Molecular mechanisms of mechanotransduction in mammalian sensory neurons

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Abstract | The somatosensory system mediates fundamental physiological functions, including the senses of touch, pain and proprioception. This variety of functions is matched by a diverse array of mechanosensory neurons that respond to force in a specific fashion. Mechanotransduction begins at the sensory nerve endings, which rapidly transform mechanical forces into electrical signals. Progress has been made in establishing the functional properties of mechanoreceptors, but it has been remarkably difficult to characterize mechanotranducer channels at the molecular level. However, in the past few years, new functional assays have provided insights into the basic properties and molecular identity of mechanotransducer channels in mammalian sensory neurons. The recent identification of novel families of proteins as mechanosensing molecules will undoubtedly accelerate our understanding of mechanotransduction mechanisms in mammalian somatosensation.

Mechanoreceptor
A sensory receptor that responds to mechanical pressure or distortion by causing membrane depolarization and action potential firing.

Mechanotransducer channel
An ion channel present in the cell membranes of prokaryotes and eukaryotes, capable of generating an ion flux signal as a response to mechanical stimuli.

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The ability of living organisms to perceive mechanical forces is crucial for interacting with the physical world. Mechanotransduction, the conversion of a mechanical stimulus into a biological response, constitutes the basis of fundamental physiological processes, such as the senses of touch, balance, proprioception and hearing, and makes a vital contribution to homeostasis.

Mechanotransduction occurs ubiquitously in eubacteria, archaea and eukarya, suggesting an early emergence of mechanotransducers during evolution. The first mechanosensitive channel in bacteria and archaea arose as a mechanism for cell protection and survival[1], and subsequently evolved into a more complex apparatus as part of organismal specialization[2–5].

In mammals, detection of mechanical forces by the somatosensory system is performed by primary afferent neurons. Their cell bodies are located in trigeminal ganglia and dorsal root ganglia (DRG), and they project long axons to the skin and to deeper body structures. These somatosensory neurons detect a wide range of mechanical stimuli. Some are specialized to detect external mechanical stimuli, whereas others inform the nervous system about self-generated stimuli[6,7]. There are many functionally distinct subtypes of mechanosensory neurons with specific threshold sensitivities and encoding capabilities, each of which is thought to transduce specific kinds of mechanical stimuli[7,8].

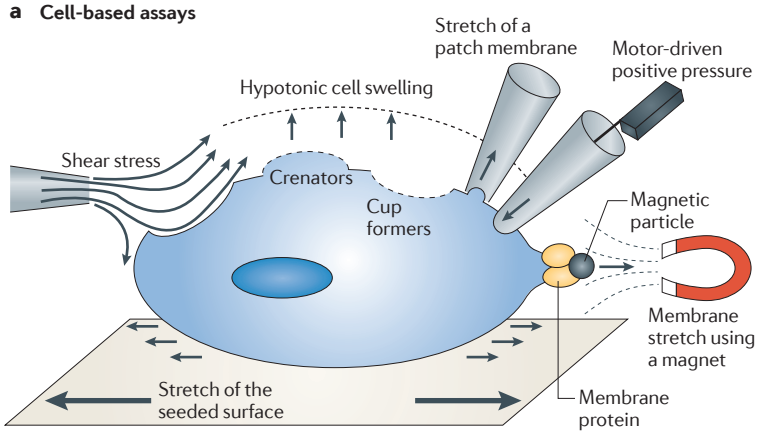
The ability of mechanoreceptors to detect mechanical cues relies on the presence of mechanotranducer channels on sensory nerve endings that rapidly transform mechanical forces into electrical signals and depolarize the receptive field; this local depolarization, called the receptor potential, can generate action potentials that propagate towards the CNS. With the notable exception of mechanotransduction in auditory cells[9–13], the properties of mechanotransducers in mammals are largely unknown[14–16]. It is thought that receptor potentials are caused by opening of excitatory channels that depolarize the terminal, analogously to sensory receptors in invertebrate species[17]. The small size and inaccessibility of sensory nerve endings have hampered investigation of mechanical transduction processes. Several assays of cellular responses to mechanostimulation have been developed in recent years (BOX 1) and have begun to uncover the molecular basis of mechanotransduction.

Recent work has uncovered specific properties of mechanotransducer currents in different subsets of mechanosensory neurons that mediate the senses of touch and pain. Such analyses suggest that mechanical stimulation activates cation channels that differ in their sensitivity to pressure and desensitization rates, and that may define different classes of mechanotransducer channels. In this Review, we provide a brief overview of mechanoreceptor structure and functions, discuss emerging data

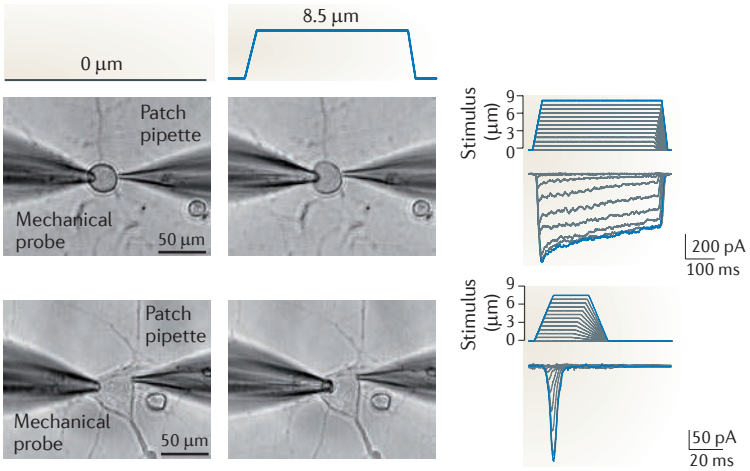
Box 1 | **Experimental strategies to probe mechanotransduction**

The development of various techniques for studying mechanotransduction has opened up new pathways for the investigation of molecular mechanisms of mechanosensation. These techniques can be used to bridge the gap between the properties of mechanotransducer currents *in vitro* and the characteristics of mechanoreceptors *in vivo*.

a **Cell-based assays**



b **Whole-cell mechano-clamp**



Cell-based assays

Several types of mechanical challenges can be used to activate mechanosensitive channels (see the figure, part **a**). These strategies are based on membrane deformation, yet each has the potential to recruit different populations of mechanosensitive channels.

Motor-driven pressure. Focal deformation of the plasma membrane uses an electrically driven mechanical probe. This technique can be applied to cell bodies and neurites of sensory neurons *in vitro*[43,48].

Cell stretch. Two methods are commonly used — surface elongation of a flexible silicone elastomer substrate on which cells have been seeded[57] and application of positive or negative pressures to a patch membrane through a patch pipette[86,138,159]. A recently developed, related technique consists of stimulating neurites of cultured dorsal root ganglion (DRG) neurons through indentation of an elastomeric substrate adjacent to the neurite with a mechanical probe[160].

Fluid shear stress. Shear stress can be generated by changing the perfusion flow and/or the viscosity of the perfusion solution. DRG neurons are sensitive to fluid-flow changes[43].

Crenators and cup formers. Anionic and neutral amphipathic compounds, such as free fatty acids, trinitrophenol and lysolecithin, preferentially insert in the outer leaflet of the membrane and induce the crenation of the plasma membrane. Conversely, positively charged amphipathic compounds, such as chlorpromazine and tetracaine, insert in the inner leaflet of the bilayer and cause the cell to form cup shapes. Such amphipathic molecules have been shown to regulate the activities of the MscL ion channel[161] and of the two-pore domain K^+ channels TREK1 and TRAAK[138,162].

Osmotic challenges. Hypotonic conditions induce cell swelling, whereas hypertonicity causes cell shrinkage. Thus, owing to deformation of cell morphology and lipid bilayer tension, osmotic variations are considered by some researchers as a type of mechanical stimulation[82]. However, note that osmotic stress does not create uniform tension in the cell membrane and causes cytosolic alterations, including intracellular calcium elevation and exchange of osmolytes that complicate data interpretation[49].

Magnetic particles. This technique uses magnetic particles to apply forces to cells[163]. Magnetic particles can be coated with specific ligands, including adhesion molecules and antibodies, which enable them to bind to receptors on the cell surface. An applied magnetic field pulls the particles so that they deliver nanoscale forces at the level of the ligand–receptor bond.

Whole-cell mechano-clamp

Mechanical stimulation of DRG neurons using an electrically driven mechanical probe can be achieved during patch clamping. This technique involves the attachment of a glass micropipette to the surface of the cell membrane. It permits high-resolution recording of single or multiple ion channel currents flowing through the membrane. The microphotographs in part **b** of the figure show patch clamping of DRG neurons with small (upper panel) and large (lower panel) cell body diameters. Mechanosensitive currents (lower traces) activate gradually as a function of the stimulus strength (upper traces). The blue trace highlights the current evoked by the 8.5-µm stimulus.

about the characteristics of mechanosensitive currents that can mediate receptor potentials in sensory terminals and highlight recent studies aimed at identifying the transducer channels molecularly. Finally, we describe impairments in mechanosensation caused by inflammation, injury or disease. Detailed information about mechanotransduction in other cell types and sensory modalities has been reviewed elsewhere[1,10,18–22].

Mammalian mechanoreceptors

Progress has been made in establishing the functional properties, specificity and perceptual functions of mechanoreceptors. These receptors function as selective peripheral encoding devices that are able to extract information about the various parameters of the mechanical stimulus and to supply the CNS with a neural image of the peripheral situation.

Mechanoreceptors are distributed throughout the body, including in the skin, tendons, muscles, joint capsules and viscera. Proprioceptors monitor position of joints, tension in tendons and ligaments, and the state of muscular contraction. Of all sensory receptors, the proprioceptors are the most structurally complex. Examples of this complexity can be found in Golgi tendon organs, which are sensors for detecting strain, and in muscle spindles, which monitor the way that a muscle contracts and stretches.

The best known mechanoreceptors in mammals are located in the skin. Cutaneous somatosensory receptors detect a wide range of mechanical stimuli, including light brush of the skin, texture, vibration, touch and noxious pressure (FIG. 1). This variety of stimuli is matched by a diverse array of specialized or encapsulated sensory nerve endings that respond to cutaneous motion and deformation in a specific fashion (FIG. 1). Some of the cutaneous fibre endings are classified as low-threshold mechanoreceptors (LTMs) because they respond preferentially to innocuous mechanical forces, whereas others are considered high-threshold receptors (HTMs) because they are excited only by injurious mechanical forces. In general, numerous specialized or encapsulated nerve endings of β-type A-fibres (Aβ endings) are LTMs, whereas Aδ nerve fibres and polymodal C-fibre nociceptors transmit pain sensation (FIG. 1).

The main innocuous-touch receptors in mammals include hair follicles, Merkel cell–neurite complexes, Meissner corpuscles, Pacinian corpuscles, Ruffini receptors and free nerve endings[23,24] (FIG. 1). Hair follicle afferents detect light touch. They are classified as rapidly adapting and are divided into type D follicle afferents, which comprise a down hair and an Aδ nerve fibre axon, and type G follicle afferents, which comprise a guard hair and an Aβ nerve fibre axon[25] (FIG. 1a). Meissner corpuscles are connected to Aβ afferents, and they selectively respond to dynamic skin deformation and transmit information about skin motion and tactile detection of slip — for example, between the skin and an object that is being handled[26,27] (FIG. 1b). The Pacinian corpuscle is the most sensitive encapsulated cutaneous mechanoreceptor of skin motion. It is connected to rapidly adapting Aβ afferents that are capable of following high frequencies of vibratory stimuli[28,29], and allow perception of distant events through transmitted vibrations[30] (FIG. 1c).

The Merkel cell–neurite complex is made of clusters of 50–70 cells connected by terminals from a single myelinated Aβ axon. These complexes, known in mammals as slowly adapting type I units[31–35], respond to indentation depth of the skin and have the highest spatial resolution of the cutaneous mechanoreceptors (FIG. 1d). They transmit a precise spatial image of tactile stimuli and are responsible for form and texture perception. Ruffini receptors, which are present on Aβ nerve endings, have been identified as the slowly adapting type II cutaneous mechanoreceptors[35,36] (FIG. 1e). They signal skin stretch more effectively than indentation and contribute to the perception of the direction of object motion through the pattern of skin stretch.

C-fibre LTMs, which respond to innocuous tactile stimulation, have been described in several species[37], including humans[38–40], in whom they signal pleasant tactile stimulation in affiliative social body contact (FIG. 1f). It has recently been proposed that inflammation or trauma may change the sensation conveyed by C-fibre LTMs from pleasant touch to pain[41].

Finally, HTMs include intra-epidermal C-fibre and Aδ nerve endings, which are not associated with elaborate auxiliary structures and respond only to injurious forces (FIG. 1g). HTMs comprise mechano-nociceptors excited only by noxious mechanical stimuli and polymodal nociceptors that also respond to noxious heat and exogenous chemicals[42].

When a stimulus is applied to a mechanoreceptor and its final intensity is maintained at a stable level, the sensory afferent responds with a series of action potentials, the frequency of which is initially high and then declines (FIG. 2a). This is called receptor adaptation. It is not yet clear whether receptor adaptation depends on the cellular environment of the sensor ending, the intrinsic properties of the mechanotranducer channels or the properties of the axonal voltage-gated ion channels (FIG. 2a).

Mechanosensitive currents in sensory neurons

Recording mechanosensitive currents. Technical difficulties have impeded the characterization of mechanosensitive currents. However, during the past decade, the development of techniques for studying mechanotransduction has opened up new pathways for the investigation of molecular and cellular aspects of this process (BOX 1). The most notable of these techniques has been the development of the mechano-clamp, which allows force to be applied to the surface of cultured cells via an electrically driven glass probe while performing patch-clamp recordings[43] (BOX 1). A key limitation of this approach is that it may not recapitulate the *in vivo* situation. Nevertheless, it is known that sensory neurons in culture retain many aspects of their native properties, including sensitivity to a range of thermal and chemical stimuli[44–47].

Different classes of mechanosensitive currents. Recordings of mechanosensitive currents in DRG neuron somata from rats were first achieved in Levine's laboratory in 1999 (REF. 43), providing the first demonstration that

Desensitization
The loss of responsiveness to the continuing presence of a stimulus.

A-fibre
An afferent myelinated fibre of large (Aβ) or medium (Aδ) diameter.

C-fibre
An afferent unmyelinated fibre of small diameter conveying input signals with a slow conduction velocity.

Neurite
Any projection from the cell body of a neuron, which can be either an axon or a dendrite.

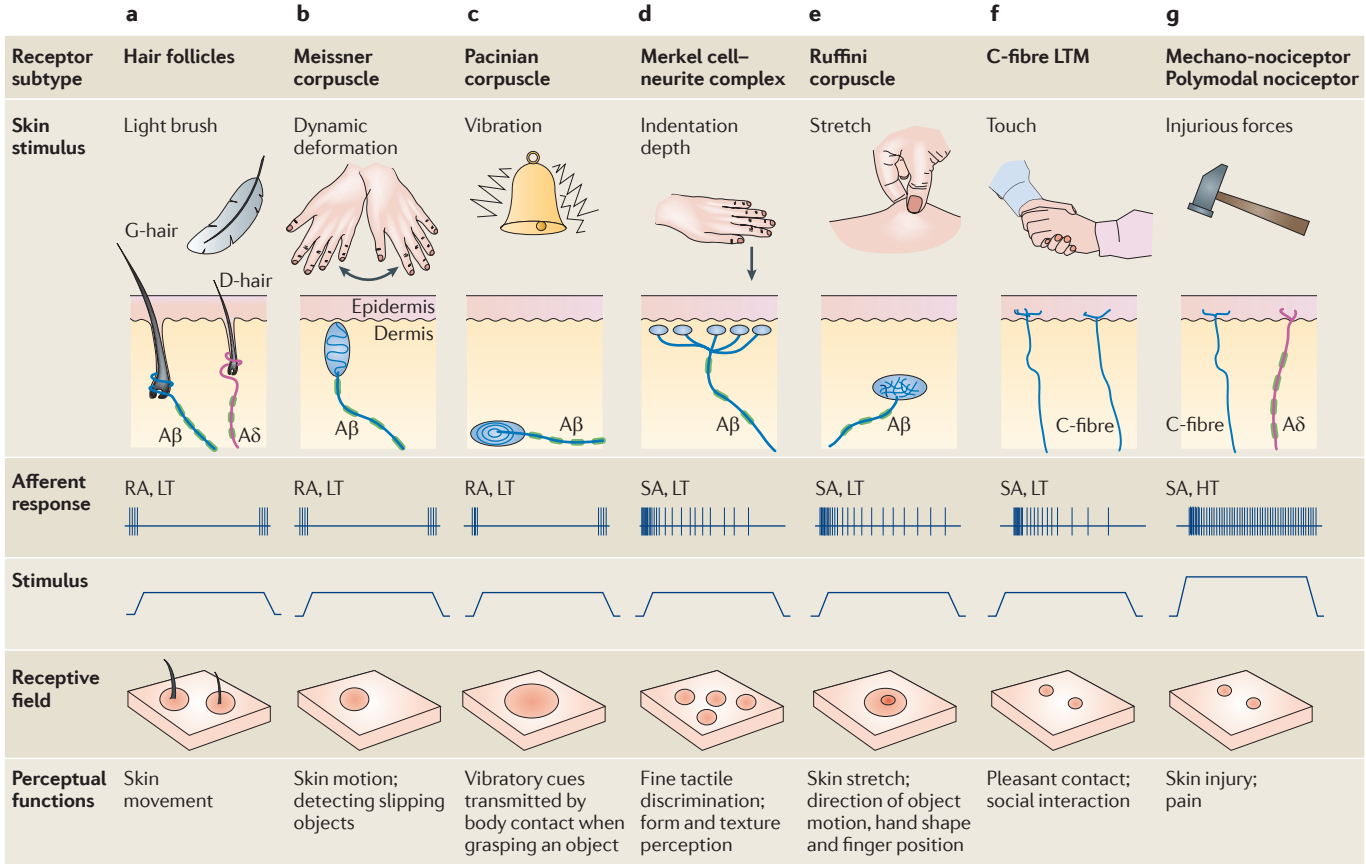


Figure 1 | **Cutaneous somatosensory receptors in mammals.** Cutaneous mechanosensory neurons differentiate into many functionally distinct subtypes — with specific threshold sensitivities and encoding capabilities — each of which is thought to transduce specific kinds of mechanical stimuli. This pertains to the detection of innocuous and noxious mechanical information that underlies our senses of touch and pain. **a** | Guard hair (G-hair) and down hair (D-hair) follicles contain nerve endings that form a circumferential array of unmyelinated nerve terminals derived from myelinated axons. These receptors are rapidly adapting (RA), low threshold (LT) afferents and detect light touch. **b** | Meissner corpuscles occupy dermal ridges in the glabrous skin. They are RA LT mechanoreceptors (LTMs) and transmit information about skin motion[26]. **c** | Pacinian corpuscles have the typical structure of an encapsulated receptor. They are RA LTMs that allow perception of distant events through transmitted vibrations[30,164]. **d** | Merkel cell–neurite complexes lie at the base of the epidermis and are formed of clusters of 50–70 cells connected to terminals of a myelinated Aβ axon. They function as slowly adapting (SA) LTMs and are responsible for form and texture perceptions[31,35,165]. **e** | Ruffini corpuscles lie in the dermis, with the distinct outer capsule surrounding a fluid-filled capsule space. They are SA cutaneous mechanoreceptors[35,36] and contribute to the perception of object motion. **f**,**g** | Free nerve endings and unmyelinated receptors terminate in the subepidermal corium. C-fibre LTMs (**f**) respond to innocuous tactile stimulation and signal pleasant stimulation in affiliative social body contact in humans[38,40]. The perception of painful touch is initiated by high-threshold (HT) C-fibre and Aδ nerve endings (**g**), which can be mechanosensitive or polymodal in nature[42].

sensory neurons are intrinsically mechanosensitive and express excitatory, inwardly flowing, mechanotransducer currents. Mechanosensitive currents evoked in sensory neurons have a relatively short latency (0.4–0.8 ms)[48], which argues against activation of a second messenger cascade and favours direct activation of mechanosensitive channels. Whether mechanosensitive currents are activated by a stress in the lipid bilayer local to the transduction channels or through a tethering mechanism anchoring the channels to the cytoskeleton or the extracellular matrix is still unclear[49]. However, evidence for a tethering mechanism has been recently proposed[50]. It was shown that neurites of light-touch DRG neurons in culture are connected to laminin substrates through 100-nm proteinaceous filaments, disruption of which abolished mechanosensitivity in putative light-touch receptors. These protein tethers do not belong to either integrin- or cadherin-based protein families and remain undefined.

In response to sustained mechanical stimulation, mechanosensitive currents decline through closure of the transduction channels. Based on the kinetics of current decay, four distinct types of mechanosensitive currents can be distinguished: rapidly adapting currents (~3–6 ms), intermediately adapting currents (~15–30 ms), slowly adapting currents (~200–300 ms) and ultra-slowly adapting currents (~1000 ms)[48,51,52] (FIG. 2b). All these currents were present in rat cutaneous DRG neurons innervating the glabrous skin of the hindpaw, although with variable incidence[51].

Latency
The delay between a stimulus and the response it triggers.

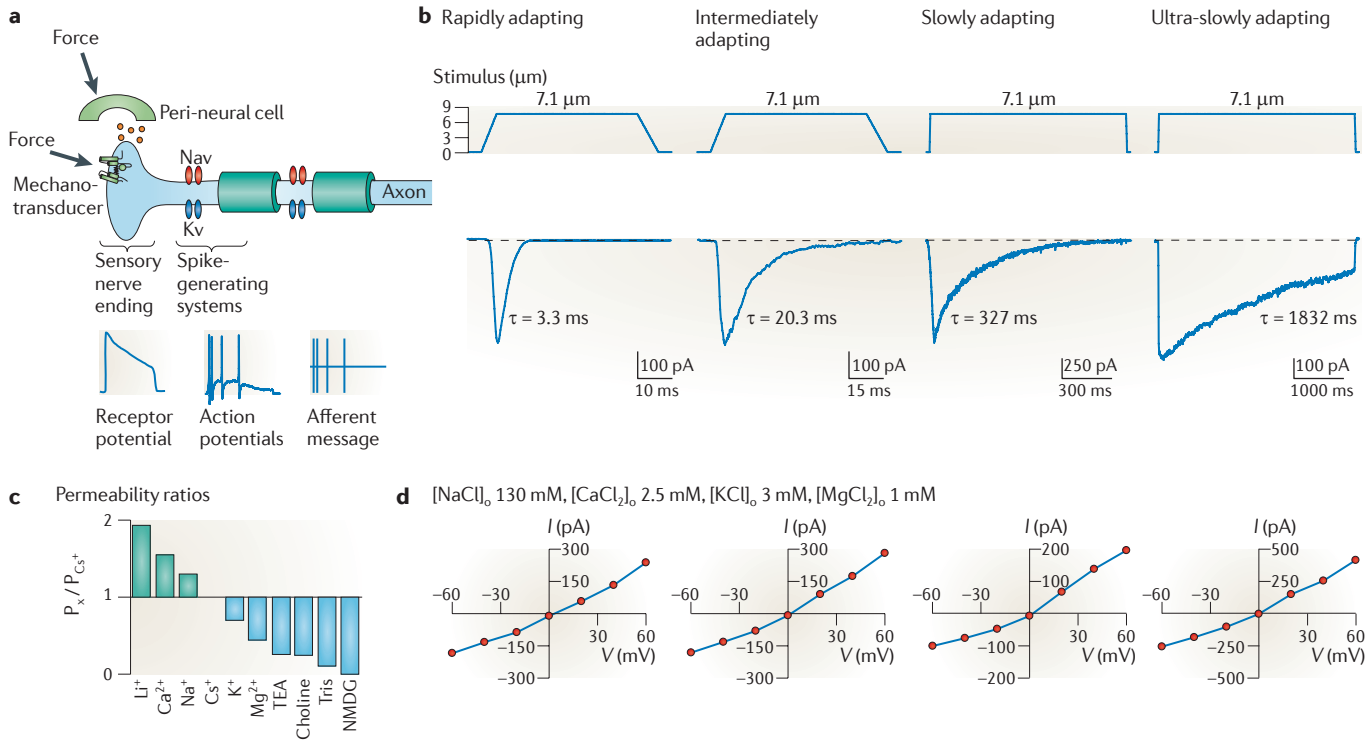


Figure 2 | **Properties of mechanotransducer currents in sensory neurons. a** | Afferent signal generation occurs at sensory nerve endings. Mechanical stimulation of the receptive field activates mechanotransducer channels in the nerve ending. The ion flow through these channels generates a local depolarization (receptor potential) that brings the membrane potential towards the threshold for triggering action potentials. Mechanoreceptors encode the parameters of the mechanical stimulus into a discharge of action potentials, whose firing frequency reflects the main features of the stimulus (the afferent message). Perineural cells have been proposed to modulate receptor potential properties, both chemically and physically[8,62,88,166,167]. **b** | Representative traces of mechanosensitive currents recorded in rat sensory neurons using the mechano-clamp technique, from a holding potential of –60 mV. Time constants of current decay are indicated in each panel. **c** | Permeability ratios of the rapidly adapting mechanotransducer current to caesium ions (Cs^+) versus various cation species. Data from REF. 64. **d** | Representative current–voltage (*I–V*) relationships for the mechanosensitive currents that are illustrated in **b**. The *I–V* curves were obtained with a Cs^+-based intracellular pipette solution, and the main ions of the extracellular solution are indicated. Mechanosensitive currents in sensory neurons are mediated by a family of non-selective cationic channels. NMDG, *N*-methyl-D-glucamine; P_{Cs^+}, permeability to Cs^+; P_x, permeability to ion; TEA, tetraethylammonium. Parts **b** and **d** are modified, with permission, from REF. 51 © (2010) Society for Neuroscience.

The mechanical sensitivity of mechanosensitive currents can be determined by applying a series of incremental mechanical stimuli, allowing for relatively detailed stimulus–current analysis. Activation of mechanosensitive currents occurs classically for small mechanical probe displacements of less than 500 nm. The stimulus–current relationships of mechanosensitive currents is typically sigmoidal, and the maximum amplitude of the current is determined by the number of channels that are simultaneously open[51,53] (FIG. 3c). The sigmoid character of the stimulus–current relationship indicates that there is no simple link between the stimulus force and the current amplitude.

Interestingly, the rapidly adapting mechanosensitive current displayed lower mechanical threshold and lower half-activation midpoint than the slowly adapting mechanosensitive current[54–56]. This prompted the suggestion that these currents might constitute the correlate of low- and high-threshold mechanotransducers *in vivo*. Although these experiments were not entirely conclusive, owing to technical challenges, support for the presence of low- and high-threshold mechanotransducers is provided by radial-stretch-based stimulation of cultured mouse sensory neurons[57]. This paradigm revealed two main populations of stretch-sensitive neurons, one with a low threshold that responds to low stimulus amplitude and one with a relatively high threshold that selectively responds to high stimulus amplitude. These results have important mechanistic implications: the mechanical threshold of sensory neurons might have little to do with the cellular organization of the mechanoreceptor but may lie in the properties of the mechanotransducer apparatus.

Neuronal distribution of mechanosensitive currents. Importantly, the different mechanosensitive currents distributed differentially in subsets of adult sensory neurons. Nociceptive neurons, which are characterized *in vitro* using several well-established criteria[56,58–60], express predominantly slowly and ultra-slowly adapting mechanosensitive currents[48,51,52,54–56,61]. By contrast,

Half-activation midpoint
The intensity of a stimulus that induces a half-maximal response.

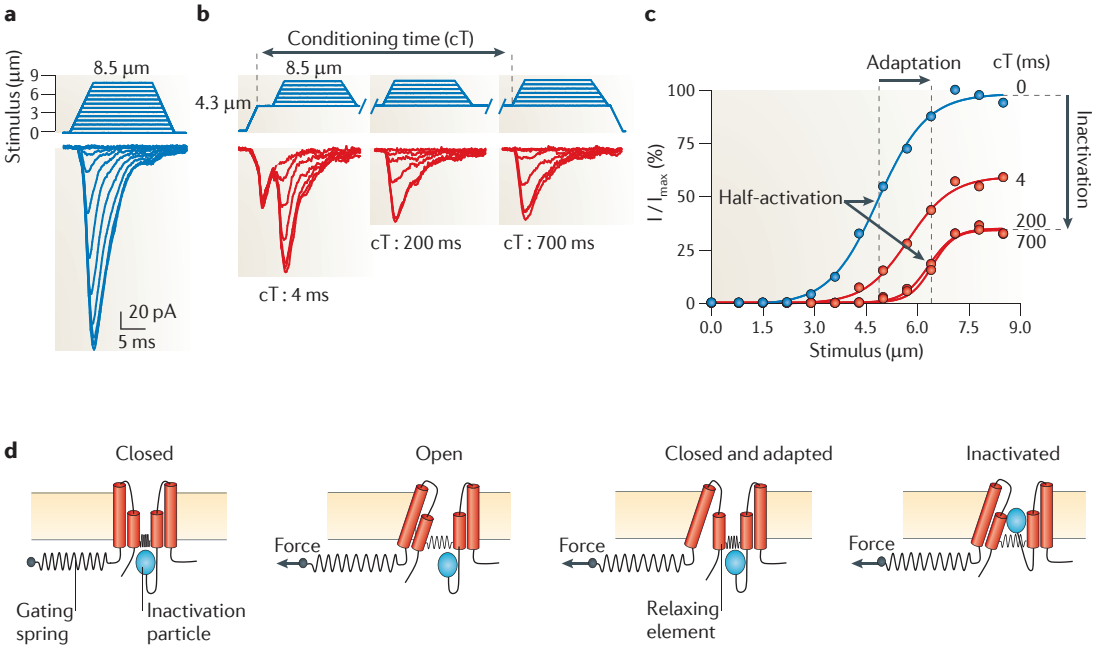


Figure 3 | **Mechanisms of mechanotransducer current desensitization.** Desensitization of mechanosensitive currents manifests as a decline in response to sustained application of the mechanical stimulus. The different desensitization rates of mechanotransducer currents relate to their functions as sensors of phasic and tonic stimuli, and contribute to the extraction of biologically important information from the stimulus. **a** | A series of mechanical stimuli applied in 0.7-µm increments in a rat dorsal root ganglion neuron elicits a family of rapidly adapting mechanosensitive currents. **b** | A conditioning stimulus of increasing duration causes desensitization, manifested as a decrease in the current response to subsequently delivered test steps. **c** | Current–stimulus (*I*–*X*) relationships derived from (**b**) at different times after the onset of the conditioning stimulus illustrate the effect of desensitization. In particular, the conditioning stimulus shifts the activation curve rightward (adaptation) and reduces its amplitude relative to the control relationship (inactivation). **d** | A cartoon representation of the main states of mechanosensitive channels in sensory neurons. Mechanical forces are conveyed to the pore-forming structure through an elastic element or gating spring, which can be a cytoplasmic domain bound to phospholipids and/or cytoskeletal elements or an associated protein. When the gating spring is stretched, channel domains are pulled apart, favouring the open state. As force is maintained, the channel either inactivates, possibly via a ball-and-chain mechanism, or adapts. The inactivating ball could be either a cytoskeletal element or part of the channel protein. During adaptation, the stiffness of the gating spring remains constant but the channel reverts to a closed conformation. cT, conditioning time; I_{max}, maximum current. Figure is modified, with permission, from REF. 51 © (2010) Society for Neuroscience.

sensory neurons with non-nociceptive phenotypes preferentially express rapidly adapting mechanosensitive currents[48,51,52,54,56]. However, this distribution is by no means exclusive as rapidly adapting mechanosensitive currents are also seen in populations of nociceptive neurons[48,51,54] and, conversely, slowly and ultra-slowly adapting mechanosensitive currents are occasionally reported in putative non-nociceptive cells[48,51].

Thus, differences in properties of mechanosensitive currents among sensory neuron phenotypes *in vitro* are consistent with the *in vivo* physiological properties of mechanoreceptors, although comparison between *in vitro* and *in vivo* data remains speculative. However, the kinetics of a particular mechanosensitive current should not be taken as a definite proof of the functional phenotype of the host cell. An exemplar case is the Pacinian corpuscle receptor's potential, which is prolonged — resembling those of slowly adapting mechanoreceptors — when the capsule that envelops the nerve terminal is eliminated by dissection[62,63]. This suggests that the difference in receptor potential kinetics between rapidly and slowly adapting receptors resides at the level of mechanical coupling between the stimulus and the sensory nerve ending.

Mechanotransducer channel properties

Determining the biophysical properties and pharmacological profiles of endogenous mechanosensitive currents is crucial in the quest to identify transduction channels at the molecular level and for probing their functions *in vivo*.

Ion selectivity. Mechanosensitive currents recorded in the cell somata of sensory neurons exhibit reversal potentials ranging from −4 to +15 mV and are carried non-selectively by cations, including divalent and organic cations[43,51,52,54,56,64] (FIG. 2d). A detailed description of the ion selectivity has been made for the rapidly adapting mechanosensitive current[64]. The channels are non-selective for cations but impermeant to anions, such as chloride and sulphate ions (FIG. 2c). Although calcium and magnesium ions can permeate the channel, at

Reversal potential
The membrane potential at which the net ion current flow becomes zero.

Table 1 | **Pharmacology of mechanosensitive (MS) currents in sensory neurons**

MS current subtype	Ionic selectivity	Blockers	Refs
Rapidly adapting	Non-selective cationic	Gd^{3+}, ruthenium red, amiloride, benzamil, FM1-43, cytochalasin B	43, 52, 54–56
Rapidly adapting	Sodium	Gd^{3+}, insensitive to ruthenium red	48
Intermediately adapting	Non-selective cationic	Gd^{3+}, amiloride	48, 56
Slowly adapting	Non-selective cationic	Gd^{3+}, ruthenium red, amiloride, benzamil, FM1-43, NMB1, HC-030031	43, 48, 54–56, 61, 71
Ultra-slowly adapting	Non-selective cationic		

physiological concentrations both cations cause partial blocking of the primary conductance[54,64]. The mechanism of blocking is still unclear, but it may be due to a calcium binding site located within the pore causing reduced permeability to sodium ions. The ability of this channel to pass large organic ions, including tetraethylamonium (TEA), choline and Tris (FIG. 2c), suggests that it has a large pore, consistent with the ability of the styryl dye FM1-43 to permeate the channel[55]. Conversely, another study found that a type of rapidly adapting mechanosensitive current present in DRG neurons of adult mice displays a reversal potential of approximately +80 mV, indicating a very high sodium permeability[48]. Whether this current constitutes a novel type of mechanosensitive current remains to be determined.

Pharmacology. Pharmacological studies of mechanosensitive channels have been dominated by the use of non-selective blockers (TABLE 1). Not surprisingly, the lanthanide gadolinium (Gd^{3+}), a widely used blocker of various mechanically gated channels[65,66], blocks all mechanosensitive currents in sensory neurons[43,48,54]. Similarly, ruthenium red has inhibitory effects on all cationic mechanosensitive currents in DRG neurons[52,54]. Amiloride and its analogue, benzamil, partially block cationic mechanosensitive currents at high (≥1 mM) but not at low concentrations[43,54,56]. These pharmacological profiles are shared by many mechano-gated cationic channels in various systems, including mechanoreceptor neurons of the spider *Cupiennius salei*, *Xenopus laevis* oocytes and auditory hair cells[67,68]. FM1-43, which is commonly used to fluorescently label cell membranes, acts as a permeant blocker of cationic mechanosensitive channels[55], a property also shared by auditory mechanotransducer channels[69,70]. Importantly, injection of FM1-43 into the hindpaw of mice decreases pain sensitivity in the Randall–Selitto test and increases the paw withdrawal threshold, as assessed with von Frey hairs[55].

A peptide that is capable of discriminating mechanosensitive channel subtypes was recently identified[71]. Noxious mechanosensation blocker 1 (NMB1), a 19-amino-acid polypeptide related to the two-loop ρ-conotoxin class, shows an approximate 30-fold selectivity in inhibiting slowly adapting mechanosensitive currents over rapidly adapting mechanosensitive currents. *In vitro*, it binds selectively to nociceptive cells, which preferentially express these currents. In behavioural assays, NMB1 reduces behavioural responses to high-intensity painful mechanical stimulation and has no effect on low-intensity mechanical stimulation or thermosensation[71]. In addition, an antagonist of the transient receptor potential cation channel ankyrin1 (TRPA1), HC-030031, also preferentially blocks slowly adapting mechanosensitive currents over rapidly adapting mechanosensitive currents[61].

The *Grammostola spatula* mechanotoxin 4 (GsMTx4), a 34-residue peptide isolated from the tarantula spider, is known to inhibit stretch-activated cation channels in cardiomyocytes, astrocytes and smooth and skeletal muscles[72,73]. Recent data also indicate that GsMTx4 decreases the rate of adaptation of the small- and large-conductance mechanosensitive channels (MscS and MscL, respectively), which act as tension-activated pressure regulators that protect bacteria from hypotonic shock[74]. In rat DRG neurons, however, GsMTx4 was found to have no effect on both rapidly adapting and slowly adapting mechanosensitive currents[71], suggesting molecular differences between mechanosensitive channels in sensory neurons and those found in muscles and astrocytes. Surprisingly, GsMTx4 injected intraperitoneally increases the mechanical threshold for paw withdrawal in the Randall–Selitto test and reduced mechanical allodynia induced by inflammation and by sciatic nerve injury[75].

Collectively, the distinct pharmacological profiles of cationic mechanosensitive currents in sensory neurons suggest that the underlying channels differ in their subunit composition. However, it remains to be shown unequivocally that mechanosensitive channels identified in cultured DRG neurons are also expressed at sensory nerve endings where they may transduce sensory information.

Mechanisms of desensitization. The mechanisms that underlie desensitization of mechanosensitive cation currents in rat DRG neurons have been recently unravelled[51,53]. Analysis of mechanosensitive current desensitization was made using a two-step protocol in which an initial conditioning step of varying duration was applied to the neuron to elicit desensitization before determining the current–stimulus (*I–X*) relationship (FIG. 3a,b). Comparison of *I–X* curves, generated at different time points during the conditioning stimulus, shows that the activation curve shifted rightward along the *x* axis following the conditioning step[51] (FIG. 3c). This mechanism, termed adaptation in auditory hair cells[13,76,77], can be described operationally as a simple translation of the transducer channel's activation curve along the stimulus axis (FIG. 3c). Adaptation allows sensory receptors to maintain their sensitivity to new stimuli in the presence of an existing stimulus.

Randall–Selitto test
A technique for the measurement of pain response in animals by observing the reaction to gradually increasing pressure on a paw.

Von Frey hairs
A range of filaments of varying diameters that are used to exert a calibrated pressure on an animal's paw.

Allodynia
Pain due to a stimulus that does not normally provoke pain.

Interestingly, adaptation has recently been described for the mechanosensitive transient receptor potential NOMPC (TRPN) subfamily channel TRP4 in *Caenorhabditis elegans* ciliated mechanosensory neurons[78], indicating that it is a common feature of several types of mechanosensory channels. Transducer channel adaptation may result from a relaxation of tension in the linkage between the hinge of the channel's gate and the tension-sensing element. It may be mediated by conformational rearrangements of the channel protein itself or of molecules in series with the tension-sensing element that connects the channel to the cytoskeleton or lipids (FIG. 3d).

A substantial fraction of mechanosensitive currents in DRG neurons cannot be reactivated following conditioning mechanical stimulation, indicating inactivation of some transducer channels[51,53] (FIG. 3b,c). Therefore, both inactivation and adaptation act in tandem to regulate mechanosensitive currents. These two mechanisms are common to all mechanosensitive currents identified in rat DRG neurons, suggesting that related physicochemical elements determine the kinetics of these channels. A numerical model incorporating the properties of rapidly adapting mechanosensitive currents replicates native mechanosensitive channel behaviour[51].

An intriguing feature of mechanosensitive current desensitization is its voltage dependence, being more pronounced at negative voltages near the resting potential and becoming progressively less evident at more depolarized potentials[51,53]. A depolarization-induced slowing of desensitization was observed for the four types of mechanosensitive currents described in rat DRG neurons. The voltage-dependence of adaptation in hair cells is explained, at least in part, by changes in the driving force on calcium entry[76,79–82]. However, this does not seem to be the case in DRG neurons[51], suggesting that the channel molecule itself — or another closely associated subunit — is intrinsically voltage sensitive, resembling the mechanism in other systems[83–87]. The physiological relevance of the voltage dependence of mechanosensitive currents is unclear.

Encoding properties of mechanotransducers

A central issue in sensory physiology is the part played by transducer current properties in shaping the evoked pattern of sensory nerve electrical activity. Recent *in vitro* data indicate that mechanotransducer kinetics may contribute by shaping the firing pattern of mechanosensory neurons[51,53]. Current clamp experiments in rat DRG neurons demonstrate that there is a marked difference in the response to mechanical stimulation of neurons expressing kinetically distinct mechanosensitive currents. Neurons with rapidly adapting currents give a brief action potential discharge in response to a ramp-and-hold mechanical stimulus, whereas neurons with ultra-slowly adapting currents generate sustained action potential discharges (FIG. 4a,b).

Although the relationship between sensory neuron behaviours *in vitro* and *in vivo* remains speculative, the reported data have important functional implications. Because slowly and ultra-slowly adapting currents are the dominant forms in nociceptors, these currents might contribute to the sustained firing of nociceptors *in vivo*[14]. Conversely, rapidly adapting mechanosensitive currents appear best suited to mediate the phasic discharges of LTMs associated with innocuous touch, although other factors including auxiliary cells and specialized terminal structures are also likely to contribute to receptor responses[8,88].

Finally, these studies show that the dynamics of mechanosensitive channels play a crucial part in stimulus representation[51,53]. Rapidly adapting mechanosensitive currents respond in full when stimulated by an abruptly applied pressure, but are largely inactive during slowly applied or static forces (FIG. 4a,b). This mechanism is clearly important for detecting small changes in the dynamic stimulus parameters. By preventing action potential firing upon slowly applied mechanical stimuli, rapidly adapting currents act as velocity detectors (FIG. 4c). By contrast, after a gradual change in applied force, only slowly and ultra-slowly adapting currents, mostly present in nociceptors, are activated and capable of carrying signals that encode the extent of tissue compression (FIG. 4d). Therefore, difference in mechanosensitive current kinetics may relate to the functions of mechanosensitive channels as sensors for phasic or tonic stimuli and enable sensory neurons to achieve efficient stimulus representation.

Different subtypes of mechanically sensitive neurons are tuned to respond specifically to static indentation or vibration stimuli, and this has been elegantly demonstrated using a compartmentalized model of cultured DRG neurons[89]. In this work, a compartmental *in vitro* chamber was designed to deliver mechanical stimulation to sensory axons, while synchronously recording Ca^{2+} transients in neuronal somata. Different types of mechanically sensitive DRG neurons — those responding to static indentation and those responding to vibration — were identified by monitoring Ca^{2+} imaging in cell bodies as a read-out of mechanical stimulation applied to the neurites. These qualitatively different, cell-specific properties of vibration stimulus responses have been attributed, at least in part, to the kinetic properties of the receptor transducer currents[89].

Candidate channels for mechanotransducers

Acid-sensing ion channels. Acid-sensing ion channels (ASICs) belong to a proton-gated subgroup of the degenerin–epithelial Na^+ channel family of cation channels[90,91]. These channels were initially implicated in mechanotransduction because their phylogenetic homologues in *C. elegans*, the MEC subunits, are essential for perception of touch. At least three members of the ASIC family (ASIC1, ASIC2 and ASIC3) are expressed in peripheral mechanoreceptors and nociceptors[92–95].

The role of ASIC channels has been investigated in behavioural studies using mice with targeted deletion of ASIC channel genes. Deletion of ASIC1A does not alter the function of cutaneous mechanoreceptors but increases mechanical sensitivity of afferents innervating the gut[96]. ASIC2 knockout mice exhibit a decreased sensitivity of rapidly adapting cutaneous LTMs and an

Inactivation
The process by which and ion channel enters a refractory state following activation. Reactivation to the conductive state cannot occur until inactivation is removed.

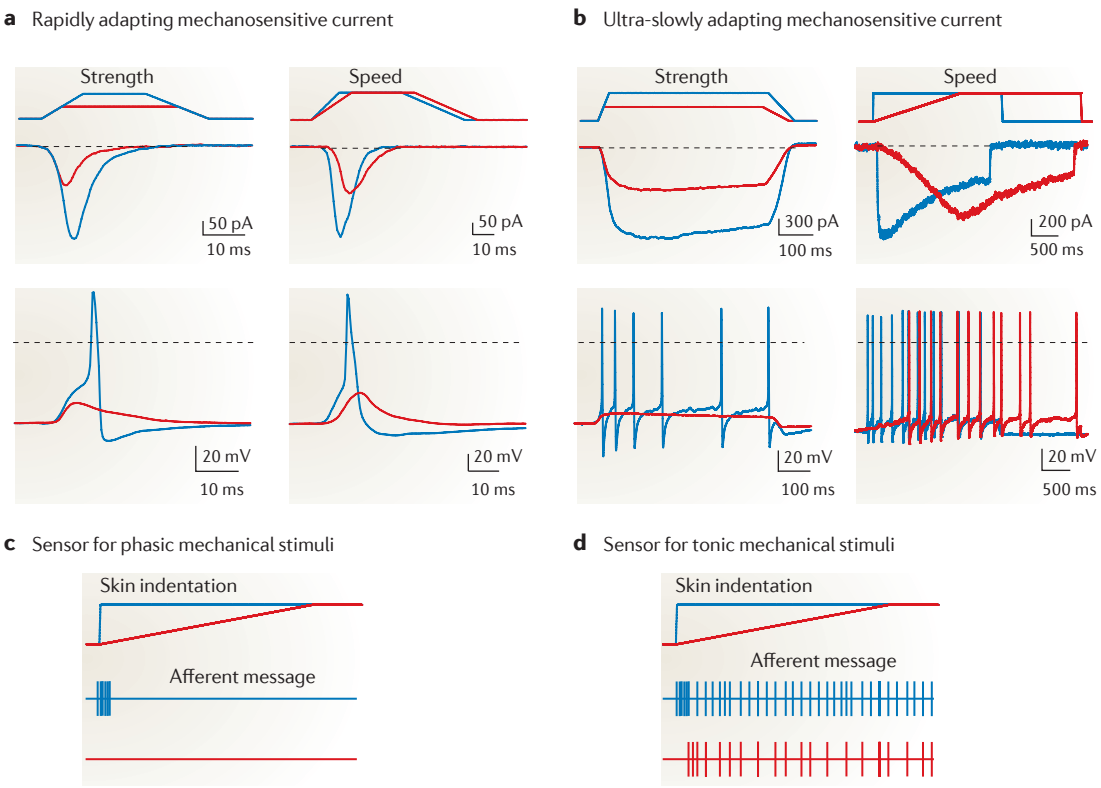


Figure 4 | **Mechanotransducer currents encode biologically relevant parameters of mechanical stimuli. a** | The rapidly adapting mechanosensitive current expressed by a non-nociceptive dorsal root ganglion (DRG) neuron. Current- and voltage-clamp responses (top traces) were evoked by mechanical stimuli with either different amplitudes (5 and 8.5 µm; red and blue traces, respectively) or different rates of onset (560 and 800 µm per s; red and blue traces, respectively). Note that increasing the amplitude of the mechanical stimulus (left panel) or the onset rate of the stimulus (right panel) makes the stimulation efficient in generating action potentials (bottom traces). The rapidly adapting mechanosensitive current therefore acts as velocity detector. **b** | The ultra-slowly adapting mechanosensitive current expressed by a nociceptive DRG neuron. Current- and voltage-clamp responses were evoked by mechanical stimuli with either different amplitudes (5 and 8.5 µm; red and blue traces, respectively) or different rates of onset (3 and 80 µm per s; red and blue traces, respectively). Note that slowing the onset rate of the mechanical stimulus does not prevent action potential discharge. The ultra-slowly adapting mechanosensitive current therefore acts as sensor for tonic stimuli. **c**,**d** | Afferent signals that might be generated by mechanosensitive sensory terminals expressing either rapidly adapting (**c**) or ultra-slowly adapting (**d**) mechanosensitive currents upon varying the velocities of the mechanical indentation. Figure is modified, with permission, from REF. 51 © (2010) Society for Neuroscience.

increased sensitivity of colonic afferents[93,97,98]. However, subsequent studies reported a lack of effects of knocking out ASIC2 on both visceral mechano-nociception and cutaneous mechanosensation[99]. More recently, it was shown that ASIC2 is expressed in aortic baroreceptor neuron somata and terminals, and contributes to the baroreceptor sensitivity[100]. ASIC2-null mice develop hypertension and exhibit a decreased gain of the baroreflex, suggesting that mechanosensitivity is diminished in ASIC2-null mice. ASIC3 disruption decreases mechanosensitivity of visceral afferents and reduces responses of cutaneous HTMs to noxious stimuli[93]. Transgenic expression of a dominant-negative form of ASIC3 leads to an increased sensitivity to noxious mechanical stimuli[101].

Although ASIC subunits are amenable to expression in heterologous cell systems, recombinant ASICs were not mechanosensitive[92,99]. Moreover, the properties of recombinant ASICs differ from those of mechanosensitive currents recorded in sensory neurons[91]. ASICs have a high permeability to sodium relative to calcium and are voltage-independent. Consistent with this, no differences in amplitude, kinetics or incidence of mechanosensitive currents recorded in DRG neuron somata were seen in transgenic mice lacking ASIC2 and ASIC3 (REFS 52,102). Altogether, these data support a modulatory role for ASICs in visceral and cutaneous mechanoreceptor functions, but do not favour a direct role for ASICs in mechanotransduction.

The TRP channel superfamily. Candidates for mechanosensitive channels are members of the TRP superfamily, which is subdivided into six subfamilies in mammals[103,104]. Nearly all TRP subfamilies have members linked to mechanosensation in a variety of cell systems[18]. In mammalian sensory neurons, however, TRP channels are best known for sensing thermal information and mediating neurogenic inflammation, and only two TRP

Baroreceptor
A type of mechanoreceptor that detects the pressure of blood flowing past and sends messages to the CNS.

channels, TRPV4 and TRPA1, have been implicated in touch responsiveness.

TRPV4 acts as an osmotransducer because, in addition to warm temperature and acidic pH, it is activated by cell swelling through an indirect mechanism requiring fatty acid metabolites[105,106]. This requirement for an upstream element means that TRPV4 cannot be considered a genuine mechanotransducer. Disrupting TRPV4 expression in mice has only modest effects on acute mechanosensory thresholds, but strongly reduces sensitivity to noxious mechanical stimuli[107,108]. TRPV4 is a crucial determinant in shaping the response of nociceptive neurons to osmotic stress and to mechanical hyperalgesia during inflammation[108–112].

NOMPC, a member of the TRPN cation channel subfamily in *Drosophila melanogaster*, together with its homologues in *C. elegans* and vertebrates, have been consistently implicated in mechanotransduction[113–118]. A unique feature of these TRPN-related channels is their large amino-terminal domains harbouring numerous ankyrin repeats, which can putatively anchor the channel to the cytoskeleton. This prompted the suggestion that these N-terminal domains may serve as tension transmission structures to the pore-forming region. Recent work has elegantly demonstrated that the *C. elegans* TRP4 is a pore-forming subunit of a mechanically gated channel that senses touch in the worm nose[78]. This channel also mediates proprioception in *D. melanogaster* larval and adult locomotion, and requires integral ankyrin repeats for proper localization and function in chordotonal ciliary tips[113].

TRPN channels are not present in the genomes of reptiles, birds and mammals[119]. The only mammalian TRP subunit with an extended domain of ankyrin repeats is TRPA1. This subunit was suggested to form the main mechanotransducing channel of the inner ear based on expression patterns and gene knockdown strategies[120,121], but this proposal was not corroborated by gene knockout strategies[122–124]. The *C. elegans* orthologue of mouse TRPA1 is expressed in some mechanosensory neurons and contributes to neural responses of these cells to touch[125]. In addition, mechanical pressure can activate *C. elegans* TRPA1 that is heterologously expressed in mammalian cells. These data suggest that *C. elegans* TRPA1 encodes an ion channel that can be activated by mechanical pressure.

The expression of TRPA1 in small-diameter neurons of mammalian sensory ganglia suggests a possible role in mechanical pain sensation[47,121,126,127]. Consistent with this idea, mice lacking TRPA1 are deficient in the detection of acute noxious mechanical stimulation applied to the extremities[123], although this finding was not confirmed in another study[122]. TRPA1 seems to have a role in mechanical hyperalgesia, as the mechanical pain threshold after bradykinin-induced inflammation is significantly higher in *Trpa1*$^{-/-}$ mice than wild-type mice[122,123]. Recordings of skin–nerve preparations from *Trpa1*$^{-/-}$ mice also show impaired firing rates of C-fibre nociceptors in response to noxious mechanical stimuli[128]. More recently, TRPA1 has been shown to contribute to normal and inflamed mechanosensory functions in visceral afferents of mice[129]. At the cellular level, it was shown that slowly adapting mechanosensitive currents are absent in small-diameter DRG neurons from *Trpa1*$^{-/-}$ mice, raising the possibility that TRPA1 mediates slowly adapting mechanosensitive currents[55,61]. However, rapidly adapting currents are also attenuated in these mice. It remains to be determined whether TRPA1 channels serve as mechanotransducer channels or play an indirect part in mechanosensation by amplifying or modulating the signal from the transduction channel.

Piezo proteins. An elegant study has recently identified a novel class of proteins, the piezo protein family, as promising candidates for mechanosensing proteins[130]. Vertebrates have two piezo members, piezo 1 and piezo 2, previously known as FAM38A and FAM38B, respectively, which are well conserved throughout multicellular eukaryotes[130]. Piezo 1 has been previously described to be upregulated in senile plaque-associated astrocytes[131] and to regulate integrin activation[132]. Piezo 2 is abundant in DRGs, whereas piezo 1 is barely detectable. Transmembrane prediction programs predict that piezo proteins are large integral proteins with 24–39 transmembrane domains (FIG. 5a). Transmembrane domains are located throughout the piezo proteins but no obvious pore-containing motifs or ion channel signatures have been identified. However, piezo-induced mechanosensitive currents are prevented by the classical blockers gadolinium and ruthenium red.

Expression of piezo 1 or piezo 2 in heterologous systems produces mechanosensitive currents differing in kinetics[130] (FIG. 5b,c). Similar to endogenous mechanosensitive currents, piezo-dependent currents have reversal potentials around 0 mV and are cation nonselective, with Na^+, K^+, Ca^{2+} and Mg^{2+} all permeating the underlying channel. Furthermore, piezo-dependent currents are regulated by membrane potential, with a marked slowing of current kinetics at depolarized potentials[130] (FIG. 5b–d). It is not yet known whether piezo proteins adapt as seen with endogenous mechanosensitive channels in DRG neurons[51,53,130]. A crucial unsolved question is whether piezo proteins are ion-conducting structures or confer mechanosensitivity to pore-forming subunits by heteromerization. The large amplitude of piezo-dependent mechanosensitive currents seen upon expression in a variety of cell lines suggests that piezo proteins themselves conduct currents, unless they are capable of trapping TRP-like channel subunits.

Using *in situ* hybridization in adult mouse DRGs, piezo 2 mRNA has been shown to be present in about 20% of DRG neurons, which were classified tentatively as both mechanosensitive and nociceptive. Small interfering RNA (siRNA)-mediated knockdown of piezo 2 in mouse DRG neurons reduces rapidly adapting mechanosensitive currents but does not affect intermediately adapting, slowly adapting and ultra-slowly adapting mechanosensitive currents[130]. These data indicate that piezo 2 may contribute to rapidly adapting mechanosensitive currents in DRG neurons. However, mRNA distribution argues for a role of piezo 2 in both innocuous

Hyperalgesia
A heightened sensitivity to a painful stimulus.

Chordotonal ciliary tips
Sensory cilia of stretch receptor organs in insects and other arthropods.

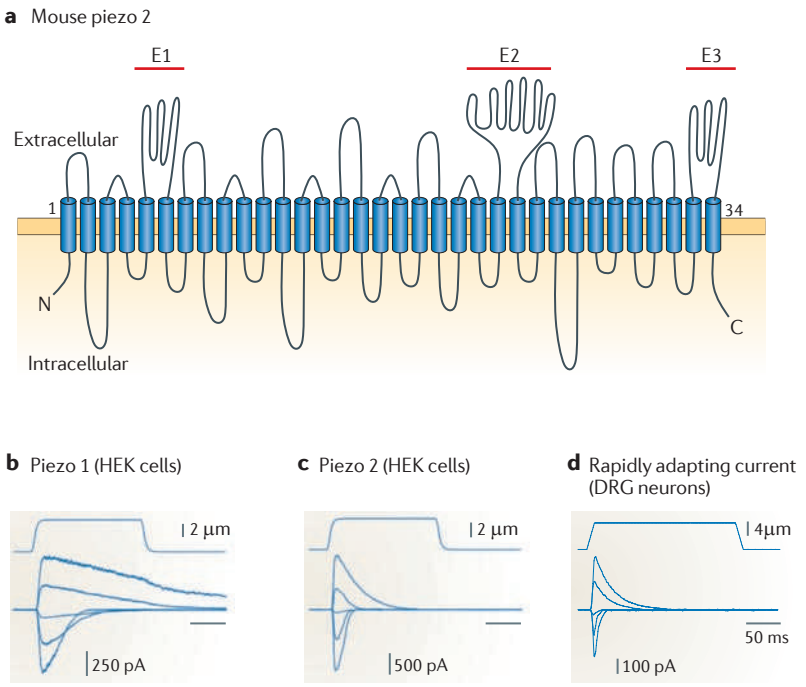


Figure 5 | **Piezo proteins contribute to mechanotransducer currents. a** | The hypothetical topology of mouse piezo 2. Assuming a plasma membrane expression of piezo 2, transmembrane hidden Markov model (TMHMM) algorithms posit that this protein has 34 transmembrane domains, 3 large extracellular loops (E1, E2 and E3) and cytoplasmic amino (N) and carboxyl (C) termini. Note that the Phobius prediction model gives 39 transmembrane domains and locates the E2 domain in the cytoplasmic compartment, and so further studies are required to confirm the precise topology. **b**–**d** | Mechanosensitive current traces elicited at different holding potentials in human embryonic kidney (HEK) cells expressing piezo 1 (**b**) or mouse piezo 2 (**c**) and in a rat dorsal root ganglion (DRG) neuron (**d**). Piezo-dependent currents were evoked from –80 mV in 40 mV increments, and DRG mechanosensitive currents were evoked from –60 mV in 30 mV increments. Note the similar properties of the piezo 2-dependent current and the rapidly adapting mechanosensitive current in DRG neurons. Part **d** is modified, with permission, from REF. 51 © (2010) Society for Neuroscience.

touch and pain sensation, which is inconsistent with the predominant expression of rapidly adapting mechanosensitive currents in non-nociceptive neurons[48,51,56]. Further experiments aiming at localizing piezo 2 on mechanosensory nerve endings in the skin, deep somatic organs and viscera, together with the study of deficient mice, are required to solve these important issues.

Thus, TRP and ASIC family channels are implicated in mechanical hypersensitivities under pathological conditions but do not seem to have a fundamental role in normal mechanotransduction. The modest phenotypes of knockout mice may reflect redundant gene functions and the need to develop new, more sensitive behavioural assays for tactile discrimination. There is no clear evidence indicating that TRP channels and ASICs are mechanically gated. In addition, none of these ion channels, expressed heterologously, recapitulates the electrical signature of sensory mechanosensitive currents observed in their native environment. This does not rule out the possibility that ASICs and TRPs are mechanotransducers, given the uncertainty of whether a mechanotransduction channel functions normally outside of its cellular context. On the contrary, piezo proteins are undoubtedly mechanosensing proteins and share many properties of rapidly adapting mechanosensitive currents in sensory neurons. Although their molecular structure remains to be determined, this novel family of mechanosensitive proteins is a promising subject for future research.

Additional modulatory proteins

Although the exact protein constituents of the transduction channels are still largely unknown, some proteins have been shown to influence touch sensitivity through a modulatory role in sensory neurons.

Stomatin. The stomatin-like protein 3 (SLP3) is related to MEC2, which is expressed in mammalian DRG neurons. In *C. elegans*, MEC2 encodes an integral membrane protein with a stomatin homology domain that serves as an accessory subunit of the touch MEC4–MEC10 receptor complex[133,134]. MEC2 exhibits a central sequence of 247 amino acids that has 64% sequence homology with the mammalian protein stomatin[135]. Studies of mutant mice lacking SLP3 suggested that SLP3 is an important determinant of skin mechanoreceptor functions[136]. Approximately 36% of sensory neurons recorded *in vitro* show no responses to mechanical stimuli in *Slp3*$^{-/-}$ mice, compared with >5% in wild-type sensory neurons. The proportion of cells that normally display rapidly and slowly adapting mechanosensitive currents decreased conjointly, suggesting that SLP3 is necessary for both types of mechanosensitive channels. At the behavioural level, the loss of SLP3 impairs tactile discrimination capability and touch-evoked pain following neuropathic injury[136]. Although its precise function remains unknown, SLP3 may be a linker between the mechanosensitive channel core domain and the underlying microtubules, as proposed for its *C. elegans* homologue MEC2 (REF. 135).

The role of stomatin protein has been tested using *in vitro* skin–nerve preparations from mice lacking stomatin[137]. In these mice, D-hair receptors, which are rapidly adapting mechanoreceptors, showed reduced sensitivity to mechanical stimulation. This deficit was selective, as properties of other cutaneous mechanoreceptors and nociceptors were unaffected in stomatin-deficient mice. Whether stomatin regulates mechanotransducer channel activity and mechanoreceptor function *in vivo* remains to be determined.

KCNK family. K^+ channel subfamily K (KCNK) members belong to the two-pore domain K^+ channel (K2P) family[138]. These K^+ channels have no intrinsic voltage sensitivity and are active at resting membrane potential. There is evidence to suggest that these channels regulate firing responses of mechanoreceptors. KCNK2 (also known as TREK1) was the first of these K^+ channels to be identified in sensory neurons. KCNK2 is expressed in a subset of C-fibre nociceptors[139,140] and is activated by heat and pressure applied to membrane patches via a recording pipette[141]. Mice with a disrupted *Kcnk2* gene displayed an enhanced sensitivity to heat and mild mechanical stimuli but a normal withdrawal threshold

to noxious mechanical pressure applied to the hind-paw using the Randall–Selitto test[141]. KCNK2-deficient mice also display increased thermal and mechanical hyperalgesia in conditions of inflammation.

Two more mechanosensitive K2P channels, KCNK10 (also known as TREK2) and KCNK4 (also known as TRAAK), which are present in sensory ganglia, are activated by membrane stretch and membrane crenation[142–144]. *Kcnk4*$^{-/-}$ mice were hypersensitive to mild mechanical stimulation, and this hypersensitivity was increased by additional inactivation of KCNK2 (REF. 145).

Increased mechanosensitivity of these knockout mice could mean that stretch normally activates both excitatory and inhibitory (KCNK4 and KCNK2) mechanosensitive channels in a coordinated way. This hypothesis suggests that the balance between these two types of channels defines the exact mechanical threshold for activation of mechano-nociceptors. However, inactivation of KCNK4 and/or KCNK2 channels, which are constitutively active, would be expected to relieve the inhibitory brake and shift the threshold for noxious mechano-perception to lower values.

KCNK18 (also known as TRESK) is related to K2P channels and contributes to background K^+ conductance that regulates the resting membrane potential of somatosensory neurons[146]. This channel is proposed to be the molecular target of hydroxy-α-sanshool, a compound found in Schezuan peppercorns that activates touch receptors and induces a tingling sensation in humans[147]. Somatosensory neurons lacking KCNK18 are hyperexcitable. KCNK18 in subsets of LTMs and nociceptors is inhibited by hydroxy-α-sanshool[148]. Although it is not known whether KCNK18 is directly sensitive to mechanical stimulation, it may play a part in mediating responses to light touch and noxious mechanical stimuli.

Taken together, these studies establish that KCNK2 and K2P-related members regulate mechanical afferent messages as well as polymodal pain perception; however, it is not yet clear whether K2P channels function as direct transducers of mechanical stimuli or as regulators of neuronal excitability.

Mechanosensation disorders

Hypersensitivity to mechanical stimuli occurs after tissue damage caused by inflammation, injury, disease and cancer therapy. In a study of patients with peripheral nerve injuries, with or without spontaneous pain, there were no significant differences in thermal thresholds between the two groups of patients, but allodynia to light touch and reduced mechanical pain thresholds were observed only in patients with pain[149]. Although both central and peripheral mechanisms may contribute to altered mechanical sensation, these data suggest that peripheral alteration may result from changes in transduction mechanisms and/or in the membrane stability of sensory fibres.

Peripheral neuropathic pain, also known as nerve trunk pain, has been attributed to increased activity in mechanically sensitized nociceptors. Following nerve section, a neuroma develops at the proximal nerve end consisting of regenerative fibres that are unable to access former nerve tracks[150,151]. Gentle mechanical stimulation over injured sites and neuromas typically evokes a stabbing sensation. Compelling evidence indicates that mechanical hypersensitivity results from an aberrant expression or activity of the transducer molecules[152,153] — for example, it has been shown that chronic compression of sensory fibres is sufficient to alter the distribution of the transducers in the peripheral membrane[154]. The aberrant response is not restricted to the point of compression or lesion, as axotomy also results in increased mechanical sensitivity in the sensory neuron somata[155], suggesting transcriptional regulation or altered targeting of transducer channels. The consequences of these alterations are the emergence of mechanical allodynia and hyperalgesia. With the identification of mechanotransducer candidates, these functional alterations in nociception and touch can now be addressed at the molecular level.

Although neuropathy and pro-nociceptive inflammatory mediators can reduce the mechanical threshold of C-fibres and cause mechanical hyperalgesia, they generally do not cause these fibres to respond to light touch of the skin that typically evokes tactile allodynia[156]. There is evidence instead that tactile allodynia is principally mediated by the activity of LTM Aβ touch afferents, which is abnormally amplified in the spinal cord and leads to central sensitization[157]. In contrast to the skin, C-fibre nociceptors play an important part in hypersensitivity evoked by mechanical stimuli in inflamed viscera, muscles and joints. Both reduced mechanical thresholds and the recruitment of normally silent C-fibre nociceptors cause these nerve fibres to be responsive to the strong forces that are experienced during, for example, weight-bearing flexion.

Concluding remarks and perspective

Electrophysiogical recordings from sensory nerve fibres have shown that mammalian mechano-nociceptors and mechanoreceptors have different mechanical sensitivity and stimulus specificity. Although this can be explained in part by the geometry of the specialized terminal structures and their interaction with auxiliary cells, this functional specificity points to distinct transduction apparatuses operating in nociceptive and non-nociceptive terminals. However, unlike other sensory systems, there has been a lack of *in vitro* models to address these questions at the cellular and molecular levels. The development of new techniques in recent years, allowing monitoring of membrane tension changes while recording mechanotransduction currents, has proved valuable in addressing many of these unresolved issues. Such studies have established that sensory neurons are intrinsically mechanosensitive and have characterized the dynamic properties of mechanosensitive currents and their encoding capabilities. Nonetheless, it is not yet clear whether rapidly and slowly adapting mechanosensitive currents identified with these *in vitro* techniques relate to LTMs and HTMs *in vivo*. Also, the extent to which the afferent signal threshold and adaptation depend on the properties of excitatory as well as inhibitory mechanotransducer channels has not been established for any mechanoreceptors.

Crenation
Cell shrinkage after exposure to a hypertonic solution.

Excitatory mechanosensitive currents present in DRG neurons fall into definable categories, although they do not display a marked heterogeneity. Whether these transducer channels belong to a single family of ion channels or to different families is a crucial question. The recent discovery of piezo proteins leads to new hypotheses regarding the identity of mammalian mechanotransducer channels. The reported data also open new avenues for other sensory systems, including auditory hair cells. Many open questions remain. Do piezo proteins form ion channels or do they serve as sensors for associated ion channels, as proposed for other receptor–ion channel complexes[158]? Do they sense forces through a protein–protein tethering mechanism or through lipid membrane tension? How does voltage regulate their kinetics?

It appears that TRP channels have aged suddenly. The lack of evidence, however, for mechano-gated mammalian TRP channels should not deter speculation regarding their implication in mechanosensation. TRPA1 is the leading candidate for mediating slowly and ultra-slowly adapting mechanosensitive currents in mammalian sensory neurons[61]. Moreover, TRPN channels have recently emerged as mechano-gated channels in *C. elegans* and *D. melanogaster*[78,113], sharing many electrophysiological features with piezo-dependent currents and native mechanosensitive currents. The possibility that structurally unrelated proteins mediate similar mechanosensitive currents is intriguing. The emerging picture therefore indicates that the molecular details of mechanotransduction differ substantially in mechanosensory cells. Future research will therefore determine how these different proteins function within the structural context of living cells and contribute to mechanosensation, both in physiological and pathophysiological conditions.

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Competing interests statement
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