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Feeling the pressure in mammalian somatosensation

Ellen A Lumpkin and **Diana M Bautista**
Department of Physiology and Department of Cellular and Molecular Pharmacology, University of California, San Francisco, 600 16th Street, San Francisco, CA 94143-2280, USA

Abstract

Mechanoreceptor cells of the somatosensory system initiate the perception of touch and pain. Molecules required for mechanosensation have been identified from invertebrate neurons, and recent functional studies indicate that ion channels of the transient receptor potential and degenerin/epithelial Na^+ channel families are likely to be transduction channels. The expression of related channels in mammalian somatosensory neurons has fueled the notion that these channels mediate mechanotransduction in vertebrates; however, genetic disruption and heterologous expression have not yet revealed a direct role for any of these candidates in somatosensory mechanotransduction. Thus, new systems are needed to define the function of these ion channels in somatosensation and to pinpoint molecules or signaling pathways that underlie mechanotransduction in vertebrates.

Introduction

The senses of touch, pain and proprioception (see glossary) enable an organism to respond to physical stimuli such as pressure, temperature changes and stretch. In vertebrates, these senses are mediated by somatosensory neurons of the trigeminal and dorsal root ganglia (DRG). The sensory afferents of these neurons terminate in the skin and other target tissues (Figure 1), where they transduce sensory stimuli into electrical impulses that are sent to the central nervous system. Somatosensory neurons fall into three groups: touch receptors that react to benign pressure; nociceptors that respond to harmful mechanical, thermal and chemical stimulation; and proprioceptors that detect muscle tension and joint position. These groups can be further divided on the basis of morphology, electrical properties and sensory thresholds (Table 1).

Given the range of stimuli detected by somatosensory neurons, their functional diversity is likely to be matched by a variety of transduction mechanisms. For example, thermosensitive ion channels of the transient receptor potential (TRP) family activate at different temperature thresholds [1], and probably act as transduction channels that span the physiological range of thermosensation. By contrast, little is known about the diversity and identity of molecules that mediate mechanotransduction in somatosensory neurons.

Corresponding author: Lumpkin, Ellen A (lumpkin@itsa.ucsf.edu).

The prevailing model of mechanosensory transduction has emerged from studies of hair cells and invertebrate mechanoreceptors. The speed of signaling in these cells (<1 ms; [2,3,4••]) suggests that transduction channels are directly activated by mechanical stimuli. This model postulates that transduction channels are tethered to the cytoskeleton or extracellular matrix, and force changes the tension between tethers and transduction channels to regulate gating. Genetic screens in *Drosophila* and *C. elegans* have identified candidate mechanotransduction molecules that fit with this model, including cytoskeletal elements, extracellular matrix proteins and ion channels of the TRP and degenerin/epithelial Na^+ channel (Deg/ENaC) families (Figure 1).

Recent attempts to elucidate the molecular basis of mechanotransduction in mammals have largely focused on homologs of these candidates. Here, we review advances in our understanding of the mechanisms of mechanotransduction in invertebrates, summarize studies of vertebrate ion channels that have been implicated in mechanotransduction, and highlight experimental models that promise to shed light on mammalian somatosensory signaling.

Invertebrate and mammalian Deg/ENaC subunits

The MEC-4 complex

C. elegans body touch neurons have been extensively characterized at the molecular level (reviewed by Syntichaki and Tavernarakis [5]). Genetic and heterologous expression studies have identified the MEC-4 complex (see glossary): a putative mechanotransduction assembly composed of the Deg/ENaC subunits MEC-4 and MEC-10, and the accessory subunits MEC-2 and MEC-6. Channel activation has been proposed to depend on links to microtubules, which are made up ofMEC-7 and MEC-12 tubulins, and extracellular proteins, which include MEC-1, MEC-5 and MEC-9 [6].

In the past two years, physiological approaches have directly tested this model. *In situ* whole-cell recordings [4••] and *in vivo* imaging [7] have shown that null mutations in *mec-4*, *mec-6* and *mec-2* specifically abolish mechanotransduction in body touch neurons. These studies strongly argue that the MEC-4 complex is the transduction channel in these cells. An important next step is to determine whether or not force directly activates these channels.

What about putative tethers? Mutations in *mec-7*, which alter microtubules, attenuate but do not abolish mechanotransduction currents [4••]. Contrary to model predictions, this finding suggests that cytoskeletal attachments are not required for activation. By contrast, the prediction that the MEC-4 complex associates with extracellular proteins is bolstered by a study showing that fluorescently tagged MEC-4 protein colocalizes *in vivo* with MEC-1 and MEC-5 [6]. Moreover, *mec-1*, *mec-5* and *mec-9* mutations disrupt the punctate distribution of the MEC-4 complex [6]. These data suggest that one important role of the extracellular matrix is to localize transduction channels; the role of extracellular links in channel activation remains to be determined.

ENaC subunits

Based on their similarity to MEC-4 and their expression patterns, mammalian β-ENaC and γ-ENaC have been proposed to act in touch reception and in the mechanical control of cardiovascular function ([8]; reviewed by Syntichaki and Tavernarakis [5]). Because genetic disruption of these channels causes neonatal lethality, tissue-specific knockouts are necessary to test these hypotheses.

ASIC subunits

Three members of the acid-sensing ion channels (ASICs), a related subfamily, have also been linked to mechanotransduction. ASIC2 (the ion channel formerly known as BNC1, BNaC1 and MDEG1) and ASIC3 (DRASIC) are coexpressed in medium and large-diameter DRG neurons [9]. In cutaneous mechanoreceptors, ASIC2 [10,11] and ASIC3 [12] are found in peripheral terminals, where transduction occurs. Interestingly, brain-derived neurotrophic factor restriction, which decreases touch-receptor sensitivity [13], reduces ASIC2 levels in cultured somatosensory neurons [14].

If ASIC2 and ASIC3 are essential components of a transduction channel, gene disruption should eliminate mechanotransduction, as is observed in *mec-4* mutants [4••]. Instead, the firing rate of touch-evoked responses is modestly decreased in ASIC2 knockout mice [10] and increased in ASIC3 knockout animals [12]. In both cases, mechanical thresholds are not affected. Moreover, an independently generated ASIC2 knockout strain shows no deficiencies in cutaneous and visceral mechanoreception [15]. Taken together, these studies indicate thatASIC2 and ASIC3 are not required for transduction in these neurons.

ASIC1 (BNaC2) is expressed in most somatosensory neurons [9]. In ASIC1 knockout mice, visceral mechanoreceptors have higher mechanically evoked firing rates, and gastric emptying is delayed, consistent with increased visceral mechanoreceptor activity *in vivo* [16]. By contrast, cutaneous mechanoreception appeared normal in knockout animals.

The broad expression of ASICs in the nervous system [17] and their pH-sensitivity have led to other proposed functions (reviewed by Krishtal [18]), including modulation of synaptic transmission and long-term potentiation. In somatosensory neurons, ASICs have been suggested to contribute to acid-evoked pain in cardiac ischemia and cutaneous nociception (see glossary).

Given these disparate functions, it is possible that ASIC subunits play a general role in neuronal excitability rather than a direct one in mechanotransduction. Alternatively, ASIC subunits could associate with other molecules to accomplish specialized tasks in different neuronal populations. To distinguish between these possibilities, new techniques will be needed to analyze mechanotransduction currents in intact and reduced preparations. For example, recent recordings from dissociated somatosensory neurons indicate that ASIC2 and ASIC3 do not mediate mechanically evoked currents *in vitro* [19].

Invertebrate and mammalian TRPV ion channels

OSM-9 and OCR-2

Ion channels of the vanilloid TRP (TRPV) subfamily are likely to function as transduction channels in numerous sensory modalities (reviewed by Moran *et al*. [20]). *Osm-9* and *ocr-2* are required for avoidance of osmotic shock, nose touch and repulsive chemicals in *C. elegans* [21,22]. Similar to touch, osmotic shock is a mechanical stimulus because it can change membrane tension by inducing cell shrinking or swelling. In polymodal sensory neurons that mediate these responses, OSM-9 and OCR-2 localize to sensory cilia. Thus, these TRPV isoforms are excellent candidates for sensory transduction channels.

NAN and IAV

Similarly, the *Drosophila* TRPV isoforms Nanchung (NAN) and Inactive (IAV) could serve as mechanotransduction channels [23•,24]. Mutant phenotypes and electrophysiological recordings demonstrate that both genes are essential for hearing and proprioception. Moreover, NAN and IAV are detectably expressed only in mechanosensitive chordotonal organs, where both subunits localize to sensory cilia. Finally, heterologously expressed NAN and IAV are activated by hypotonic solutions, indicating that they can transduce mechanical stimuli in non-native cell types.

TRPV4

Hypotonic activation was first described for mammalian TRPV4, which was examined as a candidate mechanotransduction channel because of its similarity to OSM-9 [25–27]. Indeed, TRPV4 rescues mechanosensory and osmoreceptive defects in *osm-9* mutants, suggesting that these channels are orthologous [28]. Consistent with a role in mechanotransduction, TRPV4 is expressed in hair cells, some nociceptors, and neurons that regulate osmotic balance [25,29,30]; however, it is expressed at higher levels in non-sensory tissues [25–27,31]. In non-sensory epithelial cells, TRPV4 has been proposed to mediate responses to mechanical load [32].

Several studies support a role for TRPV4 in osmotically evoked responses. For example, two independently derived knockout strains show that TRPV4 contributes to systemic fluid balance [29,33]. At the cellular level, TRPV4 activity has been linked to the regulatory volume decrease that follows hypotonicity-induced cell swelling [34]. Moreover, TRPV4 has been implicated in nociceptive responses to hypotonic solutions [30,35].

TRPV4 has been proposed to play two additional roles in somatosensation. First, TRPV4 could act in cutaneous mechanotransduction; however, disrupting TRPV4 expression modified responses to noxious pressure in some studies [29,36] but not in another [30]. Second, recent evidence indicates that TRPV4 is involved in responses to warm temperatures [1,37•].

Is TRPV4 directly activated by physical stimuli such as temperature and cell swelling? This is unlikely because TRPV4 activates over tens of seconds, which suggests the involvement of second messengers [25,26]. Consistent with this hypothesis, hypotonic activation of

TRPV4 has been shown to occur via arachidonic acid metabolites [38•], which directly stimulate TRPV4 (reviewed by Nilius *et al*. [39]). Although these studies suggest that TRPV4 is involved in cellular responses to swelling, the osmotic sensor remains to be discovered.

TRPV2

Another mammalian TRPV subunit that has been hypothesized to participate in mechanotransduction is TRPV2. Hypotonic stimulation, direct suction and radial stretch activate TRPV2 in vascular myocytes and cells expressing exogenousTRPV2 [40]. Moreover, this channel is expressed in medium and large-diameter sensory neurons, including the TrkC-positive population that is enriched in low-threshold mechanoreceptors [41]. Despite these intriguing results, there is no direct evidence that TRPV2 is required for mechanosensation, and other roles are possible. For example, TRPV2 has been proposed to transduce high-threshold heat responses in Aδ afferents. Indeed, heterologously expressed TRPV2 is activated by noxious heat [1].

Yet more TRP channels

Two TRP subfamilies that have been implicated in somatosensation are distinguished by numerous ankryin repeats. *Drosophila* TRPN1 (NompC) was identified through a forward genetic screen as a putative transduction channel in touch reception and proprioception [3]. Based on this finding, zebrafish TRPN1 has been examined as a component of the hair-cell mechanotransduction channel [42]. The ankryin repeats of TRPN1 are posited to be involved in force-dependent gating [43]. *Drosophila* TRPA1 is required for thermotaxis (see glossary) [44] and TRPA (Painless) [45] is necessary for normal avoidance of harsh prodding and heat.

Mammalian TRPA1 has also been proposed to function in mechano- and thermotransduction. For example, TRPA1 is found in hair cells and inhibiting expression attenuates mechanical responsiveness ([46]; see Gillespie, this issue [47]). TRPA1 is also found in small-diameter nociceptors [48–50], which includes high-threshold mechanoreceptors and thermoreceptors. Intriguingly, TRPA1 protein localizes to somatosensory terminals in the bladder and cornea, both of which are predominately innervated by nociceptors [50].

Although TRPA1 has been proposed to be a detector of physical stimuli, an alternative possibility is that this channel is a modulator of sensory signaling. TRPA1 is activated by a variety of pain-producing compounds such as isothiocyanates, the pungent ingredients in mustards [48,49]. TRPA1 is also activated downstream of PLC-coupled receptors, including those stimulated by inflammatory agents such as bradykinin. Thus, TRPA1 could have a general role in pain and inflammation. Genetic disruption of TRPA1 is required to define its function in sensory signaling.

TRPC1 is a canonical TRP channel that has been implicated in mechanotransduction. Whereas most studies have focused on whether TRPC1 is store-operated or receptor-operated (see glossary), Maroto *et al*. [51•] proposed that TRPC1 is activated by membrane

stretch. Because stretch activation is preserved following protein reconstitution in liposomes, mechanosensitivity is likely to be an intrinsic property of the channel, similar to some two-pore domain K^+ channels, yeast TRPY1, and the bacterial channels MscS and MscL (see [52] this issue). Whether TRPC1 contributes to mechanotransduction in somatosensory neurons is unknown.

In vitro approaches for studying mammalian somatosensation

Touch reception and nociception have been extensively studied using a skin–nerve preparation, which enables mechanical stimulation of the skin and extracellular recordings from sensory afferents. This has been invaluable for determining response properties of mechanosensory neurons; however, understanding the molecular events underlying transduction requires the direct analysis of transduction currents. This is most easily accomplished with *in vitro* systems that approximate the biological activities of sensory neurons.

Towards this end, several groups have begun to study mechanotransduction in dissociated somatosensory neurons. Currents can be elicited by pressure applied through a recording pipette [53,54] or by directly touching the cells [55,56]. Similar to mechanosensitive neurons *in situ*, cultured sensory neurons display distinct activation thresholds and adaptation properties. Although additional experiments are required to relate these responses to touch reception *in vivo*, this is a promising system for dissecting mechanisms of mechanotransduction.

Non-neuronal cells are also likely to participate in somatosensory mechanotransduction. For example, Merkel cell–neurite complexes detect light touch. Gene-expression profiling and live-cell imaging have demonstrated that Merkel cells (see glossary) are excitable cells that express voltage-activated Ca^{2+} channels and molecules that are required for synaptic vesicle release [57]. An important unanswered question is whether Merkel cells transduce touch or modulate the activity of touch-sensitive neurons.

Conclusions

Several ion channels identified in invertebrate mechanoreceptor cells and hair cells are excellent candidates for transduction channels. A crucial question is whether or not the channels that carry receptor currents are themselves mechanosensitive. Many putative mechanotransduction channels have proved difficult to express or mechanically activate in heterologous systems. Thus, answering this question will require novel expression systems in addition to studies of genetically modified candidates in native cell types.

Although candidate gene approaches have yielded several ion channels that are expressed in mammalian somatosensory neurons, none of these channels has been shown to be essential for mechanotransduction. Moreover, the diversity of mechanosensitive cells suggests that multiple mechanisms underlie transduction. Techniques that enable high-resolution studies of mechanotransduction are needed to define the roles of TRP and Deg/ENaC subunits in sensory neurons. Existing *in vitro* approaches could be enhanced by high-throughput

methods, which will facilitate the discovery of mechanotransduction molecules and much-needed pharmacological probes.

Identifying molecules that mediate mechanotransduction is an essential step in elucidating mechanisms that initiate touch and pain. This will also promote an understanding of how sensory signaling is altered under conditions of inflammation and chronic pain.

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Glossary

Ankyrin repeat	a common protein–protein interaction motif that contains ~33 amino acids and that often occurs in tandem
MEC-4 complex	a multiprotein complex comprising MEC-4, MEC-10, MEC-2 and MEC-6. These proteins, which form ion channels when co-expressed in *Xenopus* oocytes, are proposed to make up the mechanotransduction channel in six touch receptor neurons that innervate the body in C. elegans.
Nociception	the ability to detect harsh physical, chemical and thermal stimuli that have the potential to cause tissue damage
Proprioception	the ability to sense muscle tension and joint position. This ability enables coordinated limb movements
Receptor-operated channel	an ion channel that opens or closes when a second messenger cascade is triggered by the activation of a transmembrane receptor
Store-operated channel	an ion channel that opens when intracellular calcium stores are depleted. These channels are not directly gated by calcium, but by an unknown mechanism that detects calcium-store depletion
Thermotaxis	directed movement in response to changes in temperature
Merkel cells	vertebrate skin cells that are found in areas of skin that are particularly touch sensitive such as fingertips, whisker follicles, and touch domes

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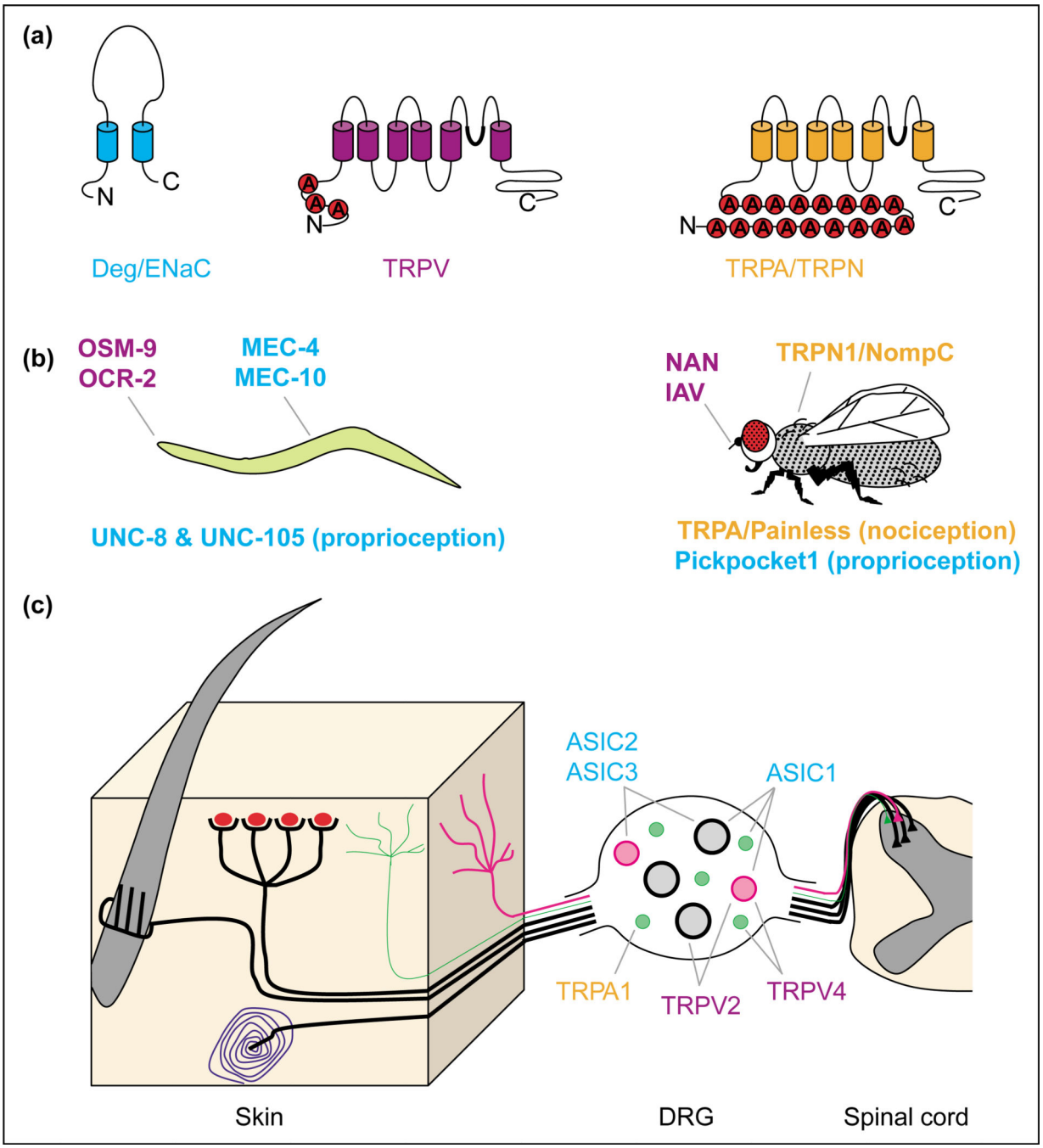

Figure 1.

Cation channels implicated in mechanosensory transduction. **(a)** Proposed topology of Deg/ENaC and TRP channels; cylinders indicate predicted transmembrane domains and bold loops indicate putative pore regions. TRP channels have a variable number of amino-terminal ankyrin repeats (see glossary; red). **(b)** In *C. elegans*, TRPV channels (purple) are thought to transduce nose touch and hypertonic shock. Deg/ENaC subunits (cyan) have been proposed to transduce body touch and to act in proprioception [5]. In *Drosophila*, TRPV, TRPN (orange) and TRPA (orange) subunits are candidate mechanotransduction channels in

bristles, which mediate touch and proprioception, in chordotonal organs, which mediate hearing and proprioception, and in multidendritic neurons, which respond to harsh mechanical and thermal stimuli. The Deg/ENaC channel Pickpocket1 has been implicated in larval proprioception [5]. **(c)** A schematic of the mammalian somatosensory system shows DRG neurons projecting to skin and spinal cord. Deg/ENaC and TRP channels are expressed in different classes of somatosensory neurons, the cell bodies of which are indicated by circles in the DRG. C nociceptors (green) and Aδ afferents (pink) have free nerve endings; light touch receptors (Aβ; black) include Merkel cell–neurite complexes (red), lanceolate endings around hair follicles (gray), and Pacinian corpuscles (dark blue spiral).

Table 1

Classification of mammalian somatosensory mechanoreceptors.

Modality	Conduction velocity	Myelination	Soma diameter	Subclasses
Proprioceptors	Aα	Thick	Large	Muscle spindle Golgi tendon
Touch receptors (low-threshold mechanoreceptors)	Aβ	Thick	Large	Slowly adapting type I (Merkel cell–neurite complex) Slowly adapting type II Rapidly adapting (e.g. Pacinian corpuscle)
Nociceptors	Aδ	Thin	Medium	Low-threshold mechanoreceptor (D-hair) High-threshold mechanoreceptor Polymodal (e.g. mechanoheat, mechanocold)
Nociceptors	C	None	Small	Mechanoreceptor Polymodal (e.g. mechanoheat, mechanocold)

Somatosensory mechanoreceptors can be grouped according to sensory modality and conduction velocity of action potentials, which correlates with myelination and soma diameter. Classes can be further divided by their terminal morphologies, adaptation properties and activation thresholds.