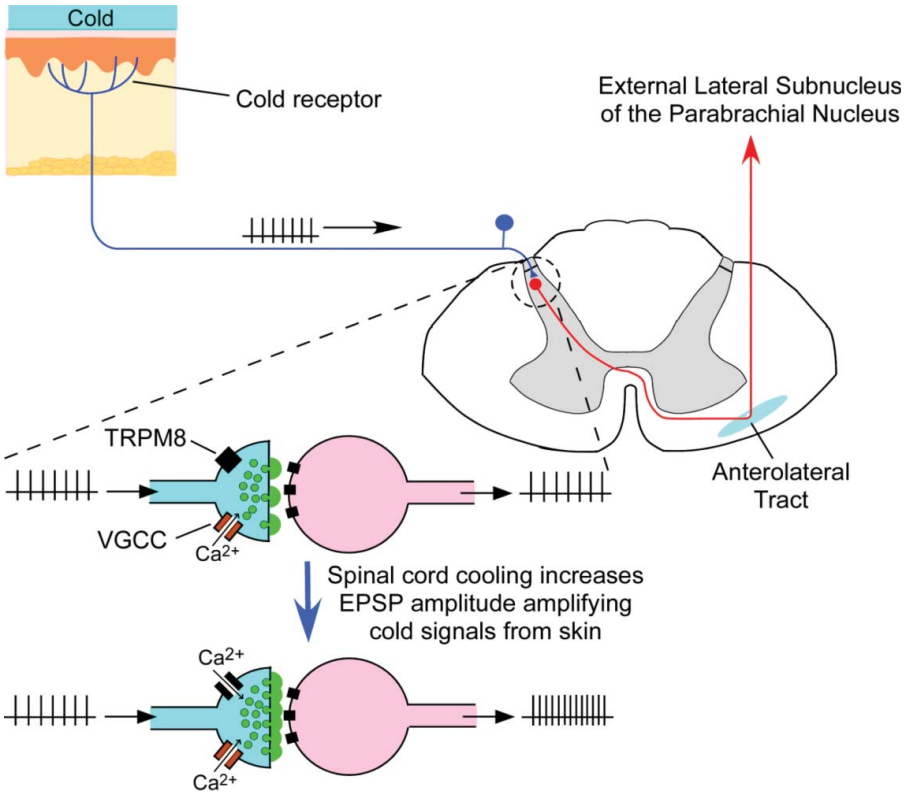

Figure 1. Spinal cold sensing. Diagram showing suggested mechanism whereby spinal cooling enhances neurotransmission at the first synapse of the cold afferent pathway, and spinal warming attenuates transmission. Abbreviations: TRPM8, transient receptor potential ion channel M8; VGCC, voltage-gated calcium channel; EPSP, excitatory postsynaptic potential.

then be that spinal cooling only works when the skin is cold – and that is exactly what happens! In goats,[19] rats[5] and pigs [6] the metabolic response to spinal cooling is present at low ambient temperatures but disappears once the ambient temperature reaches 30°C or more (when skin temperature would be high and cold afferent discharge suppressed). We cannot exclude the possibility that the increased miniature synaptic events in the cold spinal cord could themselves initiate action potential firing in second order neurons, but the above finding that warm ambient temperatures prevent the metabolic effects of spinal cooling suggests that such a mechanism is of minimal significance.

Given that cold afferents show distributed axonal cold-sensitivity,[44] could spinal cooling also work by generating spike activity in the intraspinal parts of their axons? We do not believe so, for 2 reasons. First for this to be functionally significant, the central part of the axon would need to generate action potentials at a higher rate than those incoming from the skin. This is because action potentials conduct in both directions, and those generated from the central terminal would conduct centrifugally, collide with and annihilate incoming afferent traffic. The overall effect would thus be minimal. Second, this is intrinsically unlikely to happen because spinal temperature would almost never be lower than skin temperature.

We propose that spinal cold sensitivity is due to potentiation of transmitter release evoked by incoming action potentials at the first synapse of the cutaneous cold pathway (Fig. 1).

Mechanisms of spinal warm sensitivity

For spinal warm sensing, related but distinct mechanisms may apply. Spinal dorsal horn temperature would almost always be >35°C, which is within the range where the transduction channels of warm-sensitive primary afferents are activated. Within this physiological range, thermosensitivity has been investigated *in vitro* in 2 studies that we consider directly relevant to our topic. In the first, Pehl and colleagues[31] made extracellular unit recordings in layers I and II of the dorsal horn in slices of rat lumbar spinal cord, where they found a population of spontaneously active neurons, over half of which were excited by warming in

the range 33-41°C.[31] In stark contrast to the *in vivo* studies discussed above, only 2% of this neuronal population was excited by cooling.[31] The warm-activated neurons responded with a high Q_{10} (median 7), and in most cases (9/13), their response to warming survived synaptic blockade with a low [Ca^{2+}], high [Mg^{2+}] solution. The cold responsiveness of the one cold-activated neuron tested in this study did not survive synaptic blockade.

In the second study, Largent-Milnes and colleagues from the Andresen laboratory made whole cell recordings from cells in the homologous region of the trigeminal dorsal horn (Lamina I/II of trigeminal *nucleus caudalis*).[22] These workers found that about 2/3 of the cells recorded in this region showed a high rate of spontaneous miniature excitatory postsynaptic currents (sEPSCs), whose frequency was exquisitely temperature-sensitive (mean $Q_{10} = 17.8$). No cold-sensitive neuronal responses were seen. The rate and amplitude of these warm-sensitive sEPSCs was unaffected by tetrodotoxin, indicating that they were presynaptic in origin but independent of any incoming afferent action potentials; i.e., they were miniature EPSCs resulting from the ongoing vesicular discharge of glutamate from the afferent nerve terminals. Importantly (in recordings under current clamp), those spontaneous synaptic events were evidently sufficient to generate action potentials in the postsynaptic cell, which they did at a rate that increased proportionately with local warming over the range 32-37°C.[22]. It is important here to point out that synaptic blockade with a low [Ca^{2+}], high [Mg^{2+}] solution (see above) does not exclude a presynaptic site for thermal transduction. This is because miniature EPSC frequency is not greatly affected by inhibiting Ca^{2+} influx into nerve terminals.[13] Instead, the frequency of miniature EPSCs can be regulated by Ca^{2+} released from intracellular stores and/or by regulation of the exocytotic machinery.[13] There is now growing recognition that such action potential-independent transmitter release may be functionally important in diverse circumstances.[20] Interestingly, temperature-sensitive miniature EPSCs were also reported by the Andresen group to occur at the primary visceral afferent synapse in the nucleus of solitary tract (NTS): these, however, showed somewhat lower temperature sensitivity ($Q_{10} \approx 4$),[12,37] and this was attributed to activity of the TRPV1 (capsaicin-sensitive) ion channel.[37] At the somatic primary afferent synapse in the trigeminal dorsal horn, by contrast, the highly temperature-sensitive miniature EPSCs occurred independently of TRPV1 expression.[22] We may speculate that the predicted but unidentified warm-sensitive TRP channel was responsible.

The studies discussed above may thus be reconciled by a common mechanism – spontaneous transmitter release that happens to be highly warm-sensitive. This mechanism seems sufficient to account for spinal warm sensitivity, although possible additional mechanisms (e.g. postsynaptic warm sensitivity of dorsal horn neurons) have not yet been excluded.

It therefore seems that spontaneous transmitter (glutamate) release from the primary afferent terminals - independent of any incoming afferent action potentials - is a mechanism that activates second order neurons in a warm-sensitive manner (Fig. 2).

Note that the mechanism here is distinct from that proposed for spinal cold sensing, in that it does not require any incoming afferent traffic. It is still unclear which warm-sensitive afferent pathways might be co-opted to signal spinal warming, but they may well not be cutaneous. As mentioned above, dorsal horn neurons receiving cutaneous warm afferents are rare. Moreover, if extra action potentials were fed into a cutaneous afferent pathway as it traversed the spinal cord, this would be expected to distort cutaneous thermal discrimination, which we know is unaffected by body core temperature.[26] No such sensory conflict would arise if spinal warming activated the pathway from visceral warm receptors, however, so these are a plausible target. Alternatively there may exist a special set of warm-sensitive primary afferent fibers without any functional peripheral terminal outside the spine. More critical information is needed before any further conclusions on this topic can be reached.

Overview

Spinal cold and warm sensing are thus both attributable to presynaptic actions on temperature-sensitive afferent terminals. The answer to the first question we posed is therefore a partial 'yes', but not in the way we first imagined: in neither case does it involve ectopic generation of action potentials in the afferent fiber itself. The distinct mechanisms of spinal warm and cold sensing help explain why spinal cold sensing depends on incoming sensory traffic but spinal warm sensing does not. They also fit with the experimental observation that *in vitro*, when afferent inputs are

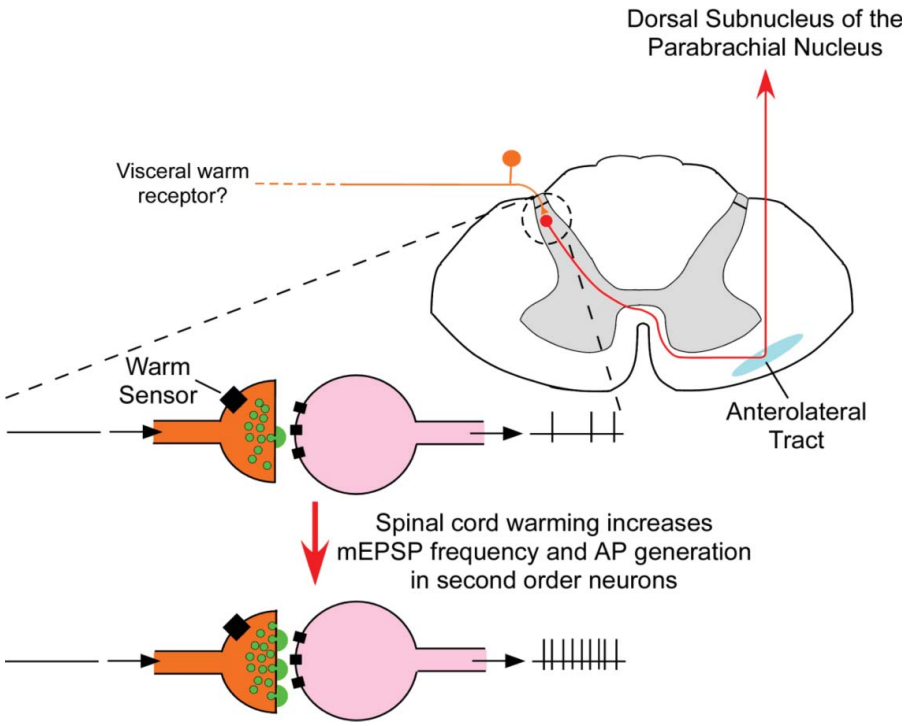

Figure 2. Spinal warm sensing. Diagram showing suggested mechanism whereby spinal warming generates action potentials in the secondary neurons of unidentified, possibly visceral, warm-sensing pathways. Abbreviations: mEPSP, miniature excitatory postsynaptic potential; AP, action potential.

disconnected, warm- sensitive neural activity is abundant but cold-sensitive responses are essentially absent.[22,31] What still need to be resolved are the nature and origins of the inferred warm-sensitive afferent neurons, whose effects are so frequently found *in vitro* yet which have been so rarely detected *in vivo*.

In vivo, we predict that the 2 presynaptic mechanisms work in a complementary fashion. Under conditions when body core temperature is high and the spinal cord is warm, dorsal horn warm-responsive neurons would show ongoing activity and promote heat-loss responses. At the same time, any incoming afferent traffic from cold skin would not be potentiated at the first synapse of its pathway. Under conditions where body core and spinal temperatures are reduced, afferent inputs from peripheral cold receptors would be potentiated at their first synapse in the dorsal horn, while any opposing activity in the pathway from dorsal horn 'warm' cells would be low.

Summary and conclusions

1) Spinal cord temperature contributes physiologically to temperature regulation.
2) Parallel anterolateral ascending pathways transmit signals from spinal cooling and spinal warming: they overlap with the respective axon pathways of the dorsal horn neurons driven by peripheral cold- and warm-sensitive afferents.
3) We hypothesize that these cold and warm ascending pathways transmit all extracranial thermosensory information to the brain.
4) Cutaneous cold afferents can be activated not only by cooling the skin but also by cooling sites along their axons: we consider that this is functionally insignificant *in vivo*.
5) By a presynaptic action on their central terminals, local spinal cooling enhances neurotransmission from incoming 'cold' afferent action potentials to second order neurons in the dorsal horn; this effect disappears when the spinal cord is warm. (Fig. 1).
6) Spinal warm sensitivity is due to warm-sensitive 'miniature' vesicular transmitter release from afferent terminals in the dorsal horn: this effect is powerful enough to excite second order neurons in the 'warm' pathway independently of any incoming sensory traffic. (Fig. 2).

7) Distinct but related presynaptic mechanisms at cold- and warm-sensitive afferent terminals can thus account for the thermoregulatory actions of spinal cord temperature.

Abbreviations

AH/PO	anterior hypothalamus/preoptic area
AP	action potential
EPSC	excitatory postsynaptic current
EPSP	excitatory postsynaptic potential
NTS	nucleus of solitary tract
Q_{10}	quotient of increase over 10°C
TRP	transient receptor potential
VGCC	voltage gated calcium channel

Disclosure of potential conflicts of interest

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