PHYSIOLOGY 28: 142–150, 2013; doi:10.1152/physiol.00059.2012

Hairy Sensation

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The hairs of the skin not only function to prevent heat loss but also have important sensory functions. Recent work has now established that each hair of the skin is innervated by one or more of three types of mechanoreceptor ending. Each of these three mechanoreceptor types possesses distinct molecular features and detects distinctive information about skin touch, which is relayed to specific brain locations in a somatotopic fashion.

At some point during the evolution of hominids, hairlessness, or at least very little body hair, became a distinguishing feature of modern humans. The hairlessness of humans is a very unusual trait among land-based mammals, with some notable largely hairless species like the naked mole-rat or African and Asian elephants (13, 62, 67). It is clear that the fur of animals serves essential functions, for example, in reducing heat loss, but it is not often appreciated that almost all the hair of the body potentially serves a sensory function. Thus, in the most studied rodents like mice and rats, almost every hair is innervated by sensory endings, and it is only very recently that the anatomical, molecular, and functional diversity of these endings has become apparent. Here, we review recent progress describing the structure, function, and molecular features of primary afferents that innervate hair follicles. Primary afferents that innervate other end-organs such as Merkel cells or Pacinian corpuscles have been extensively reviewed elsewhere (31, 49) and are not subject of this review. Taken together, these recent studies suggest that there are specific streams of sensory information carried by different subsets of hair follicle afferents.

Hair Types of the Mammalian Skin

In the nonglabrous skin of most mammals, three major types of hairs are found: guard hairs, awl/auchene hairs, and zigzag hairs (17, 18). Guard hairs (also called monotrich hairs because they always stand alone in the hair follicle) are the largest and least abundant hairs, constituting only 1–2% of the hairs in the trunk and limb regions. They have two rows of medulla cells and are usually associated with a pair of sebaceous glands. Particularly thick and long guard hairs that are surrounded by a loop of capillary blood vessels and associated with a cluster of Merkel cells are termed tylotrich hairs (68). Awl and auchene hairs are much thinner and shorter than guard hairs. They have up to four rows of medulla cells and constitute ~25% of the trunk hairs. Auchene hairs differ from awl hairs only in having a single bend about midway along the hair and are thus rarely considered as a distinct type of hair (17, 18, 20). The most abundant hairs of the mammalian coat are the zigzag hairs (>70%). They are the thinnest and shortest hairs, have only one row of medulla cells, are usually unpigmented, and emerge in groups of up to four hairs from a common orifice in the skin.

All three types of hairs are densely innervated by sensory nerve fibers (FIGURE 1). The afferent endings are either arranged as palisades of so-called lanceolate endings parallel to the hair shaft or as circumferential endings that entangle the hair external to the lanceolate terminals. It was already suggested more than 70 years ago that morphologically distinct hairs are innervated by functionally distinct fiber types (68, 81). Zotterman showed that gently stroking the fur of a cat evokes several types of action potentials that travel at different speeds and that strokes of different intensities activate distinct fiber types (FIGURE 1). Using more accurate stimuli and higher-resolution single-unit recordings, Brown and Iggo (6) confirmed and extended these findings and showed that in cats and rabbits movement of guard hairs preferentially activates thickly myelinated fibers, whereas thinly myelinated Aδ fibers are activated by movement of the smaller zigzag hairs, termed D-hair or down hair receptors.

Thickly Myelinated Hair Follicle Afferents: Aα/β Fibers

An important observation made by Brown and Iggo was that Aβ-fiber hair follicle afferents serve as movement detectors. Thus discharges in the afferent fiber adapted rapidly and were only evoked during the movement of the hairs but not during maintained displacement. Furthermore, the velocity of the movement is encoded by the firing frequency of the action potential bursts, which increases as a function of stimulus velocity. Identical receptor properties were later also described for Aβ-hair follicle afferents in other species, including primates (52), rat (41, 43, 51), and mouse (34, 53).

Brown and Iggo also observed subtle differences in the receptor properties of guard hairs and tylotrich hairs. Similar differences between short and long guard hairs were also found in a subsequent study by Burgess and colleagues who described G1 and G2 receptors, which differed in their conduction velocity, the size of their receptive fields and their mechanosensitivity (9). Two distinct categories of rapidly adapting Aβ-hair follicle afferents were also found in primates (52), but no attempts have been made to distinguish these two groups in rat or mouse hairy skin (34, 41, 51).

The insensitivity to static stimuli and the exclusive sensitivity to movement allow rapidly adapting mechanoreceptors (RAMs) to faithfully transduce vibrotactile stimuli into spike trains of the same frequency. An interesting feature of the vibration sensitivity of RAMs is that it is "tuned" to a narrow range of frequencies, which means that, within this range, RAMs are particularly sensitive to vibrotactile stimulation. Aβ-fiber RAMs in the hairy skin are tuned to frequencies between 10 and 50 Hz (see FIGURE 3H) (24, 36), which is very similar to the frequency tuning of RAMs that innervate Meissners corpuscles (41, 72). In contrast Aβ-fiber RAMs that innervate Pacinian corpuscles are most sensitive to vibrations above 100 Hz (4, 29). Intraneural microstimulation of single mechanoreceptors in the human hand revealed that Meissner corpuscles mediate the sensation of flutter evoked by low-frequency vibrotactile stimulation of the glabrous skin (56). Likewise Aβ-hair follicle afferents have been implicated in the sense of flutter in the human hairy skin. Although direct evidence is missing, a comparison of the responses of mechanoreceptors in the hairy skin of monkeys with the sensations evoked in humans by identical stimuli strongly supports this hypothesis (52).

Although the functional properties of hair follicle afferents are well characterized, still relatively little is known about the molecular makeup that determines the specific sensory function of these afferent fibers. The signaling event that ultimately leads to the generation of the afferent message begins with the transduction of a mechanical stimulus into an electrical signal at the peripheral nerve terminal of the primary afferent. This process, collectively termed mechanotransduction, was found to be mediated by three biophysically and pharmacologically distinct types of mechanically activated transduction currents, termed rapidly adapting (RA) (FIGURE 2A), intermediately adapting (IA), and slowly adapting (SA) current (16, 27, 38, 39). The molecular identity of the ion channels that mediate these currents in mammals is still unknown, but several mechanotransduction genes have been identified in model organisms such as *Caenorhabditis elegans* and *Drosophila melanogaster* (14, 19, 40, 61). In primary cultures of DRG neurons, nociceptors and mechanoreceptors can be distinguished by means of their action potential configuration, but such physiological signatures do not allow one to discriminate between different mechanoreceptor subtypes (21). At present, it is believed that all mechanoreceptors possess the same type of mechanotransduction current (an RA current), and thus differences in the coding properties of the primary afferents are thought to be largely determined by the specific combination of voltage-gated ion channels expressed in different mechanoreceptor subtypes (FIGURE 2). Indeed, we could recently show that the voltage-gated potassium

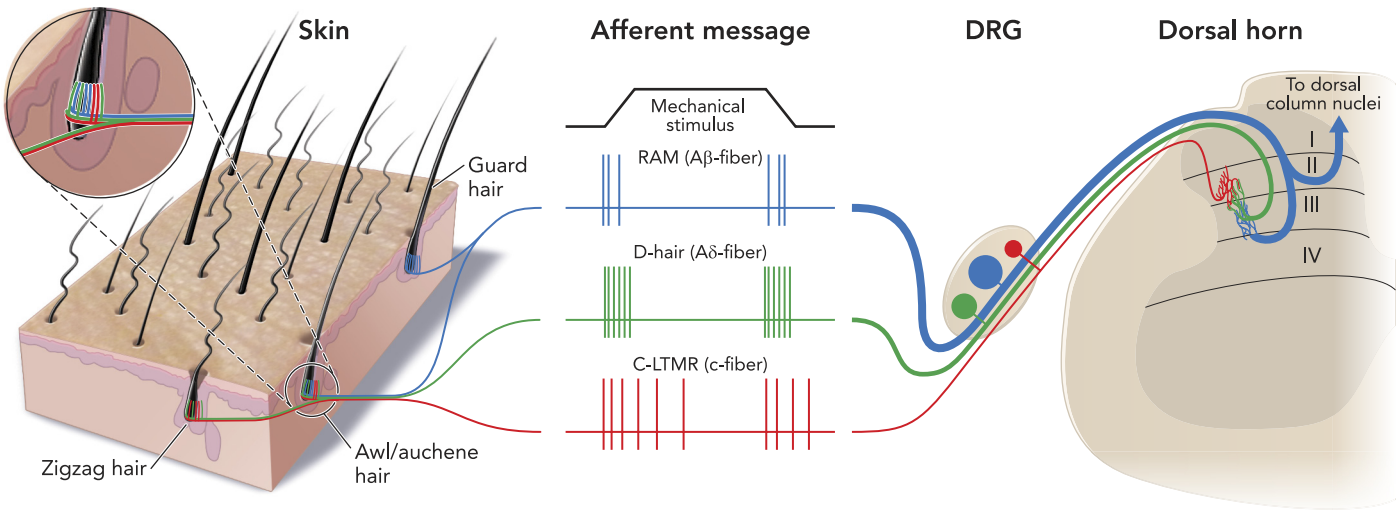

FIGURE 1. **Organization of mechanosensory pathways**
The three major hair types in the hairy skin are densely innervated by sensory afferents. It should be noted that other sensory receptors such as Merkel cells and Pacinian corpuscles, which are not shown for reasons of simplicity, are also present in the hairy skin. Guard hairs are only innervated by Aβ-fibers (blue), whereas awl/auchene hairs and zigzag hairs are innervated by multiple fiber types (Aδ-fiber, green; c-fiber, red). In the spinal cord, Aβ-, Aδ-, and c-fibers terminate in a columnar manner in distinct but overlapping laminae.

channel KCNQ4 is specifically expressed at the peripheral nerve endings of Aβ-hair follicle afferents (FIGURE 3A) and Meissner corpuscles and is required for the proper velocity coding and frequency tuning of these receptors in both mice and humans (24) (FIGURE 3F). One prediction of the physiological experiments with mice was that loss of KCNQ4 function may in fact render the mice better able to detect low-amplitude, low-frequency vibrations. Using psychophysical testing in humans carrying loss of function mutations in KCNQ4, it was shown that these people are in fact better at detecting low-frequency vibrotactile stimuli compared with controls. Thus humans with KCNQ4 mutations could be considered super-touchers, although this ability arises from a loss of tuning in RAMs, which may in fact be important in certain behavioral contexts (24). In a subsequent study, we observed similar, yet even more dramatic, changes in the firing properties of hair follicle afferents in mice lacking the transcription factor c-Maf (79) (FIGURE 3F). C-Maf expression in DRGs starts around *embryonic day 11* (E11) (79), which coincides with the onset of functional maturation of low-threshold mechanoreceptors (38). In mice lacking c-Maf, mechanical stimulation of Aβ-hair follicle afferents evokes up to five times more spikes compared with wild-type receptors. The inter-spike intervals are significantly reduced, and action potential bursts adapt more slowly (i.e., in c-Maf mutant mice, firing typically extends into the static phase of a mechanical ramp-and-hold stimulus). Although the former effect can be attributed to the lack of KCNQ4 (FIGURE 3F), which is a downstream target of c-Maf (FIGURE 3D), altered expression of other yet unidentified channels is likely to underlie the slowing of adaptation. In addition to the functional deficits in Aβ-hair follicle afferents, c-Maf mutant mice also exhibit marked changes in their end-organ morphology. Thus lanceolate endings of Aβ-hair follicle afferents are thinner and more branched in c-Maf mutant mice, Meissner corpuscles display severe hypotrophy, and Pacinian corpuscles are dramatically reduced in number. Similar changes in end-organ morphology were also observed in mice lacking the GDNF receptor Ret (5, 50), whose expression is regulated by c-Maf (79).

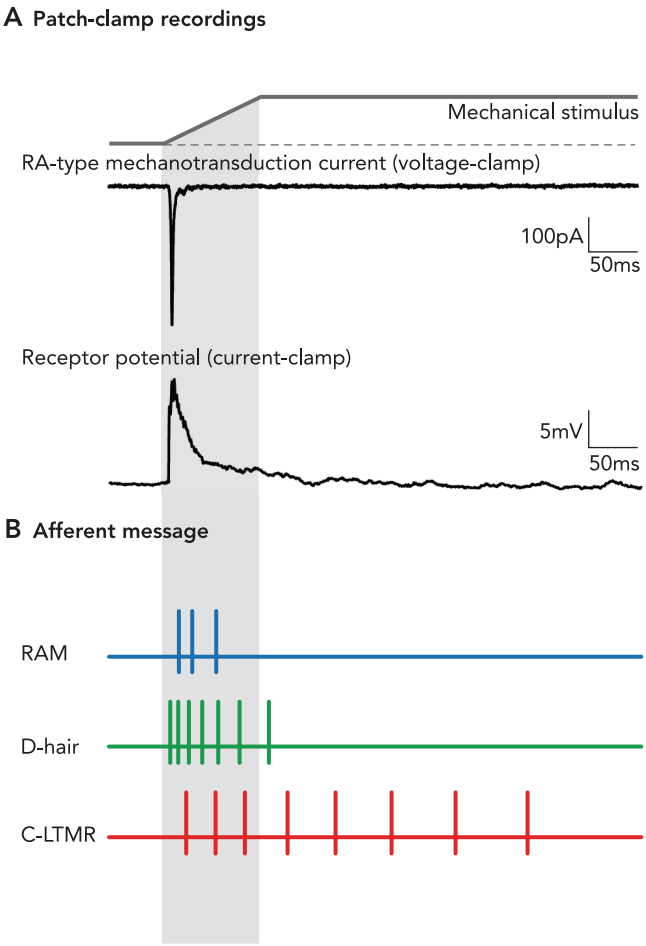

FIGURE. 2. **Mechanotransduction in low-threshold mechanoreceptors**
A: the *top* trace shows a patch clamp recording (voltage-clamp) of an RA-type mechanotransduction current evoked by mechanical stimulation of the cell body of a putative mechanoreceptor in a primary culture of DRG neurons. The *bottom* trace shows the receptor potential evoked by the same stimulus in the same neuron recorded in the current-clamp configuration. *B*: schematic of the primary afferent responses of RAMs (blue), D-hairs (green), and C-LTMRs (red) evoked by a ramp-and-hold stimulus. Note that the three fiber types fire different afferent messages in response to the same mechanical stimulus.

D-Hair Receptor a Quintessential Hair Receptor

D-hair receptors are named after the down hair of the cat's fur coat (6). While making a detailed survey of the functional properties of sensory afferents innervating the hindlimb of the cat, Brown and Iggo identified afferents with conduction velocities in the Aδ range, which is typically around half the conduction velocity of Aβ axons in the same species. D-hair receptors have several distinguishing characteristics that have since been found to be consistent in many species. First, they are very clearly the most sensitive mechanoreceptor of the hairy skin; typically the force thresholds needed to activate D-hair receptors in a variety of species are at least 10 times lower than the minimum forces needed to activate classical Aβ mechanoreceptors (44). D-hair receptors are unique among hair receptors in that they tend to have large receptive fields and are activated by moving virtually every hair within the receptive field area. In contrast, classical Aβ-mechanoreceptors are usually only activated by movement of a few hairs within the receptive field. It has also been consistently noted that the conduction velocity distribution of D-hair receptors is very tightly distributed in several species

(6, 53, 60), so that an afferent barrage from D-hair receptors would arrive at central synapses in a temporally focused manner.

What are D-hair receptors for? This is a very hard question to answer since, although in every animal looked at, including sub-human primates, D-hair receptors are present, there is practically no direct evidence for their existence in the hairy skin of humans. Microneurographic studies have shown the existence of Aδ fibers in humans with low-threshold receptive fields, but these were not examined in sufficient detail to determine whether they were D-hair receptors (1). Thus there are no experiments using intraneural microstimulation in humans to at least answer the question of whether D-hair receptor activity leads to a conscious sensation in humans. Compressive nerve blocks are commonly used to dissociate the A-fiber effects from C-fiber effects, for example when the mechanisms of hyperalgesia are studied in humans. It is interesting that touch sensation disappears before first pain detection, which is subserved by Aδ-fiber nociceptors (80), suggesting that information from D-hair receptors may not contribute to the conscious appreciation of discriminative touch.

Interestingly, mutant mice that specifically lack D-hair receptors were identified more than a decade ago since the neurotrophic factor neurotrophin-4 (NT-4) is required specifically for the adult survival of these sensory neurons (70, 71). We used this fact to identify specific molecular markers that are either highly enriched or even exclusively expressed in D-hair receptors. We identified two genes expressed primarily in sensory neurons that are lost in adult NT-4$^{-/-}$ mice: the BDNF receptor trkB and the low-voltage-activated T-type calcium channel gene $Ca_V3.2$ (66) (FIGURE 3B AND C). There is, however, good functional evidence that slowly adapting mechanoreceptors SAMs are also responsive to BDNF, presumably while they express trkB receptors. Thus lack of BDNF leads to reduced sensitivity of SAMs, which can be rescued in adult mice by exogenous application of recombinant BDNF (11). Recently, elegant genetic experiments have confirmed that many trkB-positive sensory neurons are indeed D-hair receptors and that they form lanceolate endings on practically

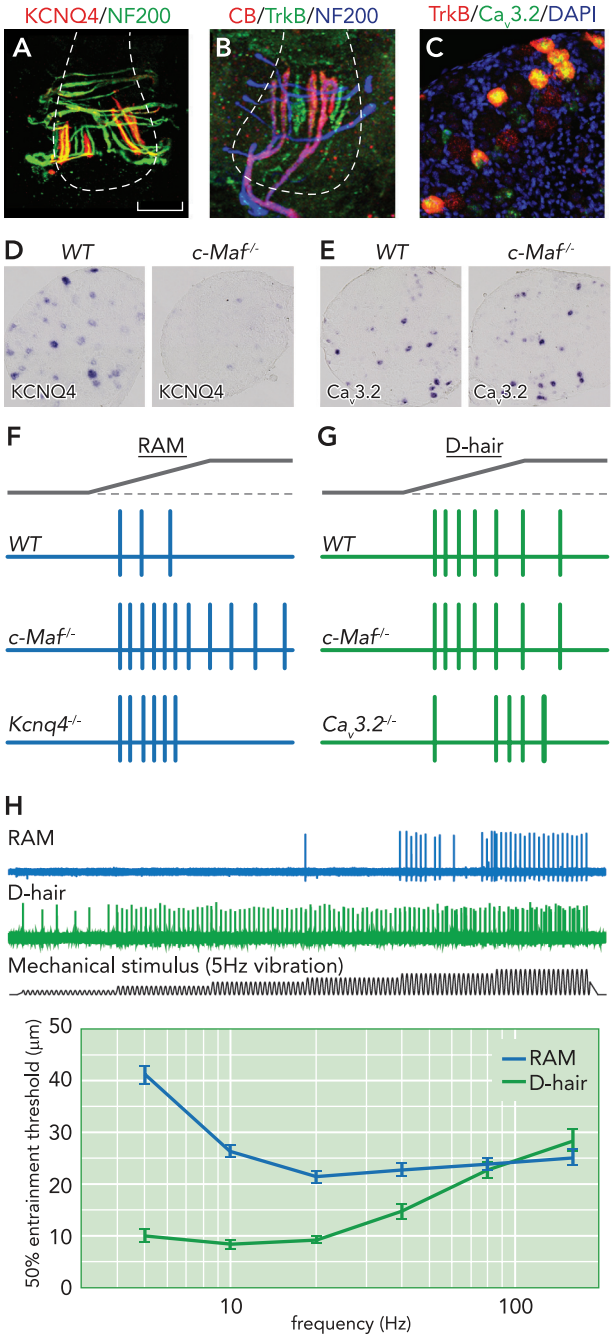

FIGURE 3. **Molecular determinants of mechanoreceptor function**
A: hair follicle innervated by KCNQ4 (red) expressing myelinated (NF200, green) nerve fibers. *B*: hair follicle afferents stained for calbindin (CB) and TrkB. Note that not all lanceolate endings around a single hair in *A* and *B* express the same proteins, indicating that different primary afferents innervate the same hair. KCNQ4 and calbindin are only expressed in Aβ-fiber afferents (24, 79). *C*: DRG neurons that express high levels of TrkB co-express the voltage-gated calcium channel Cav3.2, which is specifically expressed in D-hair mechanoreceptors (66). Hence, CB-negative and KCNQ4-negative lanceolate endings in *A* and *B* most likely represent D-hair mechanoreceptors. *D* and *E*: in situ hybridization showing the regulation of KCNQ4 and Cav3.2 expression by the transcription factor c-Maf. *F* and *G*: schematic drawing of RAM and D-hair afferent responses in wild-type (WT), c-Maf, KCNQ4, and Cav3.2 knockout mice. *H*: comparison of the frequency tuning of RAMs (blue) and D-hair (green) mechanoreceptors. Vibration amplitudes at which RAMs and D-hairs exhibit 50% entrainment are plotted as a function of vibration frequency. The mechanical thresholds for 50% entrainment were determined by applying vibration stimuli of increasing amplitudes (*top*, black trace) to the receptive fields of RAMs (*top*, blue trace) and D-hairs (*top*, green trace). Data for RAMs is taken from Ref. 24, whereas the D-hair tuning curve is previously unpublished data. *A* is reused from Ref. 24, with permission from *Nature Neuroscience*, and *B–E* are reused from Ref. 79 with permission from *Science*.

every hair follicle within a single receptive field in the skin (45). The lanceolate endings formed by D-hair receptors are distinct from those formed by Aβ-fiber RAMs since they are negative for the KCNQ4 channel that regulates the tuning of RAMs (24, 79). The extraordinary sensitivity of D-hair receptors can in part be explained by the presence of the voltage-gated calcium channel $Ca_V3.2$ (T-type calcium channel). This channel is activated with relatively modest depolarizations (59) and can thus amplify small depolarizing voltage shifts initiated by the opening of mechanosensitive currents, such that the threshold for action potential firing is reached with smaller stimuli than in other mechanoreceptors (25, 66). Data supporting this model were obtained from mice lacking the $Ca_V3.2$ gene. D-hair receptors in these mice responded with significantly longer delays to ramp mechanical stimuli, indicating elevated mechanical thresholds in the absence of $Ca_V3.2$ (FIGURE 3G). Other mechanoreceptors in these mice were unaffected by $Ca_V3.2$ gene deletion, which confirms the highly specific role that this channel fulfills in D-hair receptors (78). The fact that specific markers of D-hair receptors exist suggests that it may be possible to find small molecules or natural substances that selectively activate D-hair receptors. A naturally occurring substance obtained from extracts of Szechuan peppercorns called hydroxy-α-sanshool has been shown to activate sensory neurons and can apparently cause tingling sensation in humans (2). It has been proposed that the excitatory effects of this substance are mediated by its ability to inhibit two pore background potassium channels, in particular KCNK3, KCNK9, and KCNK18. Single-fiber recordings have shown that, among identified cutaneous afferents, D-hair receptors are very strongly activated by hydroxy-α-sanshool (42). However, this substance activates C-fiber nociceptors directly as well as RAMs; therefore, the behavioral effects of this substance will be the result of the ensemble activation of both mechanoreceptors and C fibers (32). Selective ways of activating D-hair receptors could be useful tools in the future to probe their precise functional role in sensation from the hairy skin.

Unmyelinated Hair Follicle Afferents: Tactile c-Fibers

The hairy skin is also innervated by a population of low-threshold mechanoreceptors that have unmyelinated axons and have been called C-LTMRs (c-fiber low-threshold mechanoreceptor), also sometimes referred to as C-tactile afferents. The existence of C-LTMRs has been known for many decades (28, 58, 81), and a very early report from the recently deceased Ainsley Iggo (12) showed that some C-LTMRs are in fact driven by hair movement (28). Iggo's work was the focus of some controversy in the 1960s when it became clear that most cutaneous C fibers in fact have properties characteristic of nociceptors (3). Thus the existence of C-LTMRs was known but actually largely ignored for several decades. However, human microneurography experiments again showed in the late 1990s that C-LTMRs are relatively common in human skin (30, 58). Anatomical studies had provided hints that some hair follicles may be innervated by unmyelinated afferent fibers (23, 77), but until recently direct evidence had been lacking.

C-LTMRs were first described in the cat (81) and were subsequently found in the hairy skin of many species including mouse (65), rat (41), monkeys (37), and humans (30, 75). C-LTMRs are activated by innocuous mechanical stimuli and typically have von Frey thresholds below 2 mN. In response to a maintained mechanical stimulus, they initially fire a high-frequency burst of action potentials, which usually completely adapts within 5 s. C-LTMRs thus have adaptation rates intermediate between slowly and rapidly adapting mechanoreceptors. Several studies reported that C-LTMRs also respond to innocuous cooling (45, 55, 65) and that simultaneous cooling and mechanical stimulation gives a more vigorous response than mechanical stimulation alone (58).

The functional role of C-LTMRs is still largely unknown. The original hypothesis that C-LTMRs might underpin ticklish sensations was soon discarded in favor of the idea that C-LTMRs signal the pleasant sensation often associated with gentle touch. Several lines of evidence support this idea. Stimuli that are usually perceived as pleasant are particularly effective in activating C-LTMRs (48). Moreover, one patient suffering from sensory neuronopathy (a complete lack of Aβ-fiber low-threshold mechanoreceptors) described gentle mechanical stimuli applied to the hairy skin as being moderately pleasant, and functional magnetic resonance imaging (fMRI) showed that stimulation of c-LTMRs in this patient evoked activity in emotion-related cortical systems (57). However, earlier reports of another patient with large-fiber sensory neuropathy described a complete lack of hairy skin touch sensitivity (74).

The discovery a decade ago of a large family of G-protein-coupled receptors (GPCR), the so-called *Mas1*-related GPCRs (*Mrgs*) (15), expressed in subpopulations of small DRG neurons, was followed by efforts to assign specific functions to cells expressing just 1 mrg. Anderson and colleagues used genetic labeling techniques to show that small neurons expressing one receptor MrgprB4 innervate hairy skin and not glabrous skin. However, hair follicles are not contacted by such afferents

(47). The authors speculated that these neurons are identical to C-LTMRs. However, in a very recent study from the same authors, direct recording from such cells failed to show activation of MrgprB4-expressing neurons by any mechanical thermal or chemical stimuli (76). Remarkably, the authors persisted in their assertion that MrgprB4 neurons mediate pleasant touch and show that calcium signals can be measured in the spinal synapses/axons of these cells in the spinal dorsal horn upon gentle stroking of the skin. How such signals arise centrally in the absence of action potential propagation is not explained, but secondary activation by primary afferent depolarization after activation of classical mechanoreceptors may be a plausible explanation for these findings.

In contrast to the above studies, Ginty and colleagues have suggested that sensory neurons positive for tyrosine hydroxylase (TH) (8) are in fact identical to C-LTMRs (45). TH-positive cells are unmyelinated neurons, as indicated by the lack of NF200 expression, but they neither express any of the classical markers for peptidergic nociceptors, such as CGRP, TrkA, and TRPV1 nor bind isolectin B4 (IB4), a marker of nonpeptidergic nociceptors (69). By carrying out an immunohistochemical analysis of electrophysiologically characterized neurons, these authors could show the expression of tyrosine hydroxylase (TH) is apparently confined to C fibers with properties characteristic of C-LTMRs. Indeed, direct recordings from TH-positive neurons indicated that they do respond to low-threshold mechanical stimuli with stimulus response profiles very similar those described for C-LTMRs in humans (45, 48). The TH-positive small sensory neurons also co-express c-Ret, which is also important for the development of Aβ-fiber mechanoreceptors. The TH neurons are also positive for VGLUT3, which has on the basis of BAC transgenesis previously been suggested to be required for C-LTMR connectivity and function (65). Importantly, genetic labeling of TH-positive neurons revealed that their peripheral terminals branch and form longitudinal lanceolate endings around zigzag and awl/auchene hairs (45), thus providing direct evidence that C-LTMRs innervate hair follicles. The TH-positive afferent fibers do not appear to innervate guard hairs, nor do they project to the glabrous skin of the paw, which is consistent with previous studies indicating that C-LTMRs are absent from glabrous skin (58).

In addition to their proposed role in coding pleasant touch, there is also indirect evidence suggesting that C-LTMRs may play a role in mechanical hypersensitivity after nerve or tissue injury. Thus mice lacking the vesicular glutamate transporter VGLUT3, which in the spinal cord may be specifically expressed at the central termini of C-LTMRs, were found to develop significantly less mechanical hypersensitivity in several animal models of neuropathic and inflammatory pain (65). However, others have not observed such a specific localization of VGLUT3 as did Seal et al. (45). Hence, the reduction in pain behavior in VGLUT3 mutant mice may also result from functional deficits in the brain that are independent from VGLUT3 expression in C-LTMRs. A recent study in humans suggests that C-tactile afferents mediate mechanical allodynia that accompanies experimentally induced muscle pain (54). Muscle pain was induced by infusing hypotonic saline into the muscle, and allodynia in the hairy skin overlying the muscle was evoked with a vibrotactile stimulus. During compression block of myelinated Aβ fibers, the sense of vibration was abolished, but the vibration-evoked allodynia persisted. In contrast, the sense of vibration persisted, but allodynia was abolished after anesthesia of unmyelinated afferents, suggesting that C-LTMRs are required for allodynia. The experiments presented do not, however, exclude the possibility that D-hair receptors play a role in the allodynia. It should be noted that both pleasant sensations and mechanical hypersensitivity can also be experienced in the glabrous skin, which is reportedly devoid of both C-LTMRs and D-hair receptors (41). The prevailing weight of clinical data also clearly shows that allodynia in neuropathic pain patients is primarily driven by activation of Aβ-fiber mechanoreceptors (10, 22, 35, 64, 73).

Central Connectivity of Mechanoreceptors Driven by Hair Movement

We can thus imagine that when the hairy skin is brushed or is stimulated as the animal actively explores its object-filled environment, three distinct groups of mechanoreceptors will be activated (FIGURE 1). Aβ-fiber RAMs with low thresholds, small receptive fields, and highly tuned velocity sensitivity relay information in a somatotopically organized way directly to neurons in layers III–IV of the dorsal horn as well as the dorsal column nuclei (7). D-hair receptors with ultra-low mechanical thresholds, large receptive fields, and broadly tuned velocity sensitivity (FIGURE 3H) (53) also produce somatotopically organized focused flame-shaped central terminals on lamina III–IV of the dorsal horn (46). In contrast to Aβ-RAMs, D-hair receptors apparently do not directly project via the dorsal columns to directly transfer tactile information to the dorsal column nuclei (26). Similarly, C-LTMRs with small broadly tuned receptive fields are predicted to activate a group of as yet undefined neurons at the border between outer lamina

III and lamina II in a somatotopically organized manner (45). However, there is no evidence that C-LTMRs provide information that is carried via the dorsal column nuclei to higher centers like the insular cortex (57). The central circuits activated by the three sets of hair movement-activated mechanoreceptors are, with the possible exception of classical Aβ-fiber RAMs, poorly understood. However, it is fair to say that we now have a pretty complete understanding of nature of the total afferent inflow that will be seen by spinal circuits as well as in higher centers when a moving stimuli impinges on hairy skin.

Hairy Stimulation, What Information is Relayed to the Brain?

The hairy skin will encounter moving stimuli either because the animal is moving adjacent to objects in its environment or alternatively in a social context when the animal comes into contact with other con-specifics. We can imagine a roughly shaped stimulus that bends hairs as it traverses the skin, the irregular leaves and branches of a typical hedge for example. The first mechanoreceptors to be activated strongly by this stimulus are likely to be D-hair receptors, which on the basis of their ultra-low thresholds, broad tuning, and large receptive fields will activate lamina III and IV neurons (33). As the intensity of the stimulus increases, then Aβ-fiber RAMs are activated, and these fibers convey the arrival of the stimulus with high fidelity and speed to spinal cord lamina III and IV neurons but also via the dorsal column nuclei more directly to the cortex (63). Information about vibration or flutter is analogous to the "hedge" stimulus mentioned above, since intermittent strong activation of mechanoreceptors by a moving stimulus will produce a spike train just like a vibration with the frequency being a function of object roughness and the velocity with which the stimulus moves across the skin. If the frequency with which the mechanoreceptors are activated approximates the best tuning frequency of Aβ-fiber mechanoreceptors, then this information can reach conscious perception remarkably quickly (63). Information provided by D-hair receptors reaches the spinal cord with a distinct delay (~5–10 ms) compared with that conveyed by Aβ-fiber mechanoreceptors. However, this calculation does not take into account the fact that D-hair receptors are likely to detect the oncoming stimulus earlier than Aβ-fiber mechanoreceptors primarily due to their ultra-low thresholds (53). The time delay mentioned above may then become irrelevant since information derived from D-hair receptors may provide a sentinel function that will strongly depend on the velocity of the stimulus. A typical mouse moves with a velocity of up to 200 mm/s; a stimulus brushing by the skin at this velocity would traverse a typical D-hair receptive field with a diameter of 4 mm in 0.02 s or 20 ms. If the approaching strong moving stimulus activates D-hair receptors first because of low thresholds and larger receptive fields, it is easily conceivable that D-hair will provide advanced information about stimuli despite their slow axonal conduction velocities. Since it appears that the D-hair receptor information is only relayed via spinal circuits, not via the dorsal column pathway, it is possible that D-hair receptor information serves to prepare central circuits for the onset of touch information. The contrasting frequency tuning of D-hair receptors and classical Aβ-fiber mechanoreceptors (FIGURE 3H) might actually make this modulation dependent on the strength (roughness) as well as velocity of the stimulus in question. It is clear that new experimental, especially behavioral, paradigms are required to adequately test such speculations.

The role of C-LTMRs is harder to judge in such a scenario since these fibers have relatively high thresholds for activation compared with Aβ-fiber RAMs and D-hair receptors, and will convey information to dorsal horn neurons in lamina III with a huge delay compared with information coming from myelinated fibers. In humans, the conduction delay for C fibers is in the order of a few seconds compared with a few milliseconds for Aβ fibers. It thus seems very unlikely that C-LTMRs participate in conveying information about discriminative touch processes, hence the speculation that these fibers may provide sensory drive for emotional aspects of touch or pleasant touch.

Conclusions

The hairy skin of mammals probably represents the largest sensory surface used to interact with the environment. It is clear that the hairy skin is not routinely used for fine discriminative behaviors like manipulating objects and tools as one can observe in humans and nonhuman primates for the glabrous skin of the fingers. The hairy skin has also received very little attention compared with the specialized role played by vibrissae in active touch in rodents. Nevertheless, hairy sensation certainly provides animals with detailed and important information about the objects or other animals that are encountered as well as spatial cues about the position of such things in relation to the animal's personal space. The physiological properties of hairy skin mechanoreceptors have been measured and appreciated for many decades. However, it is only in the last few years that a more complete picture has emerged of the physiology and anatomy of hairy skin mechanoreceptors.

Thus we now not only have a detailed view of the anatomy of peripheral endings of physiologically defined mechanoreceptors, but in some cases the molecular features of these endings are beginning to be defined. An especially interesting example here is the developmental program controlled by the transcription factor c-Maf that controls the morphological development of peripheral endings associated with three RAM types: Aβ-fiber hair follicle receptors, Meissner's corpuscle receptors, and Pacinian corpuscle receptors. Interestingly, c-Maf does not just control the morphological differentiation of such receptors but specifically controls the expression of ion channels like KCNQ4 that are essential for receptor tuning. The recently discovered molecules that differentiate between mechanoreceptors, e.g., $Ca_V3.2$ and KCNQ4, may only be the tip of the iceberg as new high throughput methods combined with mouse genetics are bound to reveal many more new molecular players. The mouse has become an important model organism to study the physiology and connectivity of mechanoreceptors from the hairy skin, but it is already clear that new behavioral paradigms are required to answer important open questions. For example, how is information from the different hairy skin mechanoreceptors actually used in a realistic behavioral context? The advent of tools such as optogenetics combined with the ability to genetically trace molecularly defined sensory populations should spur the development of such paradigms. ■

The authors work has been supported by grants from the Deutsche Forschungsgemeinshaft, in particular collaborative research center 665.

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

Author contributions: S.G.L. and G.R.L. prepared figures; S.G.L. and G.R.L. drafted manuscript; S.G.L. and G.R.L. edited and revised manuscript; S.G.L. and G.R.L. approved final version of manuscript.

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