Mechanical sensibility of nociceptive and non-nociceptive fast-conducting afferents is modulated by skin temperature

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Boada MD, Eisenach JC, Ririe DG. Mechanical sensibility of nociceptive and non-nociceptive fast-conducting afferents is modulated by skin temperature. J Neurophysiol 115: 546–553, 2016. First published November 18, 2015; doi:10.1152/jn.00796.2015.—The ability to distinguish mechanical from thermal input is a critical component of peripheral somatosensory function. Polymodal C fibers respond to both stimuli. However, mechanosensitive, modality-specific fast-conducting tactile and nociceptor afferents theoretically carry information only about mechanical forces independent of the thermal environment. We hypothesize that the thermal environment can nonetheless modulate mechanical force sensibility in fibers that do not respond directly to change in temperature. To study this, fast-conducting mechanosensitive peripheral sensory fibers in male Sprague-Dawley rats were accessed at the soma in the dorsal root ganglia from T11 or L4/L5. Neuronal identification was performed using receptive field characteristics and passive and active electrical properties. Neurons responded to mechanical stimuli but failed to generate action potentials in response to changes in temperature alone, except for the tactile mechanical and cold sensitive neurons. Heat and cold ramps were utilized to determine temperature-induced modulation of response to mechanical stimuli. Mechanically evoked electrical activity in non-nociceptive, low-threshold mechanoreceptors (tactile afferents) decreased in response to changes in temperature while mechanically induced activity was increased in nociceptive, fast-conducting, high-threshold mechanoreceptors in response to the same changes in temperature. These data suggest that mechanical activation does not occur in isolation but rather that temperature changes appear to alter mechanical afferent activity and input to the central nervous system in a dynamic fashion. Further studies to understand the psychophysiologic implications of thermal modulation of fast-conducting mechanical input to the spinal cord will provide greater insight into the implications of these findings.

primary sensory neurons; mechanical sensitivity; multimodal stimulation; in vivo electrophysiology

SENSORY PERCEPTION BEGINS in the periphery with detection of specific stimulus modalities. Environmental information and stimuli are coded into electrical activity that is transmitted to the central nervous system via peripheral sensory neurons (PSNs). Peripheral afferents primarily respond with electrical activity to thermal and mechanical forces acting on the skin or the hairs of the skin. PSNs are customarily classified based on three general characteristics: the type of energy they respond to (mechanical, thermal, chemical, or a combination), the amount of energy required for activation (low threshold = non-nociceptive; high threshold = nociceptive), and their conduction velocity (CV) (Lumpkin and Caterina 2007). However, even in neurons that only respond to mechanical forces, there is evidence that this response can be modified by changes in environmental temperature.

Fast-conducting mechanically sensitive afferents do not generate action potentials in response to changes in temperature in the absence of thermally induced injury. However, temperature may modulate mechanical activation of the fastconducting PSNs in unique ways that provide valuable environmental information that could alter the central nervous system’s functional output. Evidence exists for such modulation of PSN activation by thermal changes whereby the perception of roughness depends on the temperature of the skin. Thus either cooling or heating reduces the perception of roughness (Weitz 1941; Mackworth 1953; Mills 1956; Provis and Morton 1960; Stevens et al. 1977; Green 1977; Green et al. 1979). However, far less is known about any modulatory effect of temperature on mechanosensitive nociceptors. Furthermore, it is unclear if these findings exist in other mammals.

In rodents, mechanosensitive specific afferents (unresponsive to thermal stimulation) have been roughly categorized into two classes: those with tactile sensitivity (punctate pressure, vibration, tactile spatial acuity, and roughness), and those serving fast/first pain encoding. Both classes of sensory neurons have myelinated, large diameter fibers conducting within the A range (1.2–11.5 m/s; Aβ-Aδ fibers). Modulation of information transmission from PSNs may be relevant to the perception of pressure and vibrotactile stimuli as well as nociceptive input. Furthermore, since tactile inputs have been reported to have important inhibitory effects on nociceptive throughput (Narikawa et al. 2000; Green and Schoen 2005), any change in their normal encoding capabilities may impact central pain processing. Little is known about the modulatory effects of temperature on selective mechano-nociceptive afferents or how simultaneous multimodal activation of different types of tactile sensory neurons changes normal discharge patterns and the resulting signals entering the central nervous system.

The current study addresses these questions and shows how temperature affects different types of selective mechanoresponsive PSNs (nociceptive and non-nociceptive) along with two dermatomes (T11 and L4) in young adult rats. We show that the skin temperature greatly modifies their normal excitability and responsiveness, sometimes in opposite directions. We speculate that these changes in encoding capabilities could profoundly alter the function of cross-fiber inhibition at central integration sites.

METHODS

Animals

Thirty-six male Sprague-Dawley rats (4–6 wk of age) were used. Some of these animals were studied in protocols examining the effect of...
of incision (Boada et al. 2012) or differences between mechanosensory afferents innervating glabrous and hairy skin (Boada et al. 2010). When a cell was obtained meeting criteria for study in the current protocol, it was examined according to the methods below. None of the cells in the current study have been previously reported or were affected by any other experimental manipulation of their receptor field (RF; e.g., incision). Animals were housed together in pairs in a climate-controlled room under a 12-h light-dark cycle. The use and handling of animals were in accordance with guidelines provided by the National Institutes of Health and the International Association for the Study of Pain and the procedures, and experiments were approved by the Institutional Animal Care and Use Committee of Wake Forest School of Medicine.

**Electrophysiology**

Animals were deeply anesthetized with isoflurane 3%. The trachea was intubated and the rat ventilated using pressure controlled ventilation (Inspira PCV; Harvard Apparatus, Holliston, MA) with humidified oxygen. Heart rate and noninvasive blood pressure were monitored throughout as a guide to depth of anesthesia. Anesthetized animals were immobilized with pancuronium bromide (2 mg/kg) and inspired and end tidal isoflurane concentration maintained at 2% throughout the study (Tevan Pharmaceutics). As illustrated in Fig. 1, a dorsal midline incision was made in trunk skin and either L4, L5, or T11 dorsal root ganglion (DRG) and adjacent spinal cord were exposed by laminectomy as previously described (Boada et al. 2010). The tissue was continuously superfused with oxygenated artificial cerebrospinal fluid [aCSF (in mM): 127.0 NaCl, 1.9 KCl, 1.2 KH₂PO₄, 1.3 MgSO₄, 2.4 CaCl₂, 26.0 NaHCO₃, and 10.0 D-glucose]. The spinal column was secured using custom clamps and the preparation was transferred to a preheated (32–34°C) recording chamber where the superfusate was slowly raised to 37°C (MPRE8; Cell MicroControls, Norfolk, VA). Rectal temperature (RET-3; Physitemp) was maintained at 34°C throughout (MicroPower1401; CED).

**Cellular Classification Protocol**

The procedure used in this study to classify primary sensory afferents in vivo has been described in detail (Boada et al. 2015). Briefly, RFs were located with the aid of a stereomicroscope using increasing mechanical stimulation; the latter progressed from light touch with a fine sable hair paintbrush to searching with blunt probes and ultimately gentle to noxious pinch with fine-tipped forceps. Although cellular RFs were found across the entire dermatome in these intact preparations, only those along the medial portion of the dermatome were used in this study [Fig. 1A; animal flank (T11); posterior-lateral of the animal leg and paws (L4/L5)]. RFs located near the incision site or in areas not accessible to simultaneous mechanical and thermal stimuli were not studied further.

Mechanical thresholds were determined with calibrated von Frey filaments (VHF; Stoelting, Wood Dale, IL) and the area of maximal sensitivity was clearly marked, using a red fine point marker. Adaptation rate was evaluated using suprathreshold probes mounted in a micromanipulator; skin stretch and vibratory stimuli (tuning forks of 256 and 512 Hz; SKLAR Instruments, West Chester, PA) were also tested in many cells.

The electrophysiological recordings from L4, L5, or T11 DRG neurons were limited to a maximum duration of 75 min to diminish the likelihood that experimental manipulation would result in sensitization. DRG neuronal somata were impaled with quartz micropipettes (80–250 MΩ) containing 1 M potassium acetate. All included cells satisfied the following requirements: resting membrane potential more negative than −40 mV, action potential (AP) amplitude ≥30 mV, the presence of afterhyperpolarization (AHP), and appropriate location of receptive field (RF), as described below. DC output from an Axoclamp 2B amplifier (Axon Instruments/Molecular Devices, Sunnyvale, CA) was digitized and analyzed offline using Spike2 (CED, Cambridge, UK). Sampling rate for intracellular recordings was 21 kHz throughout (MicroPower1401; CED).

**Fig. 1.** A: schematic diagram of the in vivo rat T11 and L4 preparation (lateral view). Diagram of lateral flank (dotted line) illustrates the areas where the neuronal receptive field (RF) of the studied afferents were found in hairy skin and glabrous skin for LTMR-RA, LTMR-MC, LTMR-Hair, and AHTMR. B: schematic diagram of the stimulation protocols (SP). Gray dots and areas represent mechanical stimulation and temperature windows used in this study, respectively. MT, mechanical threshold. C: flowchart and classification of the neurons included in the study. Gray boxes represents the SP number (see METHODS) used to activate the cellular RF of every group. LTMR, low-threshold mechanoreceptor; RA, rapid adapting; MC, mechano-cold; AHTMR, A-high threshold mechanoreceptor.
Somatic Electrical Properties

Active membrane properties of all excitable neurons were analyzed including the amplitude and duration of the AP and AHP of the AP, along with the maximum rates of spike depolarization and repolarization (MRD and MRR, respectively); AP and AHP durations were measured at half-amplitude (Dₐ₉₀ and AHPₐ₉₀, respectively) to minimize hyperpolarization-related artifacts. Passive properties were analyzed including membrane resting potential (Eₑ), input resistance (Rᵢ), time constant (τ), inward rectification, and, where possible, rheobase; all but the latter were determined by injecting incremental hyperpolarizing current pulses (±0.1 nA, 500 ms) through balanced electrodes.

Conduction Velocity

Because intact thoracic and lumbar DRGs serve multiple nerves, spike latency was obtained by stimulating the RF at the skin surface using a bipolar electrode (0.5 Hz); this was performed following all natural stimulation to prevent potential alterations in RF properties by electrical stimulation. All measurements were obtained using the absolute minimum intensity required to excite neurons consistently without jitter; this variability (jitter) in the AP generation latency (particularly at significantly shorter latencies), seen at traditional (i.e., 2- to 3-fold threshold) intensity, has been presumed to reflect spread to more proximal sites along axons. Stimuli ranged in duration from 50 to 100 μs; utilization time was not taken into account. Conduction distances were measured for each afferent on termination of the experiment by inserting a pin through the RF (marked with ink at the time of recording) and carefully measuring the distance to the DRG along the closest nerve.

Maximal Instantaneous Frequency Response and Discharge Rate

Since it is extremely difficult to deliver a controlled, sustained mechanical stimulus (both force and duration) we used maximal instantaneous frequency response (IFₘₐₓ, Hz) in addition to discharge rate (AP/s), as an additional parameter to detect a change in the response characteristics of these neurons. IFₘₐₓ was calculated as the reciprocal of the minimum interval between impulses meanwhile the discharge rate were obtained as the peak cellular response (with a bin of 1 s), during multimodal (thermal and mechanical) stimulation (for details, see next section).

Cellular RF Multimodal Stimulation Protocol

Once the area of highest sensitivity to mechanical stimulation was established, a thermode (3-mm² Peltier device, feedback-controlled; Yale Instrument Repair and Design Shop, New Haven, CT) attached to a micromanipulator was carefully positioned directly over the center of this area [always perpendicular (90°) to the RF]. This thermode was then brought down in close contact with the skin and displaced laterally (parallel to the skin surface) a few times to assure both full steady contact of the thermode and constant coverage of the area under stimulation. Changes in the cellular discharge rate (AP/s) and IFₘₐₓ were evaluated at three different temperatures (cold pulses: 32, 15, and 2°C; heat pulses: 32, 43, and 50°C; SP-III).

SP-II: rapid multimodal stimulation. Two to three minutes after the initial SP-I cold-heat pulse, a second cold-heat pulse (thermal stimulation similar to SP-I) was applied. This time mechanical stimulation was simultaneously applied by a concurrent steady backward and forward lateral displacement of the thermode (0.5 mm, ~1 Hz) to produce intermittent mechanical suprathreshold (for tactile) activation of the cellular RF during changes in temperature. This procedure was assisted by the use of a stereomicroscope to assure both full steady contact of the thermode and constant coverage of the area under stimulation. Changes in the cellular discharge rate (AP/s) and IFₘₐₓ were evaluated at three different temperatures (cold pulses: 32, 15, and 2°C; heat pulses: 32, 43, and 50°C; SP-III).

SP-III: multiple rapid thermal stimulations. During SP-II, 6 cells developed an apparent thermal sensitivity (spike activity out of phase in response to the mechanical thermode movements). The thermal responsiveness of these cells was studied further by the application of three consecutive rapid cold-heat pulses as in SP-I with an interval of 5 min between pulses. If thermal responsiveness was confirmed, cells were excluded from any further analysis, as they were deemed sensitized and responding to thermal activation in the absence of mechanical stimulation.

SP-IV: sustained cold exposure. When possible, selected cells (by normal mechanical responsiveness, impalement stability, and healthy somatic electrical properties) were then stimulated by a successive continuous cold exposure (2°C, ~5 min). In some cases the thermode was replaced by a piece of ice to expose the RF to a more natural stimulus. In both cases (ice or thermode stimulation), changes in the cellular mechanical threshold were established by the application of VFH over the RF area (see Cellular Classification Protocol) in rapid succession (3- to 4-s gap between VFHs), beginning with the VFH previously established as producing the minimal force necessary to activate that RF area (threshold). In the cases that ice was used, the area was wiped of any water before using the VFH. The number of cells studied with each protocol is shown in the flowchart (Fig. 1C).

Statistical Analysis

Before analysis, parametric assumptions were evaluated for all variables using histograms and descriptive statistics. For normally distributed measurements, means ± SD are used. For measurements not normally distributed, descriptive statistics are reported using medians (and range). Standard parametric (Student’s t-test, one-way ANOVA, linear regression) or nonparametric (Mann-Whitney U-test, Kruskall-Wallis) tests were used, depending on normality. Statistical tests were carried out using multiple packages (OriginPro 9.5, Northampton, MA; InStat/Prism, San Diego, CA).

RESULTS

Intracellular recordings from 36 animals were obtained in 286 well-characterized mechanosensitive neurons innervating T11 (55/286) and L4/L5 (231/286) dermatomes. In 74/286 of these neurons, the peripheral RF was accessible to adequate thermal stimulation; 23/55 innervating the distal flank of the animal (T11) and 51/231 innervating posterior-lateral portion of the animal’s legs and paws (L4/L5). Of the 74 cells (all fast conducting), 43 were classified as non-nociceptive and 31 as nociceptive based on mechanical thresholds. The non-nociceptive low-threshold mechanoreceptors (LTMR) were further identified as: rapid adapting (LTMR-RA) (16/43), mechanical and cold sensitive (LTMR-MC) (6/43) (Boada and Woodbury 2007), or down hairs [D-hairs (6/43)] and hairs (15/43). The last two types of afferents (D-hairs and hairs) were analyzed as a single group (LTMR-Hairs) due to their physiological similarities and innervation targets. The nociceptive cells were all identified (31/31) as fast-conducting (Aβ-Aδ
Mechanosensitivity During Rapid Thermal Stimulation

No neuron in the study responded to rapid thermal changes (cold-heat pulse) during SP-I in the absence of mechanical stimulation, except for the LTMR-MC neurons. Mechanical sensibility during rapid thermal changes in the skin temperature was then evaluated by simultaneous mechanical activation during fast thermal stimulation (cold-heat pulses) during SP-II (for details, see SP I: single rapid thermal cold-heat pulse stimulation and SP-II: rapid multimodal stimulation and Fig. 1B).

LTMR-RA

These cells exhibited CV within Aβ range (median: 15.9 m/s; 11–35 m/s; Fig. 2A), although very sensitive to static mechanical stimulation (median: 0.7 mN, 0.07–1.57 mN; Fig. 2B) these afferents were particularly responsive to rapid changes in mechanical stimulation (vibration), being vigorously activated by both 265 and 512 Hz (1:1) tuning fork application (Boada et al. 2015). All these cells (16/16) remained responsive to mechanical stimulation during and after thermal stimulation [typical responses in Figs. 3A (cold) and 5A (heat)].

Cold. The discharge rate of these afferents was unaffected by rapid cooling of the skin, but the IFmax (Hz) was significantly reduced ($P < 0.001$; Fig. 4, A and B).

Heat. Mechanical activation was maintained during warming of the skin after the cold pulse. After a normal response was obtained, the heat pulse was applied (Fig. 5A). Again the IFmax was significantly reduced ($P < 0.05$), but no change in the discharge rate was discernible (Fig. 4, C and D).
These cells exhibited CV in the Aβ/H9252 range (median: 21 m/s; 8.8–31 m/s; Fig. 2A) and were exclusively found innervating hairy skin. They were responsive to static mechanical stimulation (median: 0.19 mN; 0.19–0.39 mN; Fig. 2B) as well as vibration (256 Hz) and cold exposure (median: 17.5°C, 10–19°C). Responses to mechanical stimulation were altered during and after thermal exposure [typical responses in Fig. 3B (cold) and 5B (heat)].

Cold. During the rapid reduction of skin temperature, all of these neurons (6/6) remained sensitive to mechanical stimulation. Overall, some reduction in activity was noted as a consequence of cold exposure. Below 15°C both the discharge rate and IF_{max} of these neurons to mechanical stimulation was significantly reduced (P < 0.001; Fig. 4, A and B).

Heat. The response to rapidly increasing the skin temperature was different than that produced from the cold exposure (Fig. 5B). A rapid loss in sensitivity to mechanical stimulation (threshold to change ~43°C) occurred with a significant reduction (P < 0.001) in both discharge rate and IF_{max} (Fig. 4, C and D). Insensitivity to probe movement was achieved around 50°C in three of six neurons.

LTMR-Hairs

These afferents were activated by a single hair displacement, conducted in a broad range including both Aβ and Aδ afferents (median: 13.7 m/s; 1.5–24 m/s; Fig. 2A), and had significantly lower thresholds to static mechanical stimulation than LTMR-RA afferents (median: 0.07 mN, 0.07–0.7 mN; P < 0.001; Fig. 2B). While showing a rapid adaptation rate (on-off response to static force), their ability to follow vibration (265 Hz) was compromised upon rapid temperature changes.
Hz; 1:1) was less consistent than LTMR-RA and several afferents (15/21) failed to accurately (1:1) follow 512 Hz. Responses to mechanical stimulation were altered during and after thermal exposure [typical responses in Figs. 3C (cold) and 4C (heat)].

Cold. A sudden reduction in the skin temperature briskly diminished the response to mechanical stimuli of these afferents. Median discharge rate and IF max were both significantly diminished the response to mechanical stimuli of these afferents (15/21) failed to accurately (1:1) follow 512 Hz. Insensitivity to probe movement was achieved at ~0°C in 4/21 neurons.

Heat. Similar to the effects produced by rapid cold exposure, both discharge rate and IF max were diminished with heat exposure. However, this change was smaller and less consistent than that observed in response to the cold pulse. A reduction in response only occurred either at the beginning of the heat pulse [discharge rate (32–43°C)] or after the highest temperature was reached [IF max between (43–50°C); P < 0.05 and P < 0.001, respectively; Fig. 4, C and D].

AHTMR

These cells exhibited CV primarily in the Aδ range (median: 8.4 m/s; 1.5–17 m/s; Fig. 2A) and mechanical threshold one to three orders of magnitude greater than the LTMRs (median: 147 mN; 9.8–980 mN; Fig. 2B). None of these afferents was activated during the initial thermal stimulation (cold-heat pulse; SP-I) nor during simultaneous mechanical (low-threshold displacement) and thermal stimulation (cold-heat pulse; SP-II). This is to be expected as the thresholds for the mechanical stimulation of AHTMR remain well above the mechanical stimulation used in the SP-II as defined in Fig. 2B. Most of these neurons (25/31) remained unresponsive to the application of rapid changes in the skin temperature. However, in some cases, repeated exposure to cold and heat by the end of SP-II resulted in thermal sensitivity (6/31). These thermoresponsive, sensitized cells (6/6) were exposed to multiple thermal stimulations (SP-III). Every thermal exposure generated increasingly lower thresholds and more robust responses suggestive of sensitization (Fig. 6; 6/6, cold threshold median: 0°C; −3–10°C; heat threshold median: 47°C; 46–50°C).

Mechanosensitivity After Constant Cold Stimulation

Sustained exposure to cold (for details see SP-JV: sustained cold exposure) significantly modified (P < 0.001) the RF mechanical threshold of both tactile (LTMR: 12/12) and nociceptive (AHTMR: 17/17) afferents. The tactile afferents had an approximately eightfold increase in mechanical thresholds from the sustained cold compared with baseline temperature response [median: from 0.19 mN (0.078–1.56 mN) at 32°C to 1.56 mN (0.39–39.2 mN) at 2°C; P < 0.001]. In contrast, nociceptive afferents (AHTMRs) showed an approximate 40-fold decrease in mechanical threshold from the same cold exposure [median: from 147 mN (9.8–980 mN) at 32°C to 3.9 mN (1.56–588 mN) at 2°C; P < 0.001; Fig. 4E].

DISCUSSION

In this report we describe temperature modulation of mechanical sensitivity in different types of fast-conducting afferent neurons innervating both hairy and glabrous skin at thoracic and lumbar dermatomes in rats. The principal observations and conclusions are as follow: 1) skin temperature alters the sensitivity and performance of both tactile and nociceptive afferents; 2) the importance of this effect differs by afferent subtype, but its overall effect is to reduce the sensitivity of tactile afferents while simultaneously inducing mechanical hypersensitivity and in some cases; and 3) a new responsiveness to temperature in the absence of mechanical stimulation of fast-conducting nociceptors. These changes in input functions and conclusions are as follow:

1. Skin temperature alters the sensitivity and performance of both tactile and nociceptive afferents.
2. The importance of this effect differs by afferent subtype, but its overall effect is to reduce the sensitivity of tactile afferents while simultaneously inducing mechanical hypersensitivity and in some cases.
3. A new responsiveness to temperature in the absence of mechanical stimulation of fast-conducting nociceptors.

Although this report addresses the effect of temperature on the mechanical sensitivity of these afferents, there are functional and methodological aspects that to some degree limit interpretation. In the first place, changing temperature may directly alter responses of the terminals themselves (e.g., neurogenic inflammatory response), but also other tissues (e.g., vascular response) within the interphase between the thermode and the PSNs may be altered that could affect their response. Secondly, while we try to keep as much control as possible over our experimental protocols, multimodal stimulation remains as an unresolved problem in terms of applying well-regulated force to a specific area during rapid temperature

Fig. 6. Representative effects of rapid thermal stimulation (gray trace) on the activity of fast-conducting nociceptors (AHTMRs) (black trace) in the absence of mechanical stimulation. A: cold and heat produce no activity in AHTMRs during initial exposure. However, repeated thermal exposure (both cold and heat) produces changes in AHTMRs such that thermal exposure results in neuronal activity representing an emerging thermal responsiveness that is independent of mechanical activation (B: 2nd thermal exposure; C: 3rd thermal exposure). Dotted lines represent the approximate thresholds to thermal stimulation. Scale bar = 20 mV, 5 s.
changes. Third, in our study we used fast and sustained thermal stimulation. Although changing thermal conditions are present in the animal’s environment, our study most likely reflects a nociceptive situation in an anesthetized animal and therefore cannot be extended to a more dynamic situation where a conscious individual can react to temperature stimuli with a wide variety of behaviors and autonomic responses.

Temperature Modulation of Mechanical Sensitivity in LTMRs

The vulnerability of tactile sensibility to environmental temperature variations is a well-known phenomenon in humans (Weitz 1941; Mackworth 1953; Mills 1956; Provins and Morton 1960; Stevens et al. 1977; Green 1977; Green et al. 1979). However, its occurrence in other mammals (in this case, rats) and its relationship with nociceptive neuronal activity remain unclear. In the current study, we have shown via simultaneous multimodal skin stimulation that the balance of input from fast-conducting mechanosensitive afferents shifts dramatically with skin cooling or heating in rodents. Tactile inputs appear to rapidly decrease their mechanical sensitivity (and thereby activity) to mechanical stimulation at temperatures where thermally sensitive nociceptive inputs should become active. Extreme insensitivity of these tactile afferents to mechanical stimuli was achieved around 2°C, consistent with the ultimate development of “cold block” in terminal arbors (Paintal 1965; Franz and Iggo 1968). Nevertheless, the latter could not explain the decrease in sensitivity with moderate cooling or heating of the tactile afferents and the rapidity with which changes occurred. This suggests that temperature exerts a more direct and immediate effect on either mechanotransduction properties (Inman and Peruzzi 1961; Ishiko and Lowenstein 1961; Green et al. 1979; Boada and Woodbury 2007), the vascular array around the terminals (Green 1977; Green et al. 1980), the tissue (skin) effects (Lederman and Taylor 1972; Lederman 1976), the temperature effects on ion channel function (Zimmerman et al. 2007), or a combination of these effects. Temperature resistance of specific sodium channels has been proposed (Zimmerman et al. 2007). However, the lack of clear differences in expression of sodium channels in specific neuronal subtypes is less likely to explain the clear differences in tactile and nociceptive responses to cold, but differential expression may at least be a contributing factor (Ramachandra et al. 2005; Shields et al. 2012).

Temperature Modulation of Mechanical Sensitivity in AHTMRs

In contrast to the tactile afferents, the fast-conducting mechanonociceptors (AHTMR) rapidly become hypersensitive when exposed to either moderately hot or cold temperatures. These novel findings of a shift in the informational channel input with temperature in the periphery have profound repercussions to sensory perception. Moreover, it is curious that the effects are divergent in the fast-conducting tactile afferents and the fast-conducting high thresholds or nociceptive afferents suggesting that a fundamental difference exists in the vascular array, the mechanotransductional properties, cellular specific ion channels, or sympathetic neuronal interaction to produce divergent responses to temperature in unique subsets of myelinated neurons.

Cold temperature produces loss of activity in the tactile afferents, while simultaneously decreasing the threshold and increasing activity in the nociceptive afferents. The net result is numbness to light touch with simultaneous pain in the human (Weitz 1941; Mackworth 1953; Mills 1956; Provins and Morton 1960; Stevens et al. 1977; Green 1977; Green et al. 1979). The pain component has long been thought to be solely the result of C-fiber-mediated activation, but data from this study suggest that cold pain may be at least in part a result of AHTMR activation, possibly from mechanical activation that would normally activate tactile afferents (as seen in the overlap of thresholds between LTMR and AHTMR at cold temperatures reported in this study). This may be further accentuated by the possibility that the reduction in tactile input results in all input to the spinal cord being nociceptive, increasing signal to noise for nociceptive information. Tactile inputs likely have inhibitory effects on nociceptive throughput (Narikawa et al. 2000; Green and Schoen 2005), and their loss may further impact central pain processing. Under normothermic conditions, substantial numbers of substantia gelatinosa (SG) neurons are activated by light touch (Bennett et al. 1980; Light et al. 1979). Indeed, due to a highly sophisticated repertoire of protective reflexes and voluntary behaviors that work in concert to minimize nociceptor activation, tactile afferents are routinely and preferentially activated under normal conditions and would be expected to provide input, at least indirect input but also likely direct input, to the SG (Boada and Woodbury 2008). The rapid loss of the latter during thermal episodes, however, may imply that the loss or reduction in tactile input leads to more information received by the SG being purely nociceptive. A similar divergent effect of heat occurs in myelinated tactile and nociceptive neurons, inactivation and sensitization, respectively (Fitzgerald and Lynn 1977). This may be an evolutionary biology development to enhance pain perception in the face of extreme cold or even heat, thus permitting a retained or enhanced signal to the organism for the need to prevent tissue damage in the area affected. Nevertheless, although the AHTMR may sensitize and respond to thermal activation or increase activity to mechanical stimulation at various temperatures helping to serve and protect with possible assistance of other fibers, its primary roll remains to provide rapidly conducted, mechanically driven nociceptive input.

The amplification of nociceptor inputs during temperature exposure, coupled with simultaneous release from tactile-driven central inhibition, would further facilitate activation of circuits required for appropriate evasive action. The extent to which these findings can be generalized more broadly throughout the somatosensory system is not yet clear, although hyposensitivity of the vast majority of tactile afferents by noxious heat sheds new light on a paradoxical “touch gate” identified in human psychophysical studies whereby noxious heat pain was found to suppress tactile sensation (Apkarian et al. 1994), the diametric opposite of the classic pain gate (Melzack and Wall 1965). The present findings reveal, however, that gating of touch by noxious thermal stimuli occurs, at least in part, not in the cortex as suggested (Bolanowski et al. 2000, 2001), but at the skin surface via selective change in afferent sensitivity.
Conclusion

The skin temperature plays a fundamental role in the response of the peripheral somatosensory system to mechanical stimulation that greatly simplifies computational demands placed on the nervous system during environmental exigencies.

GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: M.D.B. conception and design of research; M.D.B. performed experiments; M.D.B. analyzed data; M.D.B., J.C.E., and D.G.R. interpreted results of experiments; M.D.B. prepared figures; M.D.B. drafted manuscript; M.D.B., J.C.E., and D.G.R. edited and revised manuscript; M.D.B., J.C.E., and D.G.R. approved final version of manuscript.

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