Differing Neurophysiologic Mechanosensory Input From Glabrous and Hairy Skin in Juvenile Rats

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INTRODUCTION

Neurologic maturation influences conduction velocity and mechanical thresholds (Fitzgerald 1987; Ririe et al. 2003). However, the distribution and characteristics of the intact peripheral neuron subtypes in different skin types have not been well defined in vivo in younger animals. Understanding these fundamental neuronal properties is important in the study and interpretation of pain during development (Ririe et al. 2003). Safe exploration of the environment with distal extremities requires sensory signals to be precise and fast; moreover, physical and microneurographic experiments in humans as well as teased fiber recordings in rats demonstrate the dense innervation of the glabrous skin of the distal extremities with fast-conducting (Aβ range), low-threshold mechanoreceptors (LTMRs) (Birznieks et al. 2001; Leem et al. 1993). Safe exploration of the environment with distal extremities requires a rapid and high-contrast danger signal, typically provided by fast-conducting (Aδ range), high-threshold mechanoreceptors (A-HTMRs). Much less is known regarding the properties of A-HTMRs in glabrous skin, although sectioned and teased fiber studies in rats curiously demonstrate that they are much less prevalent in hairy skin (Leem et al. 1993). One purpose of the current study was to validate the previous studies using in vivo intracellular recording to survey and characterize fast-conducting LTMR and A-HTMR afferents innervating glabrous skin and determine their distribution in the juvenile rat.

Skin sensory neuron populations of dorsal root ganglia (DRGs) are commonly characterized by their responses to various stimuli. Originally, mechanonociceptive afferents were defined as fibers that were responsive to peripheral high-intensity mechanical stimulation only at tissue-threatening ranges (actual or potential) (Sherrington 1906). This subtype of cells, HTMRs, has been subclassified according to fiber conduction velocity for medium- and slow-conducting fibers (A/C) as Aδ nociceptors (AHTMR) and C-nociceptors (CHTMR) (Albers et al. 2006; Bessou and Perl 1969; Campbell et al. 1993; Lawson 2002; Light and Perl 1993). This classification was made assuming that the majority of tactile afferents, LTMRs, are fast-conducting fibers (Aβ/Aδ) (Perl 1992). This concept has been challenged by finding both slower tactile afferents (Aδ/C) (Boada and Woodbury 2007, 2008; Burgess and Perl 1967) and fast-nociceptors (Aβ) (in addition to the Aδ-nociceptors) (Boada and Woodbury 2007; Light and Perl 1993; Woodbury and Koerber 2003). This underscores the heterogeneity of peripheral afferents and need for multiple modalities needed for accurate classification. Variability in neuronal subtype classification may be due to the organ or, in the case of the integumentary system, the different components of the skin that are innervated by afferent subtypes. It has been previously suggested in primates that skin with different properties, such as glabrous skin and hairy skin, has a unique composition of sensory neuronal subtypes that are functionally unique with respect to thermal and mechanical transduction properties (Defrin et al. 2009; Treede et al. 1995). This may be of particular importance for fast nociceptors since there appear to be considerable differences in mechanical thresholds (Burgess and Perl 1967; Cain et al. 2001; Cooper et al. 1991; Garrell et al. 1996; Khalsa et al. 1997; Lynn and Carpenter

Boada MD, Houle TT, Eisenach JC, Ririe DG. Differing neurophysiologic mechanosensory input from glabrous and hairy skin in juvenile rats. J Neurophysiol 104: 3568–3575, 2010. First published October 6, 2010; doi:10.1152/jn.00415.2010. Sensory afferents in glabrous skin of the distal extremities, is specialized to explore the physical environment with distal extremities. Of the cutaneous submodalities—tactile, thermal, pain, and itch—tactile signals are particularly important to the exploratory function of the extremities. To efficiently explore the environment, the glabrous skin of the distal extremities, is specialized to explore the physical environment with distal extremities.
1982; Woodbury and Boada 2008) and fiber-conduction velocities (Cain et al. 2001; Lynn and Carpenter 1982; Lynn and Shakanbeh 1987). Understanding both the unique innervation of different areas of the integumentary system and fiber specific differences in transduction of sensory information are extremely valuable for accurate identification of afferent subtypes and ultimately for defining the integration and processing of peripheral afferent information in spinal cord circuits (Boada et al. 2008; Grudt and Perl 2002; Light and Perl 2003). Identifying these differences will help provide essential information about the homogeneity of electrical “fingerprints” (somatic electrical properties) of diverse mechanosensitive subtypes in functionally different tissues (for review see Djouhri and Lawson 2004) and form a stronger foundation for interpretation of biophysical properties and their relationship to nociceptive-specific molecular markers and channels (Coste et al. 2007; Dib-Hajj et al. 2009; Fang et al. 2005). This study was designed to determine the specificity of neuronal subtype in different areas and the role of skin type in the character of mechanosensory afferents in juvenile rats.

METHODS

After Institutional Animal Care and Use Committee approval, male Sprague–Dawley rats 4 wk of age (86 ± 4 g) were deeply anesthetized with isoflurane 3% with spontaneous ventilation and the hair over the lateral flank or left hindlimb was clipped between dorsal and ventral midlines. The trachea was intubated and animals were ventilated using pressure-controlled ventilation (Inspira PCV; Harvard Apparatus, Holliston, MA) with humidified 100% oxygen. The electrocardiograph was monitored throughout as a guide to the depth of anesthesia. Anesthetized animals were immobilized with pancuronium bromide (RET-3; Physitemp) was maintained at 34°C (MPREE; Cell MicroControls, Norfolk, VA). Poal temperature adjacent to the DRG was monitored with a small thermocouple (IT-23; Physitemp, Clifton, NJ). Rectal temperature (RET-3; Physitemp) was maintained at 34 ± 1°C with radiant heat.

DRG somata were impaled with borosilicate microelectrodes (80–250 MΩ) containing 1 M potassium acetate (in some cases also 20% Neurobiotin; Vector Laboratories, Burlingame, CA). Intracellular penetrations with a resting membrane potential of ≤−35 mV were characterized further. DC output from an Axoclamp 2B (Axon Instruments/Molecular Devices, Sunnyvale, CA) was digitized and analyzed off-line using Spike2 (CED, Cambridge, UK). Sampling rate for intracellular recordings was 21 kHz throughout (MicroPower1401; CED).

On stable impalement, the skin was searched with a fine sable-hair brush to locate the peripheral receptive field (RF). For afferents requiring higher intensities, subsequent searches used increasing intensities of mechanical stimuli. Afferents with cutaneous RFs were distinguished from those with deep RFs by displacing skin to ensure that RFs would track with the skin rather than remain stationary. Mechanical thresholds (MTs) were characterized with calibrated von Frey filaments (Stoelting, Wood Dale, IL). Adaptation rate was frequently evaluated using micromanipulator-based probes; responses to skin stretch, diagonal displacement of the skin instead of direct vertical force, and vibratory responses to 252-Hz vibration were also tested. In all cases, RFs were characterized and measured with the aid of a zoom stereomicroscope.

Active membrane properties of all identified sensory neurons were analyzed including the amplitude and duration of the action potential (AP) and afterhyperpolarization potential (AHP) of the AP, along with the maximum rates of spike depolarization and repolarization (MRD and MRR, respectively); durations were measured at half-amplitude rather than baseline to minimize hyperpolarization-related artifacts (D50, duration of the AP at 50% maximum; AHP50, duration of the AHP at 50% maximum). Passive properties were analyzed including membrane resting potential (E_R), input resistance (R_0), time constant (tau), 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 (CV), mechanical threshold (MT), and vibratory response (VR) were also measured. These all comprised the 12 measurements of the fibers used in analysis. Because intact thoracic/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. Because we were interested in latency from terminals, all measurements were obtained using the absolute minimum intensity required to excite neurons consistently without jitter, jitter being defined as significantly shorter latencies, seen at traditional (i.e., two- to threefold threshold) intensities and presumably reflecting spread to more proximal sites along axons. Any neuron with jitter was rejected. 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. This was used to determine CV.

Afferent classification using 12 parameters was used for mechanosensitive neurons to follow standard definitions based on response to mechanical stimuli, conduction velocity, and adaptation rate. Active and passive membrane properties were related to this classification. All included cells satisfied the following requirements: resting membrane potential more negative than −30 mV, AP amplitude ≥30 mV, and the presence of spike AHP. Passive membrane properties indicative of poor impalement were also reason for exclusion.

**Statistical analysis**

Data are presented as mean with SE or as median and ranges. Statistical analysis was performed using a 3 (fiber type: LTMR, AHTMR, CHTMR) × 2 (skin type: glabrous, hairy) MANOVA for the mechanoreceptors (with 12 domains). Additional testing was performed only if significant effects were found using the MANOVA. Univariate effects were confirmed using nonparametric tests where parametric assumptions may have been violated and are described using medians and ranges (Kruskal–Wallis). Correction for multiple comparisons was performed when appropriate. For comparison of proportion of fibers, a chi square test was used. Linear discriminant function analysis was performed to determine the weight of each of 12 parameters measured and the reliability of this model to correctly classify a fast-conducting mechanoreceptor as coming from glabrous or hairy skin and as LTMR or AHTMR. Analysis was performed with SAS 9.2. By convention, a two-tailed test at \( P < 0.05 \) was considered significant.

**RESULTS**

In the present study, a total of 173 physiologically identified and well-characterized DRG sensory neurons were recorded intrasomally from both thoracic and lumbar levels in vivo in adult rat spinal preparation (115 skin sensory neurons and 58 putative muscle spindles; only the 115 mechanosensory neurons from the skin were included in analysis). Of the skin sensory neurons, 32 neurons were recorded in T11 DRG (14 LTMRs, 10 AHTMRs, 8 CHTMRs) and 84 in L5 DRG (44 LTMRs, 29 AHTMRs, 10 CHTMRs) and 84 in L5 DRG (44 LTMRs, 29 AHTMRs, 10 CHTMRs) and 84 in L5 DRG (44 LTMRs, 29 AHTMRs, 10 CHTMRs) and 84 in L5 DRG (44 LTMRs, 29 AHTMRs, 10 CHTMRs) and 84 in L5 DRG (44 LTMRs, 29 AHTMRs, 10 CHTMRs) and 84 in L5 DRG (44 LTMRs, 29 AHTMRs, 10 CHTMRs) and 84 in L5 DRG (44 LTMRs, 29 AHTMRs, 10 CHTMRs)

A clear difference in CV distribution of AHTMR and LTMR relative to CHTMR in glabrous skin can be appreciated. This difference from CHTMR is smaller in L5H and T11. Neuron types: LTMR, AHTMR, CHTMR.

**Comparison of mechanosensory population in glabrous and hairy skin**

The comparison of different afferents was made only on those neurons with superficial RF (skin dermis) identified by pulling their RF away or by pinching the skin using fine forceps.

The population distribution of afferents in both lumbar (L5) and thoracic (T11) dermatomes varied (Fig. 2A). In glabrous skin from L5 (L5G) 43% (24/56) of the neurons were identified as fast nociceptive afferent units (AHTMRs), whereas 46% (26/56) of the neurons were identified as tactile units or LTMRs. In hairy skin, the balance of these populations changed in the ganglia at both L5 and T11. This was greatest in the L5 hairy skin, with 28% (5/27) of the cells AHTMR and 67% (18/27) LTMR. The population distribution found in the T11 dermatome was 31% (10/32) being AHTMR and 44% (14/32) being LTMR neurons and no significant difference between the populations was detected. The fast-conducting nociceptive fiber proportion compared with the slow nociceptor mechanosensitive population was greater in all dermatomes. However, the ratio of fast to slow mechanosensitive nociceptors was much larger in the glabrous skin (fourfold), compared with hairy skin in either the L5 or T11 (1.3-fold) dermatome (\( P < 0.05 \)).

**Analysis of sensory fiber specificity**

Using the 12 main measurements to generate a model (MT, CV, AHP, AP, AHP50, D50, \( E_m \), \( R_\text{g} \), \( \tau \), MRD, MRR, and VR) overall differences were tested (Table 1). Significant
differences in cell fiber type (LTMR, AHTMR, CHTMR) were found \((P < 0.001)\). In addition, the location of the mechanoreceptor (hairy vs. glabrous skin) was found to have significant differences in mechanoreceptor properties \((P < 0.001)\) and the interaction of fiber type and location was also significant \((P < 0.001)\). This allowed further analysis of the individual measurements in post hoc testing. Statistical data for post hoc univariate testing are also presented in Table 1.

**General receptive field properties and mechanical thresholds**

At both lumbar and thoracic ganglia the LTMR subtype showed common response features: 1) low mechanical threshold in response to nonnoxious mechanical stimuli (<0.16 nN) and 2) tracking of high-frequency (>252 Hz) stimuli. Two rapidly adapting (RA) LTMR subtypes could be discerned based on differences in RF properties and CVs. These included hair follicle afferents (HFAs) with an exquisite mechanical sensitivity (<0.007 mN) and units classified simply as “RA.” The latter “RA” exhibited highly phasic response properties and CVs that were indistinguishable from Aδ HFAs, although mechanical thresholds were higher (>0.04 mN) and direct skin contact appeared to be required at threshold intensities; all of these neurons followed vibratory stimuli of 512 Hz in a 1:1 fashion, suggesting innervation of Pacinian corpuscles. Slowly adapting afferent (SA) LTMRs were less frequently observed in skin (2 L5G, 1 L5H, 2 T11), but still clearly distinct from the nociceptive population based on their low mechanical thresholds (<0.01) and fast CV (>15 m/s). Interestingly, some L5H and T11 HFAs showed slow CVs, very near the A/C cutoff (Fig. 3, C and D). Further, these cells were classified as D-hair cells based on their fine dynamic sensitivity normally indicative of these afferents (e.g., Boada and Woodbury 2007, 2008; Woodbury et al. 2001). Both types of mechanosensitive afferents (RA and SA) were included as plain LTMRs in our comparative analysis against the mechanosensitive nociceptive population.

In contrast with the tactile afferents, the nociceptive cellular subtypes (A and C) both showed high mechanical thresholds (>0.6 mN). None of these cells was successfully activated by high-frequency vibratory stimuli. MT was found to be significantly different for both fiber type and location, also with a significant interaction \((P < 0.05)\) (see Table 1). MT was higher in the glabrous skin for AHTMR and LTMR, but lower in hairy skin (see Table 2). LTMR had lower MT for hairy and glabrous skin than either AHTMR or CHTMR.

**Conduction velocity properties of fiber types and location**

CV differences were significant for fiber type. CV was not significant for differences in hairy skin versus glabrous skin. However, when compared with the phenotypically similar neurons from hairy skin in either ganglia, the AHTMRs from the glabrous skin had faster CV (Fig. 2B). L5G AHTMRs showed an average CV (10.7 ± 0.7 m/s) more than twofold faster than L5H (3.9 ± 0.7 m/s) and almost twice as fast as the nociceptors recorded from T11 (5.7 ± 0.4 m/s) \((P < 0.05)\). There were no slow-conducting tactile afferents (CV < 7 m/s) or slow-conducting Aδ nociceptors (CV < 5 m/s) detected in our sampling of L5G. The entire fast-conducting fiber population was >5 m/s (with all CVs being >7 m/s, except for just one AHTMR with a CV of 5.2 m/s). A more gradual CV distribution was observed on hairy skin in both dermatomes (L5H and T11) for AHTMR and LTMR fibers, with overlap of CV of the two fiber types. Furthermore, a much smaller difference, or “a smaller gap,” in CVs between AHTMR/LTMR and the CHTMR population in L5H and T11 was identified when compared with the L5G.

**Variability of electrical properties of fast nociceptors in different skin types**

Significant differences were found between fiber types for all parameters except MRR. The differences in D50 were also significant for skin type, with a significant interaction component. There were also significant effects in interactions between skin type and fiber type for AHP and AHP50. L5 fast nociceptors or AHTMR (both glabrous and hairy skin afferents) had significantly shorter AP durations (D50) and amplitudes than those of AP from AHTMRs from T11 \((P < 0.001)\). This set of measurements makes it clear that there are significant differences in phenotypic properties of neurons in different skin types.
T5 and L5 AHTMR showed APs that lacked a “hump,” or inflection, on their falling phase. The D50 of the AHTMR in the T11 neurons had significant overlap with the D50 of the CHTMR from the same ganglia (Fig. 3B), whereas significant differences were present between the D50 of the AHTMR of L5 glabrous skin and T11 hairy skin. However, significant differences in the AHTMR log10 AHP50 were readily apparent from both the LTMR and the CHTMR in T11 (Fig. 3C), whereas overlap occurred between LTMR and AHTMR of both L5G and L5H AHTMR and LTMR. There was also a significant difference between the log10 AHP50 of the AHTMR of L5 and T11.

Linear discriminant function model and bivariate plots

Modeling for classification of neurons into hairy and glabrous location and LTMR and AHTMR was generated using the 12 measurements. Prior probability of characterizing a given sensory neuron correctly into both glabrous or hairy origin and LTMR or AHTMR ranged from 15 to 31% (based on observed group size). However, through use of our model the probability of accurately characterizing the neuron both anatomically and by functionality was >81%. This drops to 74% if VR is omitted. The difference between hairy and glabrous skin fiber classification was responsible for the 19% loss in classification accuracy.

DISCUSSION

The present study provides data on distinct differences in phenotypic characterization of fast-conducting peripheral afferent mechanosensitive neurons from glabrous and hairy skin in juvenile rats. Additional regional anatomic differences between thoracic and lumbar dermatomes were also found. Our approach using multivariate analysis refines the approach to multiple comparisons used with the myriad of electrophysiologic parameters routinely obtained. Using this approach we have been able to demonstrate both fiber-specific differences and anatomic differences based on skin type, glabrous or hairy skin. Without this approach rigorous statistical analysis would have made it difficult to detect these differences without much larger numbers or may have led to incorrect conclusions arising from increased error (type 1). This is a powerful and rigorous approach to analyzing the electrophysiologic data and its value is demonstrated in the data set. This type of approach has been used previously, but never gained widespread use (Chung et al. 1986). Using this approach, the fiber type is always distinguished correctly using multivariate modeling, but the 19% inaccuracy of the model is a result of overlap of fibers between hairy skin and glabrous skin. The 81% accuracy in fiber characterization based on skin type is still remarkable and clearly emphasizes the distinct differences in properties of different mechanosensitive neurons from glabrous and hairy skin. Without this approach rigorous statistical analysis would have been able to demonstrate both fiber-specific differences and anatomic differences based on skin type, glabrous or hairy skin. The 81% accuracy in fiber characterization based on skin type is still remarkable and clearly emphasizes the distinct differences in properties of neurons from these different locations. This result was cross-validated (i.e., leave one out repeat analysis iteration).

These data demonstrate that the phenotypic characterization, or “fingerprint,” of neurons is not solely dependent on CV and anatomic differences based on skin type, glabrous or hairy skin. Without this approach rigorous statistical analysis would have been able to demonstrate both fiber-specific differences and anatomic differences based on skin type, glabrous or hairy skin. The 81% accuracy in fiber characterization based on skin type is still remarkable and clearly emphasizes the distinct differences in properties of neurons from these different locations. This result was cross-validated (i.e., leave one out repeat analysis iteration).

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et al. 1995). The distribution of different neurons in dermis of glabrous skin and hairy skin has been previously studied (Johansson and Vallbo 1979; Leem et al. 1993; Provitera et al. 2007), but the population of specific neurons from a given DRG innervating these areas has not been previously assessed in juvenile rats. Different populations of receptors in different skin areas exist in the rat (Fleischer et al. 1983), whereas density of innervation is variable even within glabrous skin (Johansson and Vallbo 1979). Our data suggest that the population of the neurons in a given skin region may be related to the distribution of fiber endings in the skin and thus may directly affect response characteristics of given neurons in different skin types. This has implications for studies of afferent activation both in vivo and in vitro, most notably the study of pain, in neurons from different locations and skin types and interpretation of findings in adult and younger animals.

A number of studies have investigated mechanosensitive afferents in different animal models (Albers et al. 2006; Brown et al. 1997; Cain et al. 2001; Fang et al. 2006; Hoheisel et al. 1994; Koerber et al. 1988; Lawson et al. 2002; Leah et al. 1985; Leem et al. 1993; Xu and Zhao 2001; Ye and Woodbury 2010). In previous studies, afferents from different skin types on the same ganglia are combined or use only hairy skin (thoracic) for the study of nociceptor biophysical properties (Fang et al. 2005; Lawson et al. 2002), whereas in our study the CV obtained is orthodromic, in a manner as near to physiologic as possible. One possible area of alteration in CV calculation, which could artificially decrease CV, is an underestimate of the nerve fiber length, particularly in fibers closer to the DRG (i.e., hairy skin). Every attempt was made to get the most accurate length of these nerve fibers, but inability to fully “stretch” the nerve may have resulted in underestimated length and therefore underestimating CV (Boada and Woodbury 2007). An underestimate of CV in the neurons closer to DRG could possibly lead to lower CV as found in the hairy skin at T11.

This report is valuable to further substantiate previous concepts of neuronal properties because the integrity of the neurons is maintained. Using in vivo, intact preparations of single neurons from the DRG with intact projections and blood supply is seemingly closer to physiologic than commonly used models of neuronal physiology. In previous reports it was common to have <50% of the neurons meet criteria for AP evaluation, suggesting many of the nerves were not healthy. In addition, it is common to still include neurons not meeting AP criteria in studies of CV and responses. In our study >75% of cells routinely meet AP criteria (unpublished observation) and any cell not meeting AP criteria is not used in any part of the study. AP criteria are also distinct in our study because the AP is altered by age and also by the temperature (Boada and Woodbury 2007; Boada et al. 2010).

It is generally accepted that mechanonociceptors can be readily recognized by the diversity of their neuronal properties, attributed to both interspecies variability and potential functional polymodality (Djouhri and Lawson 2004). However, just a handful of studies have addressed this problem from the standpoint of comparing responses between glabrous and hairy skin in the same species of mammal (Cain et al. 2001; Treede et al. 1995). The current report addresses whether AHTMR mechanosensitive nociceptors have the same properties and density in both types of skin. Our observations show they do not, at least not entirely. In terms of electrical properties and CV, both types of afferents (LTMR and AHTMR) are too similar to directly relate electrical properties with function. Despite these electrical similarities, both AHTMR and LTMR can readily be distinguished based on vastly different properties of their respective RFs. With the skin at normothermic values (32°C) both cellular subtypes have clearly different mechanical threshold and high-frequency sensibility (>215 Hz), making a potential misclassification of faster AHTMR as SA-LTMR afferents unlikely, as suggested elsewhere in another species (Cain et al. 2001). We focused only on mechanosensitive afferents and therefore the mechanosensitive afferent population distribution is not included (Handwerker et al. 1991). We also did not classify the AHTMR population.
based on temperature responses, a population that would be distinguished in hairy skin. This was due to the concerns of changes in mechanosensitivity that can occur from exposure to heat in noxious ranges.

We observed that mechanosensitive fast nociceptors appear to be far more abundant, faster, and narrower than previously reported for glabrous skin (Cain et al. 2001; Djouhri and Lawson 2004; Leem et al. 1993; Sanders and Zimmerman 1986). In these previous studies, the number of Aδ or AHTMR neurons was underrepresented when compared with neuronal histology (Sanders and Zimmerman 1986). The results from our study of the population contribution of AHTMR in glabrous skin are more in line with the population based on histology data previously reported. The number of SA-LTMR was very small in our study relative to previous work (Leem et al. 1993). The etiology of this is unclear, but may be related to age differences in the rats from the different studies. The C-fibers in our study are a smaller population than generally accepted. This is largely because the C-fibers in this study are mechanosensitive fibers innervating skin only and other C-fibers in the dermatome (including deeper and mechanosensitive) are not included. The combination of some key properties (short D50 and AHP50) on these cells (L5G AHMTMR) makes them potentially more excitable (number of AP/stimuli) than those from hairy skin. At the same time we also observed that both tactile and nociceptive afferents cluster their CV on the border between Aβ/Aδ fibers. This cluster also un-masks a striking observation. As in humans and primates (Olausson et al. 2002; Treede et al. 1995; Vallbo et al. 1999), rat glabrous skin is not innervated by C-LTMR unmyelinated fibers nor slow Aδ nociceptors (CV < 5 m/s). Thus it is possible a higher volume of nociceptive mechanosensitive information is using very fast myelinated pathways, changing the relative weight of those circuits involved in processing and conducting nociceptive information into the CNS.

In this study, the data on mechanosensitive CHTMR were reported. The relative populations of these cells in the LSG (12%), L5H (15%), and T11 (25%) were not as striking as the differences in the AHTMR and LTMR populations. These cells were included in the study to demonstrate clear and distinct differences between this population of slow-conducting mechanosensitive afferents and the fast-conducting LTMR/AHTMR population, the focus of this study. The relationship of fast-conducting to slow-conducting high-threshold mechanosensitive afferents was three-fold greater in glabrous skin compared with that in hairy skin. Analysis of the CV alone can be readily used to discriminate the CHTMR neurons from other types of mechanosensitive afferents. This was most evident in the LSG because of its deficiency of slow-conducting tactile units and the clustering of fast afferents quite far from the CV range of the CHTMR. However, since the number of the CHTMR neurons was low and temperature was not used to further distinguish the subpopulations of C-polymodal and C-mechanoreceptors, further analysis of these neurons was not a part of this study.

The majority of behavioral studies of acute and chronic pain use glabrous skin responses in the plantar surface of the paw in the distribution of the injured nerve or, in the case of incision, in the area of the incision itself, as markers for nociceptive activity (Bennett et al. 2003; Brennan et al. 1996; Decosterd and Woolf 2000; Ririe et al. 2003; Zahn and Brennan 1999). These studies commonly relate changes in behavior with cellular electrical properties and even central connectivity. It is important to recognize that studies of glabrous skin may be quite different from responses or affects in the spinal cord from similar studies in hairy skin, or even similar studies in different dermatomes in similar skin types. Therefore studies of responses in hairy skin will also be valuable in understanding responses of mechanoreceptors in response to injury, particularly since most clinical incisions occur in hairy skin (Duarte et al. 2005; Martin et al. 2004).

The higher density of faster-conducting AHTMR in the glabrous skin may have implications for spatial and temporal summation of inputs from this skin type, an idea that has been proposed for other modalities (Defrin et al. 2009). In particular, the higher CV of these AHTMRs may alter input from other cell types from other areas that are synapsing on the same second-order neurons. This may contribute to higher spatial resolution, higher fidelity, and more rapid integration of information from glabrous skin. This type of specialized neuronal physiology may be critical for exploration of the environment. In our studies, roughly 75% of the neurons in the L5 DRG are from glabrous skin (unpublished observation). This further emphasizes the importance and increased resolution capable in the glabrous skin in this dermatome. This is also consistent with a higher density of fibers in glabrous skin, especially in the fingers and toes (Blake et al. 2002).

The idea of differences in sensibility of skin types is well accepted. These data bring clarity to many of the perceived discrepancies between different skin types and the neuronal populations by demonstrating that CV alone cannot be used to clearly and unequivocally phenotypically classify a mechanosensitive neuron. This also becomes important as age changes and the properties of the different neurons change during development. The notion that differences in neuronal populations and responses differing in dermatomes is also important. These concepts make studies of afferent activation and their central responses important in both hairy skin and glabrous skin. Furthermore, the inclusion of studies in different regions of the body is valuable to gain a full understanding of the variability in responses to tissue and nerve injury throughout the body and their differential impact on the CNS at different ages.

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