Neuron. Author manuscript; available in PMC 2014 Feb 21.
Published in final edited form as:
Neuron. 2013 Aug 21; 79(4): 10.1016/j.neuron.2013.07.051.
doi: 10.1016/j.neuron.2013.07.051

PMCID: PMC3811145
NIHMSID: NIHMS514231
PMID: 23972592

The Sensory Neurons of Touch

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Abstract

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The somatosensory system decodes a wide range of tactile stimuli and thus endows us with a remarkable capacity for object recognition, texture discrimination, sensory-motor feedback and social exchange. The first step leading to perception of innocuous touch is activation of cutaneous sensory neurons called low-threshold mechanoreceptors (LTMRs). Here, we review the properties and functions of LTMRs, emphasizing the unique tuning properties of LTMR subtypes and the organizational logic of their peripheral and central axonal projections. We discuss the spinal cord neurophysiological representation of complex mechanical forces acting upon the skin and current views of how tactile information is processed and conveyed from the spinal cord to the brain. An integrative model in which ensembles of impulses arising from physiologically distinct LTMRs are integrated and processed in somatotopically aligned mechanosensory columns of the spinal cord dorsal horn underlies the nervous system's enormous capacity for perceiving the richness of the tactile world.

Introduction

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Our tactile world is rich, if not infinite. The flutter of an insect's wings, a warm breeze, a blunt object, raindrops, and a mother's gentle caress impose mechanical forces upon the skin, and yet we encounter no difficulty in telling them apart and react differently to each. How do we recognize and interpret the myriad of tactile stimuli to perceive the richness of the physical world? Aristotle classified touch, along with vision, hearing, smell, and taste, as one of the five main senses. However, it was Johannes Muller who, in 1842, introduced the concept of sensory modalities (Müller, 1842), prompting us to ask whether nerves that convey different qualities of touch exhibit unique characteristics. Indeed, sensations emanating from a cadre of touch receptors, the sensory neurons that innervate our skin, can be *qualitatively* different. Understanding how we perceive and react to the physical world is rooted in our understanding of the sensory neurons of touch.

The somatosensory system serves three major functions; exteroreceptive and interoceptive, for our perception and reaction to stimuli originating outside and inside of the body, respectively, and proprioceptive functions, for the perception and control of body position and balance. The first step in any somatosensory perception involves the activation of primary sensory neurons whose cell bodies reside within dorsal root ganglia (DRG) and cranial sensory ganglia. DRG neurons are pseudo-unipolar, with one axonal branch that extends to the periphery and associates with peripheral targets, and another branch that penetrates the spinal cord and forms synapses upon second order neurons in the spinal cord gray matter and, in some cases, the dorsal column nuclei of the brainstem. Within the exteroreceptive somatosensory system, a large portion of our sensory world map is devoted to deciphering that which is harmful. Thus, a majority of DRG neurons are keenly tuned to nociceptive and thermal stimuli. The perception of innocuous and noxious touch sensations rely on special mechanosensitive sensory neurons that fall into two general categories; lowthreshold mechanoreceptors (LTMRs) that react to innocuous mechanical stimulation and high-threshold mechanoreceptors (HTMRs) that respond to harmful mechanical stimuli.

Sensory modalities have been, for the sake of simplicity, described as anatomically and physiologically discrete channels, or "labeled lines" that faithfully convey particular modalities of cutaneous sensory information from the periphery to the somatosensory cortex. However, both anatomical and physiological measurements indicate that sensory integration begins at subcortical levels, providing a compelling argument against a labeled-line theory of somatosensation. Today, with the use of molecular genetics, and equipped with strategies for acute ablation and/or silencing of neuronal subtypes, we can test the idea that the exquisite combination of ion-channels, organizational properties of cutaneous LTMR endings, and central nervous system circuits are the substrate of tactile perception.

This review describes the anatomical and physiological characteristics of LTMRs and their associated spinal cord circuits responsible for translating mechanical stimuli acting upon the skin into the neural codes that underlie touch perception. We begin by highlighting key features that endow each LTMR subtype with its unique ability to extract salient characteristics of mechanical stimuli and then describe the neuronal components of the spinal cord that receive LTMR input and how these components are assembled into circuits that process innocuous touch information. Pain and touch are intricately related, and insights into pain processing may reveal fundamental

principles of normal touch sensations. Thus, whenever possible, we have highlighted pain pathways as they relate to our understanding of the processing of innocuous touch information. Interested readers should consult more comprehensive reviews on pain circuits and processing (Basbaum et al., 2009; Smith and Lewin, 2009; Todd, 2010).

Part I: Anatomical and physiological properties of low-threshold mechanoreceptors Go to:

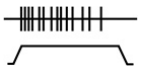
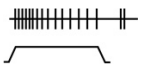
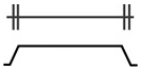
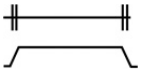
Combined psychophysical and neurophysiological studies have resulted in a complex picture of the peripheral neural pathways involved in tactile perception. Psychophysical and microneurography techniques in humans and non-human primates have offered the most comprehensive view of how stimuli give rise to perceptions and what fiber types may elicit those perceptions. However, neither of these strategies is designed to elucidate the sensory circuits and pathways underlying touch perception. On the other hand, electrophysiological recordings from model organisms have provided a wealth of information regarding the unique physiological properties of cutaneous somatosensory receptors, and in the case of the *ex-vivo* preparation and post-recording intracellular labeling, compelling physiological correlations to anatomical features of touch receptors (Koerber and Woodbury, 2002). More recently, transgenic mice engineered to express molecular markers in LTMR subtypes have broadened our understanding of touch receptor biology. In combination with physiological recordings in skin-nerve preparations, mouse transgenic tools have enabled definition of LTMRs by their anatomical and physiological attributes (Li et al., 2011; Seal et al., 2009).

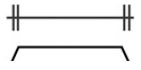
All cutaneous sensory neurons can be classified as either Aβ, Aδ, or C based on their cell body sizes, axon diameter, degree of myelination and axonal conduction velocities (Table 1). C-type sensory neurons are the smallest and most abundant, with unmyelinated axons and the slowest conduction velocities (ranging from 0.2–2m/s). Aδ and Aβ sensory neurons have medium and large cell body sizes with lightly and heavily myelinated processes, thereby exhibiting intermediate and rapid conduction velocities, respectively. Aδ conduction velocities can vary from 5–30m/s, while Aβs range from 16–100m/s. Most Aβ fibers have low mechanical thresholds, leading to the conclusion that Aβ fibers are light-touch receptors. The majority of thinly myelinated Aδ and C fibers are thought to be nociceptors based on responses to noxious mechanical, heat or cold stimuli. However, large subsets of Aδ and C-fibers, the D-hair afferents (referred to here as Aδ-LTMRs) and C-LTMRs display thresholds well below the nociceptive range (Brown and Iggo, 1967b; Burgess et al., 1968; Iggo and Kornhuber, 1968). By definition, LTMRs are activated by weak, innocuous mechanical force applied to the skin, though some can also be activated by phasic cooling or thermal stimuli. Lastly, LTMR firing patterns to sustained mechanical stimuli can be quite different, ranging from slow (SA) to intermediate (IA) to rapidly adapting (RA) (Table 1).

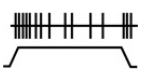
Table 1

A comparison of cutaneous mechanoreceptor subtypes

Skin is innervated by complex combinations of low-and high-threshold mechanoreceptors, each with unique physiological profiles and response properties elicited by distinct tactile stimuli.

Physiological subtype	Associated fiber (conduction velocity[1])	Skin type	End organ/ending type	Location	Optimal Stimulus[4]	Response properties
SAI-LTMR	Ab (16–96m/s)	Glabrous	Merkel cell	Basal Layer of epidermis	Indentation	
		Hairy	Merkel cell (touch dome)	Around Guard hair follicles		
SAII-LTMR	Ab (20–100m/s)	Glabrous	Ruffini[2]	Dermis[3]	Stretch	
		Hairy	unclear	unclear		
RAI-LTMR	Ab (26–91m/s)	Glabrous	Meissner corpuscle	Dermal papillae	Skin movement Hair follicle deflection	
		Hairy	Longitudinal lanceolate ending	Guard/Awl-Auchene hair follicles		
RAII-LTMR	Ab (30–90m/s)	Glabrous	Pacinian corpuscle	Deep dermis	Vibration	

Physiological subtype	Associated fiber (conduction velocity)	Skin type	End organ/ending type	Location	Optimal Stimulus	Response properties
Ad-LTMR	Ad (5–30m/s)	Hairy	Longitudinal lanceolate ending	Awl-Auchene/ Zigzag hair follicles	Hair follicle deflection	

C-LTMR	C (0.2–2m/s)	Hairy	Longitudinal lanceolate ending	Awl-Auchene/ Zigzag hair follicles	Hair follicle deflection	
HTMR	Ab/Ad/C (0.5–100m/s)	Glabrous Hairy	Free nerve ending	Epidermis/Dermis	Noxious mechanical	

[1]Notes: Conduction velocities can vary drastically across species, please see the following references for a more detailed interspecies comparisons: Leem, 1993 (rat); Brown and Iggo, 1967 and Burgess, 1968 (cat and rabbit); Perl, 1968 (monkey); Knibestol, 1975 (human).
[2]Though SAII-LTMR responses have been observed in both glabrous skin of humans and hairy skin of mice, they have only been postulated to arise from Ruffini endings, though direct evidence to support this idea is lacking (Chambers et al., 1972).
[3]Although SAII like responses are present in the mouse, Ruffini endings or Ruffini-like structures have not been identified in rodents.
[4]The stimulus described is the optimal stimulus known to elicit the response properties depicted in the last column of this table. However, it is probable, and often times documented, that multiple physiological subtypes can be recruited with any one particular tactile stimulus. For example, indentation of hair skin is likely to not only activate SAI-LTMRs associated with guard hairs but also longitudinal lanceolate endings of the Aβ-, Aδ-, and C-LTMR type (see Figure 2).

In addition to conduction velocities and adaptation properties, LTMRs are further distinguished by the cutaneous end organs with which they associate and their preferred stimuli or tuning properties. Mammalian skin can be divided into two major types: glabrous (non-hairy) and hairy skin (Figure 1). Located within glabrous skin are four types of mechanosensory end organs: Pacinian corpuscles, Ruffini endings, Meissner corpuscles, and Merkel's discs (Figure 1). One of the distinguishing features of mammalian skin is hair, and whether thick or thin, hair plays a key role in body temperature regulation. In addition, we now appreciate that hair follicles are specialized mechanosensory organs. Indeed, the first electrophysiological study of mammalian cutaneous receptors was recorded from axons innervating hair follicle receptors (Adrian, 1931). Most extensively studied in the rodent, mouse hairy skin is comprised of three major hair types: zigzag, awl/auchene, and guard, which differ not only in relative abundance and length but also in their patterns of LTMR subtype innervation (Li et al., 2011) (Figure 1B). Correlations between LTMR subtypes, peripheral innervation patterns, and optimal physiological responses present a new picture; with glabrous and hairy skin representing morphologically distinct, but highly specialized, mechanosensory organs, each capable of mediating unique functional responses or aspects of touch.

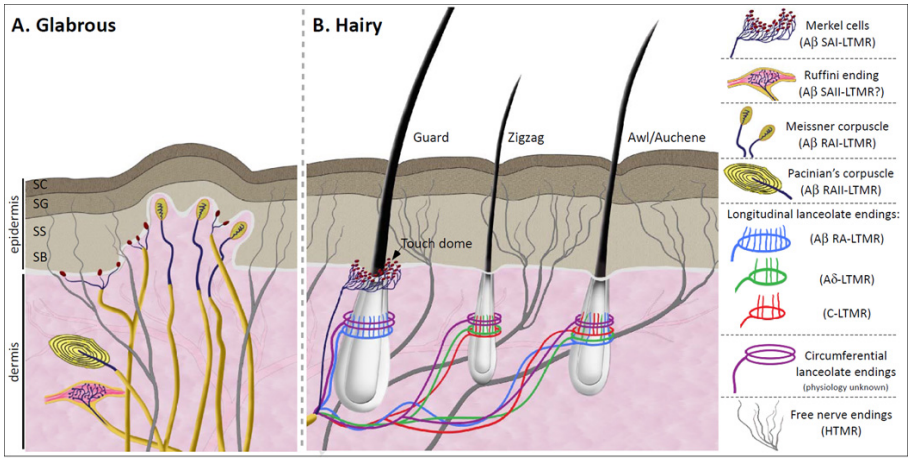


Figure 1
The organization of cutaneous mechanoreceptors in skin

A. Glabrous skin LTMRs

Low-threshold mechanoreceptors that innervate glabrous skin can be categorized into four types, each uniquely tuned to particular qualities or features of the tactile world. Here we highlight how microneurography and psychophysical studies in the human and non-human primate have helped us understand how each glabrous skin LTMR subtype contributes to complex tactile information transferred to the brain, and we integrate these findings with those of studies using model organisms that have uncovered the cellular and anatomical components underlying the unique properties of each of the LTMRs associated with glabrous skin.

Slowly adapting receptors

A large proportion of Aβ-LTMRs that innervate glabrous skin can be classified as slowly adapting, exhibiting maintained firing during sustained indentation. Slowly adapting responses can be further divided into two types that are common to most, if not all, vertebrate animal models (Wellnitz et al., 2010). Slowly adapting type I and II (SAI and SAII) responses are differentiated by the regularity of their static-phase firing rates, with SAI fibers exhibiting a more irregular inter-spike interval than SAII units. They are also differentiated by their tuning properties, tonic firing rates, and receptive field sizes.

SAI-LTMRs and the Merkel cell complex SAI-LTMRs innervate both hairy and glabrous skin and respond to mechanical forces on the skin with a sustained and graded dynamic response followed by bursting at irregular intervals that is linearly correlated to indentation depths (Coleman et al., 2001; Harrington and Merzenich, 1970; Knibestol and Vallbo, 1980; Wellnitz et al., 2010; Werner and Mountcastle, 1965; Williams et al., 2010)) (Table 1). SAI-LTMRs exhibit several remarkable physiological properties that endow them with the ability to transmit a highly acute spatial image of tactile stimuli. First, they respond maximally upon contact with corners, edges and curvatures of objects with very low thresholds of skin displacement (less than 15um in humans). Second, they exhibit high spatial resolution (up to 0.5mm for individual human SAI afferents) making them highly sensitive to stimulus position and velocity. SAI-LTMRs are silent when skin is not stimulated and insensitive to stretch of the skin or skin displacement adjacent to its receptive field, which typically ranges from 2–3mm in humans.

Friedrich Sigmund Merkel (1875) was the first to histologically describe an epidermal cell cluster forming contacts with afferent nerve fibers in vertebrate skin. A century later, the Merkel cell-neurite complex was described as the cellular substrate of SAI-LTMRs by meticulous histological analysis of SAI receptive fields mapped onto the skin (Halata et al., 2003; Iggo and Muir, 1969; Munger et al., 1971; Woodbury and Koerber, 2007)(Figure 1). Merkel cell clusters are distributed throughout the skin, with each individual Merkel cell found in close apposition to one enlarged Aβ SAI-LTMR terminal. In humans, Merkel cells are enriched in highly sensitive areas of the skin, including glabrous skin of the fingers and lips (Figure 1A). They are also present in hairy skin though at a lower density. In rodents, the largest accumulation of Merkel cells is associated with whiskers follicles, but they are also found in glabrous skin of the paws and associated with guard hairs in hairy skin (Figure 1B). Merkel cells reside in the basal layer of the epidermis where they attach to the underlying epidermis by desmosomes. A single cluster can have as many as 150 Merkel cells, with a single Aβ SAI-LTMR fiber supplying as many as 15 Merkel cells. Therefore, two or more axons can supply any given touch dome, with a single SAI-LTMR branching to supply at many as seven separate clusters within glabrous skin (Ebara et al., 2008; Pare et al., 2002; Woodbury and Koerber, 2007). The anatomical density of Merkel cell-neurite complexes and their intricate innervation patterns is related to our remarkable capacity for tactile discrimination and the ability of SAI-LTMRs to resolve spatial detail smaller than their anatomical receptive field diameters (Vega-Bermudez and Johnson, 1999).

Whether the Merkel cell, the Aβ SAI-LTMR, or both are sites of initiation of SAI-LTMR responses remains a topic of considerable debate. Early work using phototoxic destruction of Merkel cells yielded conflicting results, with one group suggesting that ablation of Merkel cells abolishes SAI-LTMR responses (Ikeda et al., 1994) and another concluding the opposite (Mills and Diamond, 1995; Senok et al., 1996). More recently, skin specific deletion of the transcription factor Atoh1 has provided genetic ablation of Merkel cells and therefore a means to test the role of Merkel cells in both tactile discrimination and SAI-LTMR responses. Indeed, mice in which Merkel cells fail to develop cannot detect textured surfaces with their feet, and stimuli that normally elicit SAI-LTMR responses are ineffective in an in-vitro skin/saphenous nerve preparation (Maricich et al., 2012; Maricich et al., 2009). However, peripheral nerve outgrowth and maintenance is dependent on proper skin/Merkel cell development, rendering developmental deletion analyses somewhat difficult to interpret (Krimm et al., 2000). Indeed, if Merkel cells develop normally but degenerate in the adult animal, as is the case in *p75* mutant mice, SAI-LTMRs remain unaltered, even after 99% of Merkel cells are lost (Kinkelin et al., 1999). Therefore, it is possible that Merkel cells play a structural role during development in organizing SAI-LTMR endings at the epidermal-dermal border. Merkel cells may also play an active role by releasing neuromodulators to regulate SAI-LTMR activity (Halata et al., 2003). Indeed, the Merkel cell-neurite complex contains several features reminiscent of chemical synapses, suggesting that the Merkel cell is a sensory receptor that transmits signals through synaptic contact with SAI-LTMRs. For example, Merkel cells and afferent terminals contact via junctions similar to synapses with electron dense secretory granules that localize with synaptic vesicle proteins consistent with a glutamatergic synapse (Fagan and Cahusac, 2001; Gu et al., 1981; Hartschuh and Weihe, 1980; Hartschuh et al., 1990; Hitchcock et al., 2004). Moreover, molecular profiling suggests that Merkel cells express the machinery capable of sending both excitatory and modulatory signals to sensory neurons (Haeberle et al., 2004). However, mechanical stimulation of isolated Merkel cells does not generate mechanically gated currents. These findings, collectively, point to a modulatory role for Merkel cells during the transmission of mechanical forces onto associated Aβ SAI-LTMR endings (Diamond et al., 1986; Haeberle et al., 2004; Yamashita et al., 1992).

SAII-LTMRs SAII-LTMRs, like SAI-LTMRs, yield a sustained response to skin indentation but differ in their interspike intervals, which are much more uniform than those of SAI afferents (Table 1). Like SAI-LTMRs, SAII afferent conduction velocities fall within the Aβ range (20–100 m/s), although this can be quite varied across species. SAII-LTMRs innervate the skin less densely than SAIs, and their receptive fields are about five times larger with one central low threshold spot on the skin for each SAII fiber (Johansson and Vallbo, 1980). SAIIs are one sixth as sensitive as SAI's to skin indentation, but two to four times more sensitive to skin stretch and changes in hand and finger shape (Edin, 1992; Johnson et al., 2000). Interestingly, SAII-LTMRs transmit information about skin stretch with little interference from other textural aspects of an object held in the hand. Psychophysical and microneurography studies suggest two major functions of SAII afferents in touch perception, both resulting from their sensitivity to skin stretch. The first is detecting hand shape and finger conformation, or proprioception, which is likely integrated with information conveyed from muscle spindles and joint afferents. In this regard, it is interesting that SAII-LTMRs share certain physiological characteristics with proprioceptors. A second potential

role for SAII-LTMRs is in the detection of object motion and velocity when the direction of object movement produces skin stretch.

Unlike SAI-LTMRs, considerable controversy surrounds SAII afferents. First, although reported regularly in microneurography studies of the human hand, neurophysiological evidence of their presence has not been observed in studies of the monkey hand (Blake et al., 1997a; Blake et al., 1997b; Connor et al., 1990; Goodwin et al., 1997; Johnson and Lamb, 1981), and only recently have neurons with SAII properties been reported in the mouse (Wellnitz et al., 2010; Woodbury and Koerber, 2003). Second, the morphology of SAII mechanoreceptors remains elusive. Unlike the well-established Merkel cell-neurite complex corresponding to SAI-LTMRs, SAII responses have only been postulated to arise from Ruffini endings, though direct evidence to support this idea is lacking (Chambers et al., 1972) (Figure 1A). The Italian histologist and embryologist, Angelo Ruffini (1894), was first to describe the small, encapsulated nerve ending in the dermis which later became known as the Ruffini corpuscle (Ruffini, 1894). Morphologically, the Ruffini ending is similar to the Golgi tendon organ, it is a large (200-100εm) and thin spindle-shaped cylinder composed of layers of perineural tissue including Schwann cells and collagen fibers, and an inner core composed of nerve terminals surrounded by a capsule space filled with fluid (Chambers et al., 1972; Halata, 1977b). In humans, each SAII axon possesses a low-threshold region, suggesting that a single Aβ fiber supplies each receptor organ (Johansson and Vallbo, 1980). Unlike the Merkel cell-neurite complex, the Aβ fibers that make up SAII-LTMRs are suggested to sense mechanical stretch applied to the Ruffini ending by collagen fibers (Maeda et al., 1999; Rahman et al., 2011). It is unlikely, however, that in the mouse Ruffini endings or Ruffini-like structures give rise to SAII-LTMR responses as such structures have not been identified in rodents. Furthermore, rodent SAII-LTMRs have been observed following stimulation of hairy skin in an exvivo skin/nerve preparation where deep structures such as muscles and associated joints are removed (Wellnitz et al., 2010; Zimmermann et al., 2009). Therefore, the functions of SAII-LTMRs in different animal species and the morphological properties of SAII-LTMR endings remain unknown.

Rapidly adapting receptors The other physiologically defined mechanosensor is the rapidly adapting (RA) receptor that responds best to objects moving across the skin, but less well to static indentation. As with SA-LTMRs, RA-LTMRs can be further divided into two categories: RAI- and RAII-LTMRs. In the simplest interpretation, they merge into a psychophysical frequency continuum, with RAI responses generally associated with small receptive fields and low frequency vibrations, such as tapping and flutter (1–10Hz), while RAII responses are associated with larger receptive fields and high frequency vibrations (from 80–300Hz) (Knibestol, 1973; Talbot et al., 1968; Vallbo and Johansson, 1984). Anatomically, both are associated with corpuscles, which may be significant to both their rapidly adaptive properties and the tactile functions they subserve.

RAI-LTMRs and Meissner corpuscles One of the hallmarks of rapidly adapting responses is the firing of action potentials only at the initial and final contacts of a mechanical stimulus (Table 1). The percept initially associated with activation of RAI-LTMRs innervating the hand was the feeling of rapid skin movement or “flutter”, and therefore, the first function ascribed to RAI-LTMRs was detection and scaling of low-frequency vibrations (Torebjork and Ochoa, 1980). However, RAI-LTMRs possess other response properties that may be specialized for a unique function in grip control. First, in comparison to SAI-LTMRs, RAI-LTMRs are about four times more sensitive, yet respond with far less spatial acuity to stimuli moving across their receptive fields. Second, RAI-LTMRs respond consistently and with very short latencies to skin stimulation. Both of these properties endow RAI-LTMRs with the ability to respond very quickly to minute motions, which may be essential for sensing when a gripped object slips. Lastly, their relative insensitivity to static force and low-frequency vibration may enable RAI-LTMRs to extract signals related to object movement and distinguish them from stimuli related to the forces required to grip the object (Johansson and Vallbo, 1979; Lamotte and Whitehouse, 1986). Like SA-LTMRs, RAI-LTMRs display conduction velocities within the Aβ range (Table 1). Physiological profiles of SAI- and RAI-LTMRs thus suggest that these afferents play complementary roles in discriminating tactile stimuli, analogous to the complementary roles of rods and cones in interpreting visual information. SAI-LTMRs, like cones in the retina, respond with higher spatial resolution but exhibit lower sensitivity. On the other hand, RAI-LTMRs, like rods, exhibit greater sensitivity but poorer spatial resolution (Johnson et al., 2000). It is therefore likely that SAIs and RAIs combine to encode a more complete picture of tactile space.

The anatomical structure associated with RAI-LTMRs in glabrous skin is a corpuscle with varied nomenclatures; in primates and rodents, RAI associated corpuscles are referred to as Meissner corpuscles. Regardless of slight interspecies variations, all RAI-LTMR associated corpuscles are thought to be evolutionarily derived from a common ending known to serve the same function in glabrous skin. The Meissner corpuscle of primates and rodents is the best characterized anatomically and it is made up of flattened lamellar cells arranged as horizontal lamellae embedded in connective tissue. They are localized to dermal papillae in glabrous skin, most notably in fingerprint skin of the human hands and the soles of feet (Figure 1A). Each individual corpuscle can be supplied by up to three large myelinated fibers that are interwoven within the capsular cells of the corpuscle (Cauna and Ross, 1960; Janig, 1971). The arrangement of lamellar cells and nerve terminals within the Meissner corpuscle is thought to play a critical role in shaping the physiological properties of RAI-LTMRs. Upon indentation of glabrous skin, collagen fibers that connect the basal epidermis to lamellar cells of the corpuscle provide the mechanical force that deforms the corpuscle and triggers action potential volleys that quickly ease as a result of the rapidly adapting nature of RAI-LTMRs. When the stimulus is removed, the corpuscle regains its shape, and in doing so it induces another volley of action potentials, generating the distinctive on-off responses of RAI-LTMRs (Table 1). One RA afferent can branch repeatedly to innervate several corpuscles. In primates, 30–80 corpuscles can be innervated by a single RAI afferent fiber (Bolton et al., 1964; Halata, 1975; Pare et al., 2001; Pare et al., 2002). In addition, up to two unmyelinated C-afferent axons, both peptidergic and non-peptidergic, are known to innervate some corpuscles; the function of these unmyelinated fibers within the Meissner corpuscle may be related to nociception (Castano et al., 1991; Cauna, 1956; Ishida-Yamamoto et al., 1988; Johansson et al., 1999; Pare et al., 2001).

RAII-LTMRs and Pacinian corpuscles The hallmark of the RAII-LTMR response is its extreme sensitivity and faithful firing to high-frequency vibration transmitted through objects held in the hand. Correlations between Pacininan corpuscles (PCs) and RAII responses were made very early in their discovery, as PCs are very large and easily detected by eye, allowing for direct stimulation while recording from their associated afferents (Bell et al., 1994). There are approximately 2500 PCs in the human hand, with the largest density located in fingers, though they are also found at or near joints. PCs are large (up to 1mm in length) and oval-shaped with a central symmetrical inner core of interdigitating lamellar cells surrounding a single Aβ fiber (Halata, 1977a). PC afferents may account for our ability to detect highfrequency vibrations and result from the remarkable response properties of RAII-LTMRs. RAII-LTMRs are extremely sensitive, with amplitude thresholds lower than those of RAI-LTMRs, often responding to motions in the nanometer range (Janig et al., 1968; Lynn, 1971). Because PCs are located deep in the dermis, their receptive fields are quite large, often encompassing the entire hand, which coupled with their extreme sensitivity, renders PC afferents unable to resolve objects with any degree of spatial acuity. The loose lamellar networks that make up the corpuscle and surround the Aβ fiber are responsible for the rapidly-adapting, high-pass filtering properties of PC (Hubbard, 1958). In fact, when deprived of their outer core, PC afferents lose their phasic responses to touch stimuli (Loewenstein and Skalak, 1966). As a result of these response properties, RAII-LTMRs help us discriminate the temporal structure of high-frequency vibratory stimuli, almost as well as our auditory system discriminates sound waves (Formby et al., 1992). Therefore, RAII-LTMRs are likely to mediate the perception of transmitted vibrations as we manipulate objects in our hands.

B. Hairy skin LTMRs

Hairy skin is a defining characteristic of mammals, with critical roles in body temperature regulation, protection from the environment and, importantly, the sense of touch. We rely heavily on hairy skin for a variety of touch sensations, ranging from social exchanges to our ability to detect the presence of foreign objects on our skin. Human and non-human primate studies of tactile perception generated by hairy skin stimulation are far fewer in comparison to studies of glabrous skin in the primate hand. Consequently, most of what we have learned about the morphology and physiology of hairy skin sensory afferents has resulted from studies in model organisms, including *in-vivo* recordings from the cat or rabbit and *in-vitro* skin/nerve preparations from the rodent (Aoki and Yamamura, 1977; Brown, 1981a; Burgess et al., 1968; Koltzenburg et al., 1997; Lynn and Carpenter, 1982). Hairy skin LTMRs are physically and functionally associated with hair follicles, and in these species hair follicles fall into three distinct types according to length, thickness and presence of kinks in the hair shaft (Schlake, 2007) (Figure 1B). As in glabrous skin, hairy skin is innervated by several LTMR subtypes that fall into distinctive Aβ, Aδ, and C-type categories depending on conduction velocities. We are beginning to appreciate the morphological and molecular diversity of hair follicle afferents and their intricate patterns of connections with different hair follicle types (Bourane et al., 2009; Li et al., 2011; Luo et al., 2009; Millard and Woolf, 1988; Wu et al., 2012). Indeed, a new picture has emerged, in which hairy skin is a highly specialized sensory organ, as or more complex than glabrous skin, with each hair follicle type representing its own unique mechanosensory unit.

Aβ-LTMRs The first category of low-threshold mechanosensors in hairy skin fall into the Aβ category of conduction velocities. As for glabrous skin, hair follicle innervating Aβ-LTMRs are divided into two groups according to their firing adaptation rates; slowly adapting (SA) and rapidly adapting (RA) LTMRs. Hairy skin SAI-LTMRs are associated with the Merkel cell complex, or touch dome, found within the epidermal/dermal junction surrounding the mouths of Guard hairs of rodents (Figure 1B) and their firing properties are similar to those recorded from SAI-LTMRs of glabrous skin (Woodbury and Koerber, 2007). SAII response properties have also been identified in rodent hairy skin; but as already discussed, the anatomical correlate of SAII units remains controversial (Wellnitz et al., 2010; Zimmermann et al., 2009). The most well characterized hairy skin physiological responses that fall under the category of Aβ/myelinated afferents are the Aβ RA-LTMRs. Historically, the physiological properties of hairy skin RA-LTMRs have been classified by responses to movement of individual hair follicle types at a controlled speed and direction (Brown and Iggo, 1967a; Burgess et al., 1974). Across species, hairy skin RA-LTMRs share some basic physiological characteristics. First, hairy skin RA-LTMRs are not spontaneously active nor do they respond to thermal stimuli. Second, their responses to hair follicle movement can exhibit either few action potentials, or a stream of action potentials proportional to velocity and final amplitude of displacement. Third, their physiological receptive field sizes vary extensively across the body, with a trend towards a decrease in receptive field size in the most distal sections of body hair, i.e. extremities. Aβ RA-LTMR responses in hairy skin arise from longitudinal lanceolate endings that surround hair follicles. In the mouse, some Aβ RA-LTMRs lanceolate endings associate with guard hairs, while others associate exclusively with awl/auchene hair follicles (Li et al., 2011; Millard and Woolf, 1988)(Figure 1B). Viewed in cross-section, each palisade of the longitudinal lanceolate ending is partially surrounded by processes of a terminal Schwann cell, with the side adjacent to hair shaft keratinocytes often devoid of a glial covering. The shape and configuration of the palisades and their associated glial cells suggests a mechanism by which Aβ RA-LTMRs are exquisitely sensitive to hair follicle deflection, with putative sites for mechanotransduction located between the nerve fiber and the hair follicle keratinocytes (Halata, 1993; Takahashi-Iwanaga, 2000). With the recent development of mouse genetic tools, anatomical features of LTMRs, such as receptive fields, can now be defined by the number of hair follicles that they associate with. We now appreciate the existence of a variety of anatomical peripheral receptive fields formed by Aβ hair follicle afferents, which can range from single hair follicles to clusters of adjacent hair follicles (Li et al., 2011; Suzuki et al., 2012; Wu et al., 2012).

Aδ-LTMRs A second major group of hair follicle-associated LTMRs are classified as Aδ-LTMRs according to their intermediate conduction velocities (Table 1). Hair follicle specific Aδ-LTMRs were originally described as D-Hair units, meant to reflect their specific response to movements of small sinus and down hairs in the cat and rabbit. Aδ-LTMR like responses are also found in humans, though not always correlated to hair follicle movement and it remains unclear how, or even if, Aδ-LTMR units influence touch perception (Adriaensen et al., 1983). The unique

physiological properties of Aδ-LTMR responses have been uncovered through *in-vivo* and *in-vitro* studies of model organisms. Most notably, studies in the cat and mouse reveal that Aδ-LTMR responses exhibit some of the lowest mechanical thresholds and highest dynamic sensitivity of any other LTMR, making Aδ-LTMRs the most sensitive mechanoreceptor in skin (Brown and Iggo, 1967b; Burgess and Perl, 1967; Koltzenburg et al., 1997). Aδ-LTMR physiological profiles are remarkably consistent and uniform within a given animal both in terms of their conduction velocity, which falls within the Aδ range, and their physiological receptive fields, which exhibit little variability from proximal to distal hairy skin. In addition, Aδ-LTMRs are sensitive to rapid cooling, but not warming of the skin (Adriaensen et al., 1983; Brown and Iggo, 1967b; Li et al., 2011). As with Aβ RA-LTMRs, Aδ-LTMR responses are rapidly adapting and silent in the absence of tactile stimulation (Table 1). During the decades in which Aδ-LTMRs were originally described and subsequently thoroughly characterized, the anatomy of Aδ-LTMRs remained largely unknown; though their sensitivity to down hair movement, in particular airjet stimulation of hair follicles, led to speculation that they form close associations with hair follicles. Indeed, recent genetic labeling revealed that Aδ-LTMRs form longitudinal lanceolate endings around hair follicles that are surprisingly similar to those described for Aβ RA-LTMRs. However, unlike RA-LTMRs that associate with guard and awl/auchene follicles of the mouse, Aδ-LTMR lanceolate endings are found around awl/auchene and zigzag, but not guard hair follicles (Li et al., 2011) (Figure 1B).

C-LTMRs Though C-fibers are often associated with painful stimuli, mechanoreceptors with conduction velocities within the C-fiber range were described in the cat as early as 1939 by Ingve Zotterman and suggested to be associated with 'tickling' sensations. Subsequent research on C-LTMRs indeed established that not all cutaneous sensory receptors with afferent C-fibers are concerned with relaying noxious information (Douglas and Ritchie, 1957; Iggo, 1960; Iggo and Kornhuber, 1977). In addition, since sensory C fibers are 3–4 times more numerous than A fibers, C-LTMRs far outnumber the myelinated fibers innervating skin (Li et al., 2011). Like Aδ-LTMRs, C-LTMRs are exquisitely sensitive to skin indentation, but are maximally activated by stimuli that move slowly across their receptive field, and are thus known as 'caress detectors'. The C-LTMR physiological profile is unique among hairy skin LTMRs. Most notably, they exhibit an *intermediately* adapting property, with a modest sustained discharge during a maintained stimulus (Table 1). Unlike other hairy skin LTMRs, C-LTMRs also show a high incidence of after-discharge, even several seconds after the stimulus is removed. The shape of their action potentials is characteristic of C-fibers, with broad waveforms displaying a prominent hump on the falling phase. As with Aδ-LTMRs, C-LTMRs are sensitive to rapid cooling, but not warming of the skin, however it is unclear whether the temperatures to which these receptors respond to are physiologically relevant for the behaving animal. One of the most striking features of C-LTMR responses is that they are only found in hairy skin. Though less common in non-human primate skin, C-LTMRs are present in human hairy skin and are speculated to play a role in mediating 'emotional touch' (Kumazawa and Perl, 1977; Loken et al., 2009; McGlone et al., 2007; Vallbo et al., 1993). Indeed, in humans lacking large myelinated fibers, activation of C-LTMRs is correlated with a sensation of pleasantness often associated with activation of the insular but not the somatosensory cortex (Bjornsdotter et al., 2009; Olausson et al., 2002). The peripheral and central anatomy of C-LTMRs was largely unknown until recent studies in the mouse have postulated that they may have several anatomical forms in hairy skin. Post-recording intracellular labeling of C-LTMRs identified in ex-vivo skin nerve recordings revealed that C-LTMRs express tyrosine hydroxylase (TH). By utilizing a CreER knocked into the *TH* locus, Li et al. (2011) were able to characterize anatomical features of mouse C-LTMRs. Like other hairy skin LTMRs, C-LTMRs form longitudinal lanceolate endings around hair follicles, and like Aδ-LTMRs, these develop only around awl/auchene and zigzag hair follicles (Figure 1B). This observation was surprising, because historically in the cat and rat C-LTMRs did not respond to movement of individual hair follicles, and therefore, were not thought to be hair receptors like Aβ RA-LTMRs found in hairy skin (Bessou et al., 1971). Remarkably, C- and Aδ-LTMR longitudinal lanceolate endings associated with awl/auchene and zigzag hair follicles are interdigitated (Figure 1B). C-LTMRs in the mouse also uniquely express the vesicular glutamate transporter VGLUT3, and behavioral deficits in *Vglut3* knock out animals have suggested that C-LTMRs may also be required for injury induced mechanical hypersensitivity (Seal et al., 2009), though this is controversial (Lou et al., 2013). Recently, MRGPRB4-expressing nonpeptidergic nociceptors, a morphologically and anatomically distinct class of C fibers of unknown physiological properties, have been implicated in pleasant touch. Similar to TH and VGLUT3-expressing C-LTMRs, MRGPRB4^{+} C fibers innervate only hairy skin (Liu et al., 2007; Vrontou et al., 2013). Thus, multiple C fiber subtypes appear to contribute to behavioral responses and the perception of light touch.

Hair follicle afferents are complex both in form and function The density and intricate innervation patterns of hair follicles and the sheer extent of hairy skin areas of mammals dictate that the major portion of our primary somatosensory neurons is devoted to hairy skin. How are the endings of hairy skin LTMRs organized and does this provide insight into larger questions of how light touch information is coded? The most abundant type of hair follicle in the mouse, accounting for 76% of follicles of the coat, is the zigzag hair follicle, which receives both C- and Aδ-LTMR lanceolate endings in a remarkable interdigitated manner. Awl/auchene hair follicles, representing roughly 23% of the follicles, are triply innervated by interdigitating endings of Aβ-RA-LTMRs, Aδ-LTMRs, and C-LTMRs. Guard hairs, the longest but least abundant, representing just 1% of hair follicles, are innervated by Aβ RA-LTMR lanceolate endings and are associated with Aβ-SAI-LTMRs that innervate touch domes (Li et al., 2011) (Figure 1B, Figure 3E). All three types of hair follicles in the rodent also receive circumferential endings, which wrap two or more times around the palisades of the longitudinal LTMR endings (Millard and Woolf, 1988)(Figure 1B, Figure 3E). Circumferential hair follicle afferents have not yet been characterized physiologically, although at the molecular level they seem to fall into two main categories; those that are neurofilament 200 positive and presumed to originate from large diameter sensory neurons, and those that expresses the nociceptive marker CGRP and are presumed to play a role in nociception (Lawson et al., 2002; Peters et al., 2002; Stucky et al., 1998; Suzuki et al., 2012; Woo et al., 2012). A major current challenge is defining the physiological properties of the neurons that form these two neurochemically distinct circumferential ending types. Therefore, each mouse

hair follicle type receives a unique and invariant combination of physiologically and morphologically distinct sensory neurons subtypes, making each hair follicle a distinctive mechanosensory end organ. However, these units do not function by themselves, they represent a cohort of exquisitely organized clusters containing one centrally located guard hair, about 20 surrounding awl/auchene hairs and about 80 interspersed zigzag hairs (Li et al., 2011) (Figure 3E). These clusters are organized in reiterative and partially overlapping patterns blanketing the mouse skin, highlighting a level of complexity, sensitivity and acuity in hairy skin previously thought to only exist in glabrous skin.

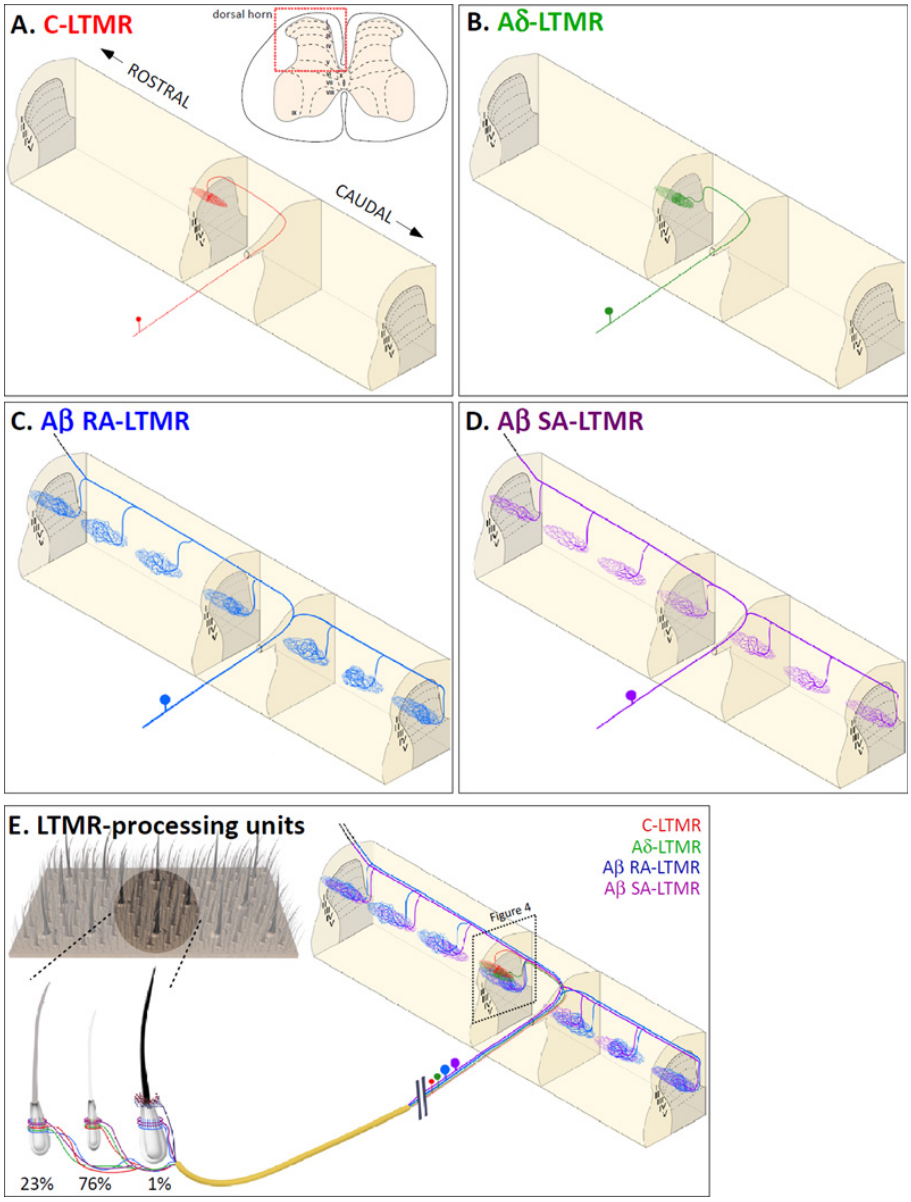


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Figure 3

The anatomy of LTMR processing units of the spinal cord dorsal horn

C. High-threshold mechanoreceptors (HTMRs) and noxious touch

Nociceptors are uniquely tuned to stimuli that cause damage or threaten to cause damage and are found uniformly in both glabrous and hairy skin. Nociceptive neurons have been historically categorized by their stimulus response properties and more recently by their molecular profiles (Lallemend and Ernfors, 2012). High threshold mechanoreceptors (HTMRs) are a broad category of mechano-nociceptive sensory neurons that are optimally excited by noxious mechanical stimuli. HTMRs include Aδ and C free nerve endings that innervate the epidermis both in glabrous and hairy skin (Figure 1). Aδ-HTMRs, also known as A-fiber mechanonociceptors (AM fibers) are thought to mediate fast mechanical pain and can be further divided into fibers that respond to either noxious heat or cold stimuli. On the other hand, C-HTMRs respond solely to mechanical but not thermal stimuli (Bessou et al., 1969; Cain et al., 2001). Nociceptors can be further categorized into two major neurochemical groups based on neuropeptide expression. Those that contain neuropeptides, like substance P or calcitonin Gene-Related Peptide (CGRP) are referred as peptidergic nociceptors, whereas those that do not express neuropeptides are

termed non-peptidergic nociceptors and most exhibit binding to isolectin-B4 (Perry and Lawson, 1998; Ribeiro-da-Silva et al., 1989a). Their peripheral innervation patterns are segregated into unique patterns, with peptidergic neurons innervating basal regions of epidermis, while non-peptidergic neurons innervate a more superficial epidermal region (Figure 1A,B). Differences in their peripheral distributions would suggest that peptidergic and non-peptidergic C fibers differ in function. Indeed, pharmacological ablation of a population of non-peptidergic neurons results in selective loss of sensitivity to noxious mechanical stimuli (Cavanaugh et al., 2009; Zylka et al., 2005). Likewise, central terminal ablation of peptidergic neurons results in selective deficits in heat nociception (Cavanaugh et al., 2009).

Although most nociceptors are associated with fine peripheral afferents, a substantial class also forms large myelinated axons (Djouhri and Lawson, 2004). Such 'myelinated nociceptors' conduct in the Aβ range and respond to mechanical stimuli well into the nociceptive range, with a graded fashion and adaptive properties that resemble SAII units (Burgess and Perl, 1967; McIlwrath et al., 2007; Woodbury and Koerber, 2003). Under normal conditions, myelinated nociceptors are also sensitive to innocuous mechanical stimuli, with von Frey thresholds as low as 0.07 mN. Some myelinated nociceptors also respond to noxious heat, but are otherwise physiologically indistinguishable from their heat-insensitive counterparts (Treede et al., 1998). Because of their wide dynamic range, myelinated nociceptors are likely to serve both LTMR and nociceptive functions. Myelinated nociceptors can be found both in glabrous and hairy skin, although their anatomical morphologies remain unknown. Proper identification and differentiation of Aβ-LTMRs vs. Aβ-nociceptors will be critical to our understanding of pain states such as allodynia and hyperalgesia. Indeed, it has been suggested that tactile allodynia following peripheral nerve injury is due to impulses carried along residual A fibers in the presence of dorsal horn sensitization (Campbell et al., 1988; LaMotte and Kapadia, 1993; Woolf et al., 1992). However, it is possible that myelinated nociceptors mediate certain aspects of tactile allodynia as they are quite sensitive to mechanical stimuli and are known to innervate lamina in the dorsal horn normally associated with nociception (Woodbury et al., 2008). Furthermore, decreases of mechanical thresholds in myelinated nociceptors following peripheral injury, as is the case with other nociceptors, may also contribute to pain states such as allodynia (Andrew and Greenspan, 1999; Jankowski et al., 2009).

D. LTMRs: an integrative view of the sense of touch

The anatomical substrate of our tactile perceptions lies in the intricate innervation patterns of physiologically distinct LTMRs and HTMRs and their respective end organs located in the skin. Each unique form, be it a rigid set of LTMR palisades surrounding hair follicles or a free nerve ending associated with keratinocytes, represents a distinct sensory unit that is uniquely tuned to a particular feature of our tactile world. Most of what we know of touch perception comes from studies on glabrous skin of the primate hand or the rodent paw. Here, conceptual leaps in the interpretation of sensory neuron form and function have distilled the essence of touch perception into four main anatomical and physiological 'channels', which transduce mechanical signals into neural codes of rapidly adapting and slowly adapting impulses. Although there's no doubt that tactile information travels along these four channels, at least peripherally, the recently revealed patterns of hairy skin innervation urge us to consider a much more integrative view of touch perception. This integrative view comprises several layers of anatomical and physiological forms, that when merged serve to extract and interpret salient and distinctive features of our tactile landscape. In this interpretation, a first layer encompasses the distinct tuning properties, sensitivities and adaptation properties of the various LTMR subtypes (and HTMRs and myelinated nociceptors). A second layer incorporates the observation that combinations of LTMR subtype endings associate with morphologically unique end organs, such as corpuscles and hair follicles. The third layer unites the unique spatial distributions of end organs and their reiterative patterns that exist throughout glabrous and hairy skin. A final layer considers the unique conduction velocities of LTMR subtypes. Indeed, Aβ, Aδ, and C-LTMR impulses propagate to the spinal cord at markedly different rates, and so there must be a temporal component to the manner in which the CNS interprets ensembles of LTMR activities. In considering this integrative view, touch perception is the product of how these four layers meld together to translate a complex touch into ensembles of activities of individual LTMRs subtypes (Figure 2). The patterns of hairy skin innervation thus allow us to formulate a simple model of how tactile stimuli may be dissected into LTMR activity codes. Indentation on hairy skin, for example, as with a poke, would most optimally activate SAI-LTMRs associated with guard hair touch domes (Figure 2A). Thus, SAI-LTMRs would be a dominant, but not the only LTMR represented in the ensemble of impulses traveling to the CNS. A firm stroke, on the other hand, like rubbing a cat's back, would result in a distinct ensemble of the activities of SA- and RA-LTMRs as well as the ultrasensitive Aδ- and C-LTMRs, which respond well to hair follicle deflection (Figure 2B). A gentle breeze is likely to activate all of the hair follicle LTMRs forming longitudinal lanceolate endings, the Aβ RA-, Aδ- and C-LTMRs, whereas SAI-LTMRs would be relatively silent in this ensemble response (Figure 2C). A slow caress of the skin is likely to activate many LTMR subtypes and especially C-LTMRs, which are particularly well tuned to gentle stroking of the skin (Figure 2C), thus providing a unique "LTMR caress ensemble".

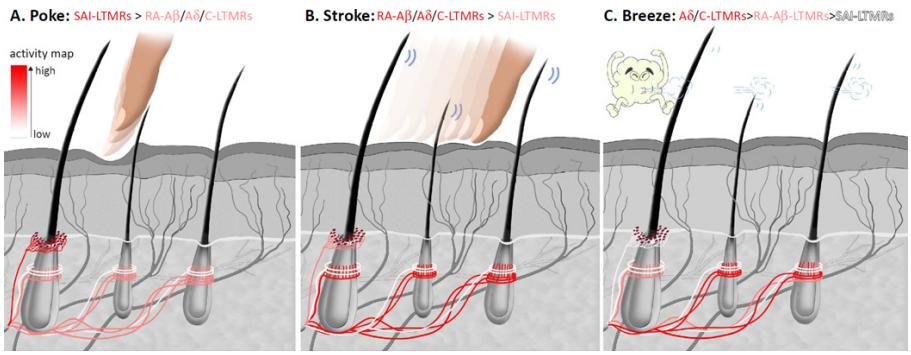

Figure 2

Postulated LTMR activity codes

Our skin, the largest sensory organ that we possess, is well adapted for size, shape, weight, movement, and texture discrimination; and with an estimated 17,000 mechanoreceptors, the human hand, for example, rivals the eye in terms of sensitivity. In fact, many of the same principles that underlie visual processing in the retina may also be at play in the processing of light touch information. Indeed, just as photoreceptors of the retina are uniquely tuned to particular wavelengths of light, LTMR endings in the skin are optimally and distinctly tuned to particular qualities of complex tactile stimuli. Furthermore, just as excitation of a single cone type is not sufficient for the perception of color, we propose that excitation of a single LTMR cannot give rise to the perception of a complex tactile stimulus. As in the retina where the relative activities of rods and cones underlies our ability to perceive a rainbow of color, the relative activities of individual LTMR subtypes innervating the same skin area underlies our ability to perceive a range of complex tactile stimuli. Ultimately, the first step in sensory perception involves processing of these unique ensemble activities of sensory subtypes by somatotopically arranged LTMR inputs in the spinal cord dorsal horn (Li et al., 2011). Recognizing and characterizing the cellular components and organizational logic of LTMR specific circuits, as well as the functions of dorsal horn projection neurons that feed higher brain centers, is critical to our understanding of how sensory information is perceived and the topic of our next section.

Part II: Processing touch information in the spinal cord

Go to:

How and where in the CNS are tactile stimuli represented, and what are the respective contributions of the spinal cord dorsal horn, brainstem, and cortex in integrating and processing the myriad ensembles of LTMR subtype activities that code for complex touch stimuli? Historically, much emphasis has been placed on a ‘direct pathway’ for the propagation and processing of light touch information. In this model, LTMRs project an axonal branch directly, via the dorsal columns, to brainstem dorsal column nuclei (DCN), the nucleus gracilis and cuneatis. Second order neurons in these nuclei, in turn feed light touch information forward to the thalamus via the medial lemniscus. Finally, third order thalamocortical neurons project to the somatosensory cortex (Mountcastle, 1957). In this simple ‘labeled line’ view, most if not all LTMR integration and processing begins in somatosensory cortex. However, we favor an integrated model in which LTMR processing begins at the earliest stages of LTMR pathways. Indeed, in the visual system, we now appreciate the retina itself as a key locus of visual information processing, and that retinal ganglion cells convey processed visual information to several brain regions. We propose that the spinal cord dorsal horn is analogous to the retina and plays a key role in the processing of touch information delivered in the form of LTMR activity ensembles. Indeed, the anatomical arrangements and locations of LTMR subtype endings strongly favor the view that the dorsal horn is the key initial locus of representation, integration, and processing of ensembles of LTMR activities for output to the brain. One key observation in support of this model is that only a subset of LTMRs actually extend axonal branches via the dorsal columns directly to the DCN while, in contrast, all LTMRs (and HTMRs) exhibit branches that terminate in the spinal cord dorsal horn (Brown, 1981a; Petit and Burgess, 1968). Here, we focus on LTMR inputs to the dorsal horn, how these inputs may be integrated, and how processed information is conveyed to the brain.

The spinal cord dorsal horn (or the trigeminal nuclei of the brainstem for trigeminal sensory neurons) receives an axonal projection and termination from every LTMR that innervates the skin (Figure 3A inset). Thus, all distinct LTMR fiber types, with their unique tuning properties and excitation thresholds, conduction velocities, spike patterns, and adaptation kinetics converge onto the dorsal horn. Remarkably, this convergence of LTMR inputs onto dorsal horn neurons occurs in a somatotopic, columnar manner, and these somatotopically arranged columns are likely to be key loci of LTMR integration and processing (Li et al., 2011) (Figure 3E). Processing of touch information by the spinal cord is thus a function of the unique branching patterns of LTMR subtypes, their distinctive termination zones within particular lamina of the dorsal horn, their synapses onto dorsal horn microcircuit components, and the cell types and connections of dorsal horn interneurons and the projection neurons that send light touch information to higher brain centers. We are just now beginning to appreciate the diversity of interneuron cell types in the spinal cord dorsal horn and their relationships to projection neurons whose cell bodies reside deep within the dorsal horn. Unlike circuits related to pain, however, remarkably little is known about the spinal cord cell types and microcircuits that receive and process LTMR information and how these in turn influence output signals of the spinal cord carried by dorsal horn projection neurons.

In this section, we summarize what is known about potential LTMR post-synaptic targets in the dorsal horn and how these components may be assembled into circuits that process LTMR information and convey it to the brain. Studies using rodent spinal cord slice physiology serve to highlight the morphological and physiological diversity of local interneurons of the dorsal horn, while *in-vivo* extracellular recordings in the cat and rabbit help decipher the complexity of long-range projection neurons in the deep dorsal horn and how natural modes of stimulation shape their response properties.

A. Organization of LTMR inputs in the dorsal horn

Somatotopy is an important guiding principle for sensory fiber organization along the rostro-caudal and medio-lateral axis of the spinal cord. Caudal inputs are integrated by caudal regions of the spinal cord, while inputs from distal to proximal skin are integrated from the medial to lateral axis of the spinal cord. General principles of input organization also relate to whether fiber types branch before entering the dorsal horn and where fiber collaterals terminate along the dorso-ventral plane of the spinal cord (i.e. which laminae).

Along the rostro-caudal axis, sensory fibers demonstrate branching morphologies that often differ according to their fiber caliber (Figure 3A–D). For example, Aδ- and C-LTMRs do not bifurcate upon entering the spinal cord, but instead travel one or two segments rostrally before entering and arborizing within the dorsal horn (Figure 3A,B) (Li et al., 2011). On the other hand, Aβ RA- and SA-LTMRs bifurcate upon exiting the dorsal root, extending branches in opposite directions along the rostro-caudal axis and then sprouting collaterals that dive deep into the dorsal horn (Figure 3C,D)(Brown, 1981a). Collateral distribution is largely similar across all Aβ-LTMR types, with each following the same principle of decreased intercollateral spacing for more medially projecting inputs to reflect increased acuity of the distal extremities like hands and feet (Brown et al., 1980a). Some Aβ-LTMRs extend a rostral branch through the dorsal columns to synapse onto dorsal column (DC) nuclei neurons, giving rise to the “direct pathway” (Figure 3C,D). Such branches from caudal Aβ-LTMRs travel through the medially positioned gracile fasciculus of the DC, and synapse within the gracile nuclei of the brainstem, while branches from more rostral Aβ-LTMRs (above ~T7 in the mouse) travel through the more lateral cuneate fasciculus and synapse onto the cuneate nucleus of the brainstem (Figure 5). Single unit recordings of axons traveling in the dorsal columns reveal that SAII-LTMRs, PC units (RAII-LTMRs), and RAI-LTMRs from both Meissner corpuscles and hair follicle afferents send a direct pathway branch to synapse onto dorsal column nuclei (Ferrington et al., 1987; Gordon and Jukes, 1964; Perl et al., 1962; Petit and Burgess, 1968). Though SAI-LTMR inputs from touch domes in forelimb hairy skin are observed in the cuneate nucleus of monkeys, SAI-LTMR axons are largely missing from dorsal column recordings, highlighting the insufficiency of the “direct pathway” in conveying to the brain all qualities of tactile information (Petit and Burgess, 1968; Vickery et al., 1994). Our own analysis of the central projections of C-LTMR and Aδ-LTMRs, which together account for more than 50% of hairy cutaneous LTMRs, indicates that these subtypes also do not project to the DCN and are limited to the dorsal horn.

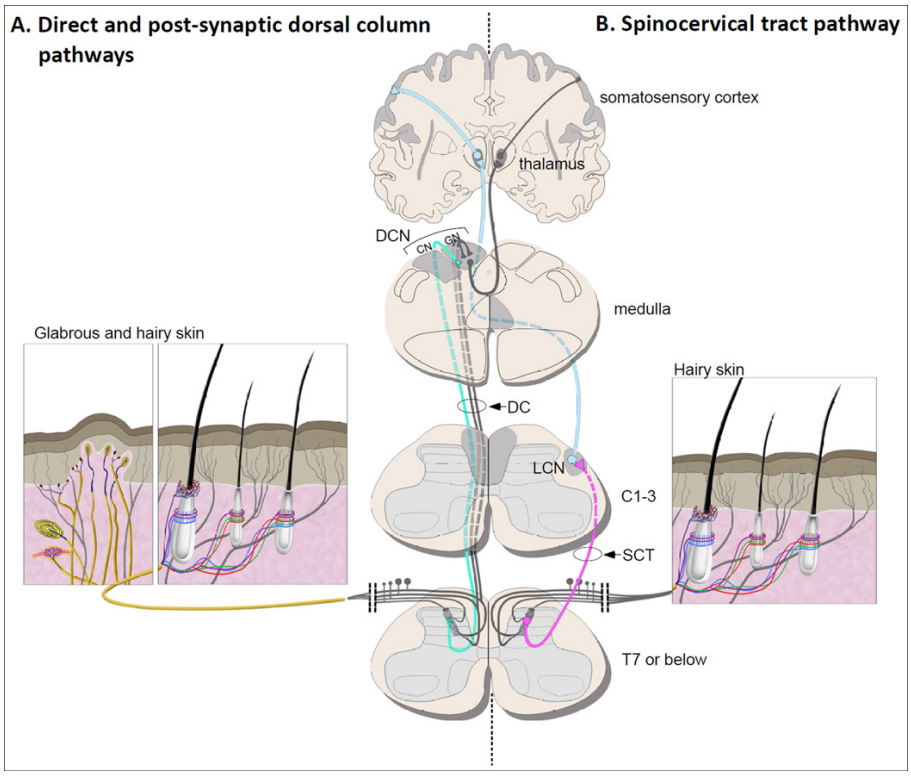

Figure 5

Touch circuits in the CNS

Within the dorsal-ventral plane, the spinal cord dorsal horn can be divided into cytoarchitecturally distinct lamina originally described by Swedish neuroscientist Bror Rexed in 1952 (Figure 3A inset). Rexed lamina I and II comprise the outermost lamina of the dorsal horn. Lamina II, also known as the substantia gelatinosa, can be easily identified in spinal cord slices as it receives mostly thinly myelinated fibers, resulting in its distinctive translucent appearance. Lamina III through VI make up the rest of the dorsal horn, and are distinguished by having cell bodies larger than those in the upper lamina. LTMR central arborizations terminate within laminar domains that are loosely related to their functional class, with C fibers generally innervating the outermost lamina and myelinated Aβ fibers innervating deep dorsal horn lamina, in patterns that can be quite overlapping (Figure 3A–D).

Individual input morphologies and their relative anatomical organization in the spinal cord highlight the intricate receptive field transformations that must occur in the dorsal horn during tactile information processing, where information from a two-dimensional structure, the skin, is funneled into three-dimensional inputs organized in a columnar fashion within the dorsal horn (Figure 3E). Each LTMR subtype displays unique central branching patterns and collateral distributions, yet within sensory columns mapping to particular regions of skin, LTMR inputs converge onto iterative units representing the first step in sensory processing.

B. The neurons of the dorsal horn

In a simplified view, information flow in the dorsal horn occurs largely along two major pathways, from lamina II to I via interneurons that contain dorsally directed axons, and from lamina III to VI via interneurons that contain ventrally oriented axons. The logic underlying this information flow is defined by the respective dorsal horn output neurons that carry light touch information to major brain centers. Output from lamina I/II processing occurs through anterolateral tract projection neurons, whose cell bodies are mostly located in lamina I, and these are mainly concerned with pain and temperature stimuli. The two principal outputs from deeper lamina conveying innocuous touch information are the post-synaptic dorsal column (PSDC) neurons and spinocervical tract (SCT) neurons, whose cell bodies are located in lamina III-V. Physiological recordings and lesion studies have revealed that it is the PSDC and SCT neurons, together with the direct dorsal column pathway, that convey innocuous touch information to the brain (Brown, 1981a). Although this scheme is streamlined for the sake of simplicity, there are additional layers of complexity and cross-talk between the major output pathways of the dorsal horn, as exemplified in diseased states such as tactile allodynia. Components of potential LTMR-specific circuits that have been identified are highlighted in Figure 4.

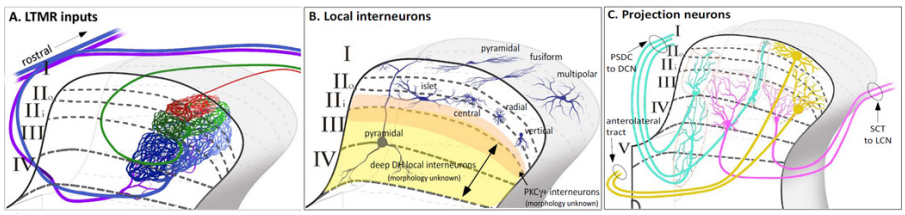

Figure 4

The neural components of the spinal cord dorsal horn

Dorsal Horn Interneurons The vast majority of neurons in the dorsal horn have axons and dendrites that remain within the spinal cord and are therefore defined as locally projecting interneurons. The most well characterized populations of dorsal horn interneurons are described in studies that have focused on the most superficial lamina, lamina I-II, and are thus important for pain, temperature, and itch perception. Although it is generally believed that deep dorsal horn lamina (III-V) are heavily populated by large projection neurons of the anterolateral, PSDC and SCT pathways, there are also many small neurons that are most assuredly locally projecting interneurons and perhaps critical for light touch processing. Some interneuron populations that reside deep in the dorsal horn are integrated into circuits related to sensory modulation of locomotor output (Bui et al., 2013; Drew and Rossignol, 1987; Duysens and Pearson, 1976; Quevedo et al., 2005). However, little is known about deep dorsal horn interneurons that modulate outputs that convey innocuous touch information to higher brain centers. Nevertheless, seminal immunohistochemical and physiological studies of superficial lamina have provided some basic principles of dorsal horn interneuron classification that will undoubtedly shape future classifications of novel interneurons populations discovered in the deep dorsal horn.

Based on neurotransmitter profile, dorsal horn interneurons can be divided into two major classes; inhibitory or excitatory. Inhibitory interneurons use GABA and/or glycine as their main neurotransmitter. Within the superficial lamina, within lamina I-III, GABA is present in one quarter to half of all neurons, while glycine is mainly present in Lamina III though largely restricted to GABA-containing cells. Immunohistochemical studies suggest that the majority of inhibitory interneurons co-release GABA and glycine, with some noted exceptions where purely GABAergic and glycinergic synapses have also been characterized (Polgar et al., 2003; Yasaka et al., 2007). Glutamatergic interneurons can also be found in the dorsal horn and are identified by staining for vesicular glutamate transporters, in particular Vglut2 (Maxwell et al., 2007; Todd et al., 2003).

The most widely accepted and well-characterized classification of dorsal horn interneurons combines whole-cell recording in adult rodent spinal cord slices with biocytin intracellular labeling for morphological correlation.

Classification of spiking patterns elicited by somatic current injections revealed a variety of physiological profiles in the superficial dorsal horn, including tonic, delayed, phasic and single spike (Grudt and Perl, 2002; Prescott and De Koninck, 2002; Thomson et al., 1989). Spiking pattern variability may reflect differences in the processing of somatosensory information by dorsal horn interneurons. For example, phasic and single spike cells may act as coincidence detectors, while tonic and delayed onset cells may act as integrators (Prescott and De Koninck, 2002). Post-recording intracellular labeling experiments have revealed a variety of dendritic morphologies in superficial lamina; These include pyramidal, fusiform, and multipolar cells of lamina I, and the well-characterized islet, central, vertical, and radial cells of lamina II (Figure 4B).

Great efforts have been made to determine a unifying classification scheme correlating morphology and physiology of spinal cord interneurons with various expression profiles, including neurotransmitter type, calcium binding proteins and neuropeptides (reviewed in Todd, 2010). Some of these correlations can be found in lamina II where radial and most vertical cells are thought to be glutamatergic, islet cells are mainly GABAergic, and central cells are of either type. Some spiking patterns can also be correlated with neurotransmitter type. For example, A-type potassium currents, which normally suppress neuronal excitability and therefore give rise to the delayed and gap firing patterns, are largely restricted to glutamatergic interneurons. Indeed, channels containing the Kv4.2 and Kv4.3 subunits are mainly found on interneurons expressing the calcium binding protein calretinin, which are thought to be glutamatergic (Albuquerque et al., 1999; Hu et al., 2006; Huang et al., 2005; Yasaka et al., 2010). Another calcium binding protein, the gamma isoform of protein kinase C (PKCγ) is expressed by a morphologically diverse group of interneurons whose cell bodies reside in the inner/ventral region of lamina II (IIiv) and outer lamina III (Figure 4B). This population is believed to be excitatory and important for mediating injury-induced hypersensitivity (Malmberg et al., 1997; Polgar et al., 1999).

A major obstacle in elucidating dorsal horn circuits related to innocuous touch pertains to the difficulty in recognizing distinct populations of deep dorsal horn interneurons. Classification schemes forged out of superficial dorsal horn studies will undoubtedly shed light on the diversity of deep dorsal horn interneurons. However, even in lamina II, the most extensively studied region of the dorsal horn, a substantial proportion of interneurons remain unclassified (Grudt and Perl, 2002; Maxwell et al., 2007; Yasaka et al., 2007; Yasaka et al., 2010). Molecular and physiological characterization of deep dorsal horn interneurons remains much more elusive and represents a major future goal for understanding LTMR related circuits in the spinal cord. The use of mouse molecular genetics will undoubtedly aid in the identification and classification of novel neuronal populations in the deep dorsal horn and their roles in processing of light touch information.

Dorsal Horn Projection Neurons Projection neurons constitute a very small fraction (< 1%) of neurons of the dorsal horn and are found in lamina I and scattered throughout lamina III-VI. Though few in numbers, dorsal horn projection neurons comprise ascending output pathways of the spinal cord, and therefore play essential roles in interpreting and propagating LTMR information to the brain. The majority of projection neurons concerned with relaying pain and temperature perceptions are concentrated in lamina I and scattered throughout lamina III-VI. These anterolateral tract neurons project contralaterally through the anterolateral white matter to brain centers, such as the reticular formation, periaqueductal grey, hypothalamus, and thalamus, making up the anterolateral system (Figure 4C).

Dorsal horn projection neurons conveying tactile information mostly reside in deep dorsal horn lamina and represent two major neuronal populations; post-synaptic dorsal column neurons and spinocervical tract neurons. Both of these populations have unique anatomical and physiological characteristics. Although the dorsal columns were originally thought to be composed exclusively of ascending branches of Aβ-LTMRs, it has been long known that many fibers in the dorsal columns arise from neurons in the grey matter of the dorsal horn and send their axons as far as the hindbrain (Brown, 1981a). These long projecting neurons are therefore termed post-synaptic dorsal column (PSDC) neurons, and they send their axons through the dorsal columns, intermingled with branches of Aβ-LTMRs, to synapse upon neurons of the dorsal column nuclei (Figure 4C, Figure 5A). The distribution of PSDCs in rats and cats has been mapped by retrograde tracers injected into the dorsal column nuclei or by antidromic activation of their axons in the dorsal columns followed by intracellular injection of horseradish peroxidase (de Pommery et al., 1984; Giesler et al., 1984; Rustioni and Kaufman, 1977). Both PSDC and primary afferent projections are somatotopically organized, with the nucleus cuneatus receiving PSDC inputs from the cervical and upper thoracic spinal cord and the nucleus gracilis innervated by PSDCs residing in the lower thoracic and lumbosacral spinal cord (Figure 5A). Most PSDC neuron cell bodies reside in lamina IV, with particular concentration in the medial region of lamina V. About a third of PSDC neurons also reside at or near the ventral border of lamina III. Estimates of the number of PSDCs in the rodent, cat and monkey range in the thousands (1000–4000), with ~40% residing in the cervical enlargement and ~30% in the lumbar enlargement (Enevoldson and Gordon, 1989a; Giesler et al., 1984). These figures are likely to be underestimates since retrograde labeling from the dorsal columns tends to be inefficient. PSDC neurons, like other neurons on the dorsal horn can be classified by morphological and physiological criteria, falling into three types based on cell body location and dendritic field shape (Figure 4C). Although their primary axons travel through the dorsal columns, the majority (~90%) of PSDC neuron axons send collaterals that arborize and perhaps form synapses ventral to the soma (Brown, 1981a).

Morin (1955) was the first to recognize the existence of a second major ascending pathway carrying light touch information to the brain, the spinocervicothalamic (SCT) tract and their cells of origin, the SCT neurons, located in the gray matter of the spinal cord dorsal horn (Figure 4C). The most distinctive anatomical features of SCT neurons are their superficial projections in the ipsilateral dorsolateral funiculus and their synapses upon cells of the lateral cervical nucleus (LCN), located in C1 to C2 levels of the spinal cord. Axons from LCN neurons in turn decussate in the dorsal spinal commissure and ascend via the medial lemniscus to synapse onto neurons of the ventral posterior lateral (VPL) nucleus of the thalamus (Figure 5B). The presence of an SCT pathway in humans is

controversial; It has been found in some human spinal cords but is argued to be vestigial (Ha, 1964; Nathan et al., 1986). In addition, the LCN is larger in carnivores like the cat, raccoon, and dog than in non-human primates (Ha et al., 1965; Kitai et al., 1965; Mizuno et al., 1967). Anatomical and physiological characterization of SCT neurons resulted from a combination of studies mostly performed in rodents, cats and rabbits, combining antidromic stimulation and retrograde labeling from the LCN and monosynaptic excitation from cutaneous afferents (Brown et al., 1980b; Brown et al., 1976; Bryan et al., 1973; Craig, 1976; Enevoldson and Gordon, 1989b; Hongo et al., 1968; Lundberg, 1964; Taub and Bishop, 1965). On the basis of fiber and cell body counts, there are an estimated 4000–6000 SCT neurons in the cat, with a much more even spread along the rostrocaudal extent in comparison to PSDC neurons, which seem to be concentrated in cervical and lumbar enlargements. Most SCT neurons are located within lamina IV and have dorsally directed dendrites that terminate abruptly at the lamina II/III border. The majority have cone-shaped dendritic trees with a few displaying more prominent ventral dendritic arborizations (Figure 4C). Like PSDC neurons, SCT neurons have axon collaterals that extend several segmental levels and may have local actions in spinal reflex pathways (Brown, 1981b).

C. Spinal cord circuits related to touch perception

The neural components of the dorsal horn, which include pre-synaptic sensory inputs, locally projecting interneurons, descending modulatory inputs, and long-range projection neurons, are linked by a highly complex set of synaptic connections. Dorsal horn neurons not only receive synaptic input from primary afferents, but also from neighboring excitatory and inhibitory neurons, each with relative input strengths that most likely differ amongst modules of neuronal connections. Though our knowledge of dorsal horn circuit organization is still in its infancy, recently gained genetic access to both pre- and post-synaptic neurons will allow for modality specific dissection of dorsal horn circuits.

LTMR terminals in the dorsal horn As with all primary afferents, LTMRs use glutamate as their principal fast transmitter; therefore all LTMR subtypes have an excitatory action on their post-synaptic targets of the dorsal horn (Brumovsky et al., 2007; Todd et al., 2003). However, synaptic arrangements between LTMR subtypes and their post-synaptic targets can be quite complex, often forming synaptic glomeruli; structures that not only include primary afferent axonal boutons and post-synaptic dendrites, but also synaptic contacts with axons of neighboring interneurons. The presence of synaptic glomeruli allows for input modulation at the very first synapse within the dorsal horn, and is thus thought to be the anatomical substrate for primary afferent presynaptic modulation. Within the dorsal horn, two main types of synaptic glomeruli have been described. Type I glomeruli are present largely in lamina II, have dark primary afferent axons, thought to arise from unmeylinated fibers, and axonal contacts that are GABA reactive, thought to arise from purely GABAergic interneurons. Type II glomeruli are found within the laminaII/III boundary, have electron-lucent primary afferent axons, most likely from myelinated fibers, and axonal contacts that contain both GABA and glycine, thought to arise from inhibitory interneurons that release both neurotransmitters.

Although GABA is found in most boutons presynaptic to primary afferents, Aδ- and Aβ-LTMR axoaxonic boutons are also enriched with glycine, consistent with the restriction of glycinergic neurons to the deeper lamina of the dorsal horn (Todd, 1990, 1996; Todd et al., 1991; Watson et al., 2002). Aβ-LTMRs tend to form simpler synaptic arrangements with much fewer axoaxonic synapses, while Aδ-LTMRs tend to display many more axoaxonic structures that resemble type II synaptic glomeruli (Rethelyi et al., 1982, 1989). Although the ultrastructural appearance of C-LTMRs is not yet known, it is possible that they resemble synaptic arrangements of other C fibers. However, like Aδ- and Aβ-LTMRs, C-fiber synaptic arrangement can be mixed, with non-peptidergic C-fibers displaying complex structures with many axoaxonic synapses similar to type I synaptic glomeruli, while peptidergic afferents form much simpler synaptic arrangements (Rethelyi et al., 1982; Ribeiro-da-Silva et al., 1989b). Thus, it is likely that presynaptic inhibitory inputs to different LTMR subtypes originate from specific types of interneurons, but the identity of such populations remains elusive.

LTMR connections to dorsal horn interneurons Much of what we know regarding primary afferent inputs onto dorsal horn interneurons comes from patch clamp recordings of lamina II in spinal cord slices, and great efforts have been made to identify modules of synaptic inputs from identified primary afferents (Lu and Perl, 2005; Wang and Zylka, 2009). We know that central and islet cells receive monosynaptic input mainly from C fibers, while radial and vertical cells receive monosynaptic inputs are from both C and Aδ fiber inputs (Grudt and Perl, 2002; Yasaka et al., 2007). C- and Aδ-LTMRs projections however terminate within laminae IIiv/III, making them likely pre-synaptic candidates for at least some of the morphological cell types found in the substantia gelatinosa (Li et al., 2011; Light et al., 1979; Seal et al., 2009; Sugiura et al., 1986). Indeed, a subset of Islet cells that receive C-fiber input conveys tactile rather than nociceptive information, making them candidate post-synaptic targets of C-LTMRs (Light et al., 1979; Lu and Perl, 2003; Rethelyi et al., 1989). Furthermore, both C-LTMRs and Aδ-LTMR inputs overlap extensively with PKCγ^{+} interneurons, a morphologically diverse group of excitatory interneurons found in lamina IIi and III, that under normal conditions are activated by innocuous stimuli (Li et al., 2011; Neumann et al., 2008). Thus, PKCγ+ interneurons are prime candidate postsynaptic targets of C-LTMRs and Aδ-LTMRs. Much less is known about candidate postsynaptic partners of Aβ-LTMR subtypes. There is some evidence that GABAergic interneurons in superficial lamina receive monosynaptic input from low-threshold Aβ primary afferents (Daniele and MacDermott, 2009). From immunohistological and electron microscopy studies, we understand that only a small percentage of dendrites that are post-synaptic to Aβ-hair follicle afferents belong to inhibitory neurons, and most of these are exclusively glycinergic (Todd et al., 1991; Watson et al., 2002). Recent molecular and functional identification of LTMR subtypes coupled with new circuit tracing technologies will undoubtedly facilitate the discovery of LTMR specific postsynaptic partners in the dorsal horn. Virus trans-synaptic tracing and channelrhodopsin-assisted circuit mapping, both of which have broadened our understanding of cortical circuits, are beginning to be applied to various sensory systems (Stepien et al., 2010; Takatoh et al., 2013; Wang and Zylka, 2009). Therefore, genetic access to both LTMR subtypes and dorsal horn interneurons will

allow for the merging of these technologies to uncover the variety of LTMR specific post-synaptic targets and their dorsal horn synaptic connectivity maps (Hantman et al., 2004; Li et al., 2011).

LTMR inputs to projection neurons We have learned a great deal about the modality of inputs onto the anterolateral tract projection neurons as a result of the identification of markers exclusively expressed in this projection neuron population and because of the enormous efforts devoted to understanding pain pathways. The lack of markers for pre- and post-synaptic partners in LTMR-associated dorsal horn circuits has hampered progress in understanding of LTMR inputs onto long-range projection neurons. However, LTMR related projection neurons in the anesthetized animal can be identified by antidromic stimulation from brain stem targets and activated by either electrical or natural stimuli to define their response properties. Therefore, *in-vivo* extracellular recordings of projection neurons in the rat, cat and monkey have resulted in insights into the type of natural stimulation that activates them and therefore the type of LTMR input that they may receive.

As introduced above, a major output of the deep dorsal horn is carried by post-synaptic dorsal column (PSDC) neurons, which can be identified in extracellular recordings by antidromic stimulation of the dorsal columns. Mechanical stimulation of either glabrous or hairy skin can activate most or all PSDCs with a minority responding best to strong mechanical stimuli. About 20% of PSDCs respond exclusively to light mechanical stimulation of mechanosensitive organs including hair follicles and touch domes, while the rest receive convergent inputs from mechanoreceptors and nociceptors. Only very few PSDCs of the cat (~6%) are excited solely by noxious mechanical stimuli. PSDC response properties can be rapidly or slowly adapting depending on the nature of the stimulus. For example, hair follicle movement elicits rapidly adaptive responses while touch dome stimulation results in slowly adaptive responses in PSDCs (Angaut-Petit, 1975; Uddenberg, 1968). Many Aβ axons are thought to form monosynaptic contacts with PSDCs, possibly including SAI-LTMRs, RA-LTMRs associated with hair follicles, and Pacinian corpuscles (Maxwell et al., 1985). Not all inputs onto PSDCs are associated with mediating tactile information, however; they may also receive inputs from group Ia muscle afferents as well as visceral afferents, highlighting a role of PSDCs in integrating somatosensory information (AlChaer et al., 1996; Jankowska et al., 1979). Consistent with this idea, PSDCs also receive inputs from non-primary sensory neurons sources, which include GABA and glycinergic interneurons as well as inputs from corticospinal and spinocervical tracts, providing opportunities for presynaptic and postsynaptic modulation of LTMR inputs onto PSDCs (Bannatyne et al., 1987; Maxwell, 1988; Maxwell et al., 1995). Therefore, we speculate that PSDC output neurons are main carriers of integrated information emanating from both glabrous and hairy skin and pertaining to a variety of stimulus modalities.

While PSDC neurons respond to a wide variety of sensory stimuli, SCT projection neurons are mainly concerned with hair follicle movement and therefore represent a main dorsal horn output for hairy skin innervating LTMRs. Nearly everything that we know about the morphological and physiological characteristics of SCT neurons come from studies performed in the cat. In comparison to PSDC neurons, we know considerably more about the physiological properties of SCT neurons, due in part to the fact that SCT neuron somata are larger and therefore easier to identify and record. Like PSDC neurons, SCT neurons can also be easily identified in physiological recording experiments by antidromic activation of their axonal tracts or brain targets; in this case, the dorsal lateral funiculus or the LCN (Taub and Bishop, 1965). SCT neurons respond maximally to hair follicle deflection, with a single impulse in a hair follicle afferent capable of evoking a large EPSP. Furthermore, SCT response properties are similar to primary hair follicle afferents, suggesting direct excitatory inputs from hairy skin LTMRs (Brown et al., 1987). Unlike PSDCs, SCT neurons do not receive SA-LTMR input from hairy skin, any LTMR input from glabrous skin, or Pacinian corpuscle (RAII-LTMR) inputs (Brown, 1981b; Hongo, 1975). Based on their response properties to electrical and natural stimulations, SCT neurons can be categorized into three main groups; low-threshold, wide-dynamic range, and high-threshold SCT neurons, presumably reflecting the types of LTMR inputs they receive. Low-threshold SCTs make up 30% of the total population and are excited solely by hair movement. Wide-dynamic range SCT neurons respond to both hair movement as well as pressure or pinch stimuli and receive inputs from axons with varied conduction velocities. This subgroup represents about 70% of the total SCT population and it is thought to receive monosynaptic input from both hairy skin Aβ- as well as Aδ-LTMRs. The remaining group, representing less than 5% of the total population, is not excited by hair follicle movement but by noxious stimuli and is therefore categorized as high-threshold SCT neurons. These may receive input from non-myelinated sensory neurons, although it is possible that these inputs are indirect as SCT dendrites seldom penetrate lamina II (Brown and Franz, 1969; Cervero et al., 1977). Ultrastructural analysis of SCT dendrites reveals that they receive both excitatory and inhibitory inputs, likely arising from hair follicle afferents and local inhibitory interneurons, respectively, with inhibitory inputs more commonly found on proximal dendrites. Furthermore, axoaxonic synapses or glomeruli are rarely found in apposition to SCT dendrites of the cat (Maxwell et al., 1992; Maxwell et al., 1991). Thus, PSDC and SCT projection neurons are anatomically, morphologically, and physiologically distinct populations with regard to both presynaptic inputs and response properties. These two projection neuronal populations convey a mixed variety of modalities of ascending information, and compelling evidence supports the notion that both PSDC and SCT neurons propagate integrated, processed cutaneous LTMR information to the brain. Thus, strong support exists for a model in which the dorsal horn serves to integrate LTMR inputs and output projection neurons propagate this processed information to the brain. Major future goals should include defining the precise nature of direct and indirect LTMR inputs onto PSDC and SCT neurons and the relative contributions of LTMR subtypes to PSDC and SCT response properties.

D. Ascending pathways and the integration of tactile stimuli

The morphological and physiological differences between the direct DC pathway and the indirect anterolateral, PSDC and SCT pathways provide evidence that these four main ascending systems sub-serve different roles in propagating tactile information from the periphery to the brain (Figure 5). Noxious and thermal stimuli are predominantly processed through the anterolateral pathway, although it is possible that anterolateral projection

neurons serve an auxiliary role to the dorsal column pathway in sensory discrimination for stimuli in the noxious range. Certainly Aβ fibers that respond to a wide variety of tactile stimuli, such as myelinated nociceptors, may contribute to sensory discrimination of noxious mechanical stimuli. In another example, temperature sensitive LTMRs, such as Aδ- and C-LTMRs, which respond to cooling of the skin, are likely to contribute to processing of thermal stimuli. For fine tactile discrimination tasks, much emphasis has been placed on the direct pathway whereby a subset of Aβ-LTMRs send direct projections through the dorsal columns to dorsal column nuclei, which in project forward to the thalamus and then to somatosensory cortex.

However, we are beginning to appreciate how the physiological and anatomical complexity of the PSDC and SCT systems can be layered on top of the direct pathway to propagate touch information to higher processing centers, including the dorsal column nuclei and thalamus, where both systems converge (Figure 5). The PSDC pathway is likely to receive both direct and indirect inputs from multiple LTMRs subtypes, thereby carrying information about the quality of tactile stimuli. Furthermore, since many and possibly all SAI-LTMRs do not send direct projections to the dorsal column nuclei, and since SCT neurons also do not receive SAI-LTMR input, the PSDC pathway is the major and perhaps sole pathway for ascending SAI-LTMR information (Brown, 1981b; Petit and Burgess, 1968). SAI-LTMRs are essential for fine texture discrimination, and thus the PSDC pathway is likely to play a major role in discriminative touch. On the other hand, the SCT system mainly receives input from hair follicle afferents, and not glabrous skin or SAI-LTMRs, and thus their tactile processing functions are likely to be limited to the coding of hair follicle movement. Spinal cord lesion studies in primates and other model organisms also offer a glimpse of the roles of each of the major ascending tracts in tactile discrimination. Indeed, dorsal column lesions impair discrimination of texture, size, and shape of objects, leading to the conclusion that the direct DC and PSDC pathways are in part involved in discerning tactile stimuli that require sequential or spatiotemporal analysis (Azulay and Schwartz, 1975; Dobry and Casey, 1972; Vierck and Cooper, 1998). There is less evidence for changes in tactile discrimination resulting from lesions of the dorsal lateral funiculus, which would include the SCT pathway. However, combined lesions of the dorsal column and the dorsal lateral funiculus have greater effects on tactile discrimination than a lesion restricted to one of these alone (Levitt, 1966). Dorsal quadrant lesions, on the other hand, produce a more severe impairment of movement detection than a dorsal column lesion, suggesting a role for SCT neurons in detecting moving stimuli (Vierck, 1974). Furthermore, latencies of evoked potentials recorded in the cerebral cortex are shorter when transmitted by the SCT pathway than those transmitted by the dorsal column pathway (Catalano and Lamarche, 1957; Mark and Steiner, 1958). Taken together, morphological and physiological comparisons between PSDC and SCT neurons are most consistent with a role of the LTMR-PSDC pathway in processing several LTMR input modalities and as a key mediator of tactile discrimination in both glabrous and hairy skin. In contrast, the LTMR-SCT pathway appears concerned with fast tactile transmission from hairy skin.

Future challenges in understanding the organizational logic and function of LTMR circuits

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The remarkable organization of peripheral LTMR endings in both glabrous and hairy skin reveals fundamental principles underlying the neuronal coding of tactile stimuli by sensory neurons. Individual mechanical properties or qualities of a complex tactile stimulus engage distinct combinations of end organs found in skin and differentially activate the unique combinations of LTMRs with which these end organs associate. Therefore, a principle feature of innocuous touch coding is that a large cadre of morphologically and physiologically distinct LTMRs endows the somatosensory system with a near infinite array of potential ensembles of LTMR activities that, collectively, extract and encode all qualities of a tactile stimulus. How each LTMR subtype, with its unique tuning property, adaptation rate, and conduction velocity, contributes to the formulation of a percept is a challenging question for the future. Recent advances in the molecular identification of LTMR subtypes coupled with technologies for selectively activating and/or silencing neuronal populations in the awake behaving animal will undoubtedly shed light on these intriguing questions (McCoy et al., 2012; Vrontou et al., 2013).

The central terminations of Aβ-, Aδ- and C-LTMRs that innervate the same region of skin exhibit exquisite organization, aligning within somatotopically arranged LTMR columns that span several laminae in the spinal cord dorsal horn. These LTMR columns signify key integration sites of the ensembles of LTMR inputs that code for distinct tactile stimuli. LTMR inputs that converge upon dorsal horn columns are likely to be heavily processed by local interneurons and descending projections that ultimately influence firing patterns of dorsal horn projection neurons comprising the PSDC and SCT pathways to the brain. Understanding how touch circuits of the dorsal horn are organized and ultimately how LTMR inputs, local interneurons, and descending modulatory inputs shape the outputs of PSDC and SCT projection neurons are not only key to understanding mechanosensory processing but also to uncovering principles of dorsal horn function that might also be at play during pain and motor circuit modulation. A major obstacle to progress in dorsal horn circuit dissection remains the difficulty in recognizing distinct populations of interneurons and projection neurons. Indeed, genetic tools to visualize and probe the functions of interneuron subtypes as well as PSDC and SCT output neurons do not yet exist. Gaining genetic access to the distinct populations of dorsal horn interneurons and projection neurons for morphological, physiological and behavioral analyses, including the use of light-assisted and chemical-genetic based connectivity mapping and silencing strategies, will greatly facilitate our appreciation of the logic, organization and contributions of touch related spinal cord circuits.

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We thank Richard Koerber, C. Jeffrey Woodbury, David Linden, Lawrence Schramm and Steven Hsiao for helpful comments on the organization and details of this review. In addition, we thank all Ginty lab members, in particular Ling Bai, Yin Liu, and Amanda Zimmerman, for providing helpful comments on sections in which they hold great expertise. The authors' research addressing the organization and function of LTMR circuits is supported by NIH

NRSA F32NS077836-01 (VEA) and NIH R01 5R01DE022750 (DDG). DDG is an investigator of the Howard Hughes Medical Institute.

Footnotes

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