# Chapter 7
# TRP Channels and Mechanical Transduction

**Ana Gomis**

**Abstract** Many physiological processes depend on correctly sensing mechanical forces, including hearing, proprioception and touch. Accordingly, much research has focused on the mechanisms and molecules responsible for mechanotransduction. Studies in the fields of genetics, genomics and electrophysiology have converged to further extend our understanding of mechanosensitive events in invertebrates and vertebrates. Indeed, candidate mechanotransduction genes have been identified in mammalian cells, some of which encode the TRP channels expressed in mechanosensitive neurons. In recent years, functional assays have permitted single or multiple ion channel currents flowing through the membrane to be recorded. Such approaches will help determine the biophysical properties of mechanosensitive currents, a crucial step in the quest to identify transduction channels at the molecular level and probe their activity *in vivo*. Here, the proposed mechanisms to mechanodetection are described, along with the different mechanosensory systems used as models to study mechanotransduction. The TRP channels that represent relevant candidates to be involved in sensing mechanical forces will also be reviewed.

**Keywords** TRP channels · Mechanotransduction · Sensory systems · Touch · Pain

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## 7.1   Principles of Mechanotransduction

In many animals, including humans, some of the most important physiological pro-
cesses occur through mechanical stimulation. These physiological processes de-
pend on the transformation of mechanical energy into ion currents in order to evoke
events such as cellular turgor in bacteria, or the sensation of touch, sound and pain
in mammals (Hamill and Martinac 2001; Lewin and Moshourab 2004). To detect
and decode mechanical stimuli, organisms possess specialised organs like the touch
receptor neurons in *Caenorhabditis elegans*, the chordotonal organ and bristles in
*Drosophila melanogaster*, and in mammals, the hair cells in the auditory system, the
cutaneous tactile receptors, the circumventricular organs that control systemic os-
molarity, the baroreceptors that detect blood pressure, and the proprioreceptors that
control muscle stretch and the position of the body. In addition, animals also possess
free nerve endings of somatosensory and visceral afferents scattered throughout the
body (Ernstrom and Chalfie 2002).

As mechanical stimuli are ubiquitous, mechanotransduction may represent one
of the oldest sensory processes developed by living organisms. Nevertheless, little
is known about the molecular machinery that mediates the sensory detection of
force stimuli when compared with our knowledge of other senses.

The mechanisms involved in olfaction, phototransduction and some modali-
ties of taste include molecular mediators that link G protein-coupled receptors to
their effector proteins, enzymes or ion channels (Arshavsky et al. 2002; Ronnett
and Moon 2002; Hardie and Postma 2008; Kinnamon 2012; Hardie 2014). These
mechanisms appear to be evolutionarily conserved and likewise, it could be pre-
dicted that there is a general mechanism for mechanical transduction, and a similar
sensor that produces different outcomes as a function of its configuration. However,
research over the past 10 years indicate that diverse mechanisms and different mo-
lecular entities are involved in mechanotransduction, both across species and within
single organisms (Sukharev and Corey 2004; Christensen and Corey 2007; Nilius
and Honore 2012).

Most mechanosensory cells or mechanoreceptors convert forces into electrical
signals, a process that relies on conserved functional principles. The result of this
stimulation is the depolarization of the nerve ending and the generation of trains
of action potentials (Shepherd 1991; Block 1992; Torre et al. 1995) through the
activation of ion channels rather than sensory receptors for odours and most tastes
(Garcia-Añoveros and Corey 1997; Sachs and Morris 1998; Hamill and Martinac
2001; Gillespie and Walker 2001) . The impulses propagated travel centrally along
sensory nerves, eventually reaching cortical structures in order to evoke a sensation.

The idea of mechanically gated ion channels was proposed by Bernhard Katz
in 1950 (Katz 1950) on the basis of studies into the muscle spindle. Years later,
experiments carried out on hair cells from the bullfrog sacculus (Corey and Hud-
speth 1979) , bristle mechanoreceptors (Walker et al. 2000) , chordotonal hearing
receptors from *D. melanogaster* (Albert et al. 2007) and touch receptors in *C. el-
egans* (O'Hagan et al. 2005) showed that mechanical stimulus produced electrical

responses in the range of microseconds. This rapid response must result from the direct activation of a transduction channel rather than the activation of second messenger systems. In addition to rapid activation kinetics, the channel must also fulfil other requirements (Ernstrom and Chalfie 2002; Christensen and Corey 2007) : first, the channel must be expressed and located in the receptor cell; second, the candidate protein must be necessary for the electrical signal to be produced in response to mechanical stimulation; and third, the mechanical gating and pharmacological properties of the channel must be similar when it is expressed in different cells.

Studies carried out over the past 15 years have also focused on discovering how these ion channels are activated and although this is still to be fully elucidated, several mechanisms have been proposed to explain how mechanosensitive channels (MS) translate mechanical stimuli into channel opening (Fig. 7.1; Voets et al. 2005; Christensen and Corey 2007; Chalfie 2009; Kung 2005). First, MS channels may be directly gated by the force stimulus. A change in the force may lead to changes in tension of the lipid bilayer, causing conformational changes in the channel and the gating of the pore (Fig. 7.1a). An alternative model for the direct activation of the channel proposes that the channels are 'tied' to cytoskeletal elements and/or the extracellular matrix (ECM), and that the tension among these tethered elements controls the gating of the channels (Fig. 7.1b). However, it is not clear whether these links are directly coupled to the channel domains or if they modulate the forces that surround the channel. This model arises from the biophysical studies in hair cells from the auditory and vestibular systems (LeMasurier and Gillespie 2005) . A third model of activation implicates an accessory protein that will transmit the force to the channel, inducing a conformational change of the channel and indirectly gating its activity (Fig. 7.1c). A fourth possibility is that channels may be activated by intracellular signalling cascades that display mechano- or osmosensitivity (Fig. 7.1d). Mechanical stimulation and osmotic stress evoke numerous changes in protein ph osphorylation/dephosphorylation cycles, and it has been shown that some of them play important roles in osmotic and mechanical regulation, acting through protein transport (Pedersen and Nilius 2007).

Multiple mechanisms can converge on a single channel and moreover, the same stimulus may activate different mechanisms. For example, osmotic cell swelling induces tension at the cell membrane that may directly activate channels (mechanism 1) and/or alter the interactions with the cortical cytoskeleton that may in turn affect a tethered channel (mechanism 2). Changes in cell volume may also initiate signalling events that involve the metabolism of membrane components, which may regulate ionic channels by altering the curvature of the membrane (mechanism 4: Pedersen and Nilius 2007) .

How these mechanosensory mechanisms can be studied will be addressed below.

**Fig. 7.1** Mechanisms of mechanical channel activation. **a** All membrane channels are exposed to lateral forces or tension produce by the modification of the phospholipid bilayer (indicated by the *arrow*), resulting in pore opening. **b** Channel activation through tethered elements, including the cytoskeleton and elements of the extracellular matrix. This interaction may be direct **b** or through proteins associated to the channel **c**. **d** Channel activation through a secondary signal generated by the activation of other proteins sensitive to mechanical forces. (Adapted with permission from Christensen and Corey 2007)
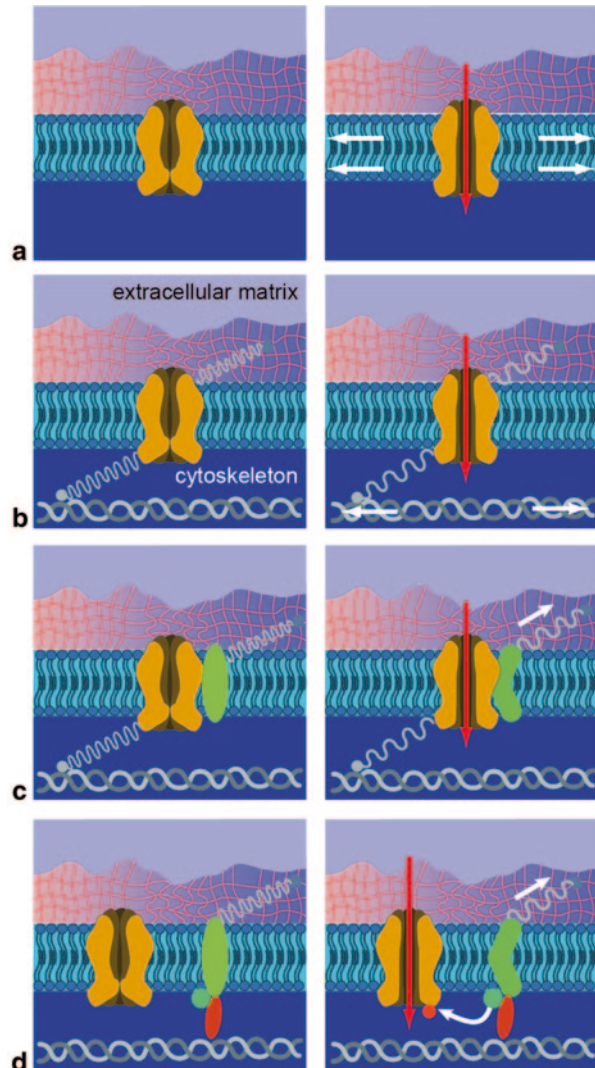


## 7.2 Animal Models in Sensory Mechanotransduction: Mechanosensory Systems

Mechanotransduction is not limited to a subset of specialized cells and tissues but rather, it is implicated in a wide range of cellular functions. The molecular bases of touch sensitivity have been investigated extensively in *C. elegans*. This transparent worm has the particularity of having only 302 neurons, 10 % of which are primary mechanosensory neurons, and they have been identified individually through
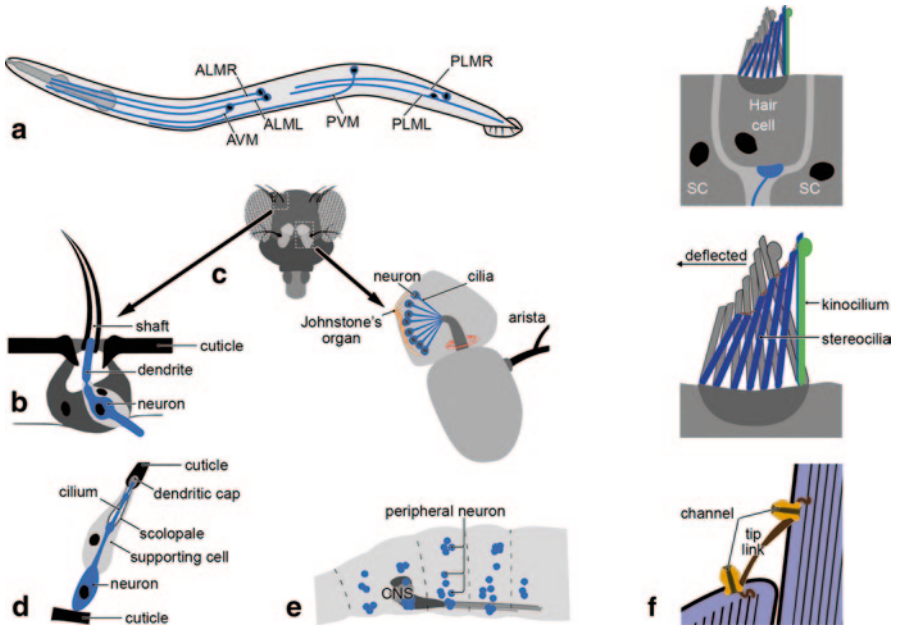
**Fig. 7.2** Mechanosensory systems. **a** Schematic drawing of *C elegans* showing the gentle touch neurons. The head of *D. melanogaster* has different mechanosensory organs, bristles (**b**), the Johnston's organ in the antennae (**c**), and chordotonal organs (ch) (**d**). A positive deflection of the bristle stimulates the neurons that innervate it. Sound waves make the arista of the antenna vibrate causing a rotational movement that stretches neurons of Johnston's organ. The characteristic feature of the ch organs is the scolopale cell. Scolopidial receptors are common in tympanal organs and in Johnston's organ, both of which are used in insects to detect external vibration and sound (**d**). Panel (**e**) shows the localization of the multidendritic sensory neurons in *Drosophila* larvae (type II mechanosensory organs). **f** *Hair cell* and supporting cells (SC) in the sensory epithelium (*upper panel*). On top of the HC the stereocilia and kinolicium in the hair bundle can be observed (*middle panel*). Deflection of the stereocilia would increase the tension in the tip links and open the ion channels (*lower panel*). (Adapted with permission from Christensen and Corey 2007 (**a** and **f**) and from Wilson and Corey 2010 (**b–e**))

laser ablation and genetic studies. Specifically, six of these cells are responsible for light touch and proprioception (Fig. 7.2 a: Chalfie and Thomson 1982) . Three cells sense touch in the anterior half of the animal (ALML, ALMR and AVM) and two in the posterior part (PLML and PLMR). Moreover, in addition to touch these cells also appear to regulate other physiological processes (Ernstrom and Chalfie 2002) . Other cell seems not to be essential for touch but they mediate movement in touch-mediated circuits (PVM neurons: Chalfie et al. 1985) . Over the past three decades, genetic screens have generated a large number of *C. elegans* mutants in which light touch is affected. The relevant proteins involved have been named MEC, from mechanosensory, and they have been numbered from 1 to 18. Two of the most interesting MEC proteins, MEC-4 and MEC-10, form ion channels of the degenerin (DEG) family, which are related to the vertebrate epithelial sodium channels (ENaCs). These two proteins form the pore of the channel, probably together

with MEC-6. This channel associates with other MEC proteins, as well as with the extracellular matrix and cytoskeletal proteins, to form a mechanotransduction complex (for extensive revisions see Garcia-Añoveros and Corey 1997; Ernstrom and Chalfie 2002; Geffeney and Goodman 2012). Genetic studies in worms defective for touch sensation have also revealed the involvement of two related TRPV channels, the OSM-9 and OCR-2 proteins, and of the TRPP2 and TRPML channels (Venkatachalam and Montell 2007).

Studies in the fruit fly **D. melanogaster** have also contributed to our understanding of mechanosensation. Flies display mechanosensation such a gravity sensing, hearing, proprioception, gentle-touch sensation and mechanical nociception. In *Drosophila* there are two types of touch-sensitive cells, the type I cells that have one sensory dendrite (Figs. 7.2b–d) and the type II cells that are multidendritic (Fig. 7.2e; Keil 1997). The most abundant cells are the type I mechanoreceptors, which are associated with accessory structures and that form complex mechanosensory organs. These organs may be associated with external cuticular structures such as bristles (Fig. 7.2b) or cuticular domes (the campaniformsensilla), or they may be attached to the apparently unspecialized cuticle through support cells (the chordotonal organs). The dendrites of these cells terminate at the base of extracellular bristles or domes (external sensory organs) that can be deflected or deformed by touch, airflow or proprioceptive stimulation, or that are surrounded by a supporting cell called a scolopale (Fig. 7.2d). Scolopidial receptors are spindle-shaped cages enclosing an extracellular cavity, into which the ciliar outer segment extends, and they are common in tympanal organs and in Johnston's organ (Fig. 7.2c), both of which are used to detect external vibration and sound (Kernan and Zuker 1995; Eberl 1999).

Type II mechanoreceptors have multiple non-ciliated dendrites, and they lack accessory cells and innervate the insect epidermis (Grueber et al. 2002).

Genetic screening has helped identify genes that are required for the function of the sensory organs in *Drosophila*, whose mutations cause impaired touch responses. One of these genes, named *nompC* (no mechanoreceptor potential C), encodes a channel protein, located in the ciliated mechanosensory organs responsible for bristle touch sensitivity (NOMPC; Walker et al. 2000). This ion channel belongs to the TRPN branch of the TRP channel family (TRPN1) and NompC mutants display an approximate reduction in 50 % in auditory nerve firing and no amplification of antennal vibration (Eberl et al. 2000), consistent with a hearing deficit. Another gene, *nompA*, was also cloned from Type I cells (Chung et al. 2001), a gene encoding an extracellular linker protein that connects the ciliated dendrites of the auditory mechanosensory neuron to the antennal receiver. Mutation of this gene results in conductive hearing loss. In addition, two more mechanosensory proteins belonging to the TRPV family have been identified, the *nanchung (nan)* and *inactive (iav)*. These proteins are found in the mechanosensory cilia of chordotonal organs, and their mutation results in the loss of auditory responses (Gong et al. 2004; Kim et al. 2003).

Other genetic screens have been performed in *Drosophila* larvae to identify genes responsible for pain responses (pinching and thermal stimuli). In larvae with

deficiencies in the sensation of pain, mutations were identified in a gene (*painless*) that encodes a fly member of the TRPA subfamily channel (Tracey et al. 2003).

More recently, studies on the dendritic arborisation of neurons in *Drosophila* larvae showed that the mechanotransducer channel *piezo* (Dm*piezo*; see below) is essential for sensing noxious mechanical stimulus *in vivo* (Kim et al. 2012), and that NOMPC is a mechanotransducer channel for gentle touch (Yan et al. 2013). However, a separate study indicates that Dm*piezo* is not implicated in the mechanotransduction and/or signal amplification for the detection of sound (Zhang et al. 2013).

**Vertebrates** possess a variety of external and internal cells that transduce mechanical stimuli. The external stimuli, touch and sound, are detected by receptors located in the skin and hair cells of the inner ear, respectively. The internal mechanoreceptors in the vascular system, muscle, tendon, organs and joints, and in the urinary bladder detect stretch and pressure stimuli. Among them, the most intensely studied mechanoreceptors are the hair cells and those located in the skin.

**Hair cells** are located in the organ of Corti in the internal ear and they transduce sound and head movements into neuronal signals. The mechanosensory structure of the hair cell consist of a bundle of cilia emerging from the surface of the hear cells (Fig. 7.2f, upper panel), a bundle that contains 30–300 stereocilia and a single kinocilium (Fig. 7.2f middle panel). The stereocilia are connected to each other by a spring protein strand called the tip link, which is thought to be attached to ion channels. The model of mechanotransduction in hair cells proposes that the stimulus produces a deflection of the kinocilia and the associated stereociliary bundle that stretches the tip link. This increase in tension opens ion channels, increasing the inward currents and depolarizing the cells, thereby triggering neurotransmitter release (Fig. 7.2f lower panel) (for extensive reviews see Garcia-Añoveros and Corey 1997; Gillespie and Muller 2009).

Many genes affecting the development and function of hair cells have been identified (http://www.jax.org/), some of which were detected due to spontaneous mutation or systematic mutagenesis causing deafness and/or balance defects (Hrabe de Angelis et al. 2000; Nolan et al. 2000; Shearer and Smith 2012). However, identifying the transduction molecules is proving to be more difficult. Evidence has recently supported a direct role for TMC1 and TMC2, members of the transmembrane channel-like family, as components of the transduction complex (Kawashima et al. 2011; Pan et al. 2013; Kim et al. 2013), although it remains uncertain whether TMC1 and 2 are pore-forming subunits and their specific role has yet to be clarified (Morgan and Barr-Gillespie 2013; Holt et al. 2014). Other channels that are candidates to participate in transduction in vertebrate hair-cells are the members of the TRP superfamily, TRPN1, TRPML3, TRPV4 and TRPA1, as will be discussed later on in this chapter.

Interestingly, novel mechanical activated currents have been recorded in auditory hair cells lacking tip links. These currents have different properties to those recorded when tip links are functional and the channels responsible is not yet clear. Nevertheless, it has been suggested that normal mechanotransducer channels with an altered distribution or configuration may be involved in producing such currents, as well as ion channels other than mechano-electrical transducer channels, or trans-

duction complex elements other than the TMC1 and TMC2 proteins (Marcotti et al. 2014). Further research should shed light on the identity of these new channels.

**The somatosensory system** in mammals is formed by neurons that innervate the skin, muscle, joints, tendons and internal organs, and that are responsible for the perception and transmission of physical and chemical stimuli originating outside and inside the body. The cell body of these neurons are situated in the dorsal root ganglia (DRG) and trigeminal ganglia (TG), receiving information coming from the body and head, respectively. Transmission of afferent somatosensory information from the periphery to the brain commences with the depolarization of a sensory neuron's terminal, caused by the activation of sensory receptors. These cells include distinct types of mechanoreceptors in function of their anatomy (localization and type of end terminals), their response properties (slow or rapid firing and sensory threshold) or their axonal conduction velocities (myelinated or unmyelinated axons). An important distinction among mechanosensitive neurons is related to the stimulus intensity required to activate their terminals. While some terminals are very sensitive to touch or mechanical displacement, low threshold mechanoreceptors (LTMR), others require stimulation above a high threshold for activation, high threshold mechanonociceptors (HTMRs). Many of the mechanonociceptors are also excited by chemical and thermal stimuli and they are called polymodal nociceptors. Mechanically-evoked nerve impulse discharges are absent in "silent" nociceptor nerve fibres, although they are recorded following local tissue inflammation. The majority of nociceptive fibres are Aδ (myelinated) and C (unmyelinated) type, which terminate with free endings in the tissue they innervate. In terms of the LTMR, the cutaneous receptors are those best known and they can be classified either as Aδ and C fibres whose endings are free nerve terminals, including the D-hair, and as Aβ (myelinated) fibres that terminate in different structures: Pacinian corpuscles, Ruffini endings, Meissner corpuscles (as described in several reviews: Lumpkin and Caterina 2007; Lumpkin et al. 2010; Abraira and Ginty 2013) (Fig. 7.3a). In addition, Merkel's discs have also been shown to function as mechanoreceptors, forming a complex structure with slowly adapting afferents (Maksimovic et al. 2014).

A major issue that is still to be resolved is the identity of the molecules that transduce mechanosensory stimuli, and whether the changes in threshold reflect the activation of different molecular sensors, the differential modulation of the same sensor, or differences in the density or coupling efficiency between the sensor and perireceptor elements. An important reason for the lack of progress regarding these issues is the very small diameter of the mechanosensory terminals and the dispersion of touch receptors in the skin. These factors have prevented the direct recording of mechanogated currents at the site of transduction. In the absence of this type of recordings, different groups have recorded three types of mechanosensory currents from the soma or dendrites of DRG neurons with different kinetics of adaptation: rapidly adapting (RA), intermediately adapting (IA) and slowly adapting (SA: McCarter et al. 1999; Drew et al. 2002; Hu and Lewin 2006; Hao and Delmas 2010) (Fig. 7.3b). Indeed, mechanically activated currents with similar properties have also been recorded in trigeminal neurons (our unpublished results). Some progress
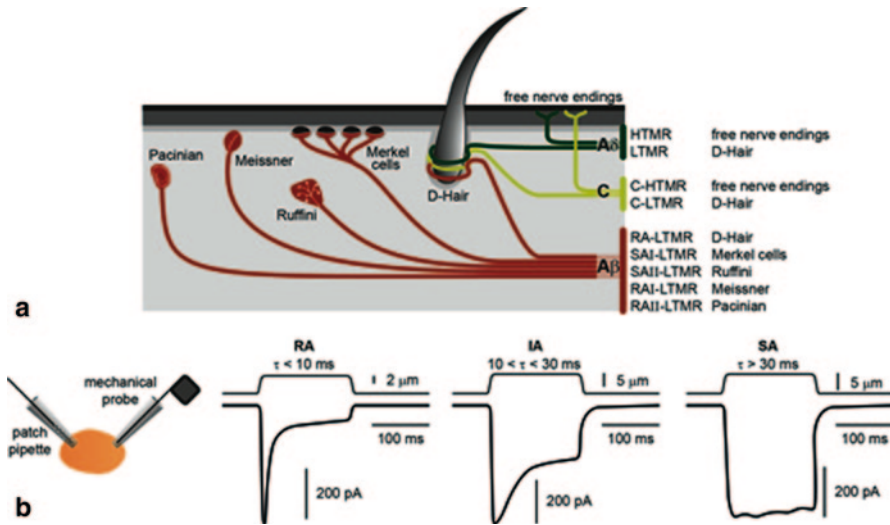
**Fig. 7.3** Cutaneous touch receptors and mechanosensitive currents in mammals. **a** Sensory afferents of neurons innervating skin propagate electrical impulses from the body to the central nervous system. Afferents are classified as Aβ (*red*), Aδ (*green*) or C (*yellow*) based on their cell body sizes, axon diameter, degree of myelination and axonal conduction velocities. Most Aβ fibres have low mechanical thresholds and Aδ and *C* fibres respond either to noxious stimuli or light touch, each with different physiological profiles and firing patterns (slowly (SA) and rapidly adapting (RA)). The peripheral afferents terminate in different end organs, Merkel cell-neurite complexes, Ruffini endings, Meissner corpuscles, Pacinian corpuscles and hair follicles, and in free nerve ending. **b** Graphical representation of inward mechanosensitive rapidly-adapting, intermediate-adapting and slowly-adapting currents expressed in mice DRG neurons using the mechano-clamp technique (shown in the *left panel*) at holding potential of −80 mV. Standard mechanical stimuli and time constants of current decay are indicated above the current trace of each panel

has also been made in identifying the mechanotransduction molecules. As such, ASIC 1–3 are expressed in peripheral neurons, although their role in mammalian mechanotransduction is not fully clear (Drew et al. 2004; Roza et al. 2004; Lingueglia 2007). Piezo proteins are pore-forming subunits of a conserved mechanical activated cation family which have recently been considered to be the most promising mechanotransducers candidate (Coste et al. 2010; Coste et al. 2012). In mammals, Piezo1 is necessary for mechanical activated currents in the Neuro2A cell line (Coste et al. 2010) and Piezo2 mediates the mechanical responses in Merkel-cells, evidence of a physiological role in mammalian mechanotransduction (Woo et al. 2014; Maksimovic et al. 2014; Ikeda et el. 2014). Nevertheless, the involvement of TRP channels in mechanotransduction cannot be ruled out, as discussed below.

Mechanotransduction also plays a fundamental role in the **vascular and renal system, and the urinary bladder** among others. These systems are permanently subjected to mechanical forces, such as shear stress and pressure, and impaired handling of these stimuli in these systems can cause severe pathologies. Many studies have focused on the molecular mechanisms of mechanical stretch in visceral

systems and thus, this issue will not be addressed in this chapter (for reviews see Haga et al. 2007; Lehoux et al. 2006; Li and Xu 2007; Orr et al. 2006; Shyu 2009; Hahn and Schwartz 2009; Weinbaum et al. 2010). Mechano-gated ion channels play a key physiological role in the visceral system including Piezo1, that plays a critical role in endothelial cell mechanotransduction (Ranade et al. 2014), and the TRP channels. This family of channels that are expressed in different cell types within the heart, kidney and bladder we will now centre out attention on.

## 7.3   Mechanosensory TRP Channels

The channel proteins that belong to the TRP family appear to mediate many forms of sensory perception, the reason why they are the focal point of the reviews in this book. There is some controversy as to whether mechanosensitive TRP channels are activated directly or if they are specifically involved in mechanical signalling. Moreover, piezo2 was recently shown to be required for Merkel cell mechanotransduction. Still, there is strong genetic evidence that a variety of TRP channels contribute to mechanosensation (Table 7.1). This includes evidence from loss-of-

**Table 7.1**  Mechanosensory channels

| Molecular identity | Family | Organism | Mechanosensitivity |
|---|---|---|---|
| TRPA1 | TRPA | Mammals, worm, fly | Pressure, stretch, osmolarity & touch |
| TRPC1 | TRPC | Mammals/*Xenopus* | Touch, stretch, osmolarity & shear stress |
| TRPC3 | TRPC | Mammals | Gentle touch & audition |
| TRPC5 | TRPC | Mammals | Osmolarity & pressure |
| TRPC6 | TRPC | Mammals | Osmolarity, pressure, touch & audition |
| TRPV1 | TRPV | Mammals | Stretch & osmolarity |
| TRPV2 | TRPV | Mammals | Stretch & osmolarity |
| TRPV4 | TRPV | Mammals | Noxious pressure, shear stress, osmolarity & stretch |
| TRPM3 | TRPM | Mammals | Osmolarity |
| TRPM4 | TRPM | Mammals | Osmolarity |
| TRPM7 | TRPM | Mammals | Osmolarity |
| TRPN1 | TRPN | Fly, fish & amphibian | Touch & audition |
| OSM-9/OCR-2 | TRPV | Worm | Osmolarity, audition & touch |
| TRPP2 | TRPP | Mammals, worm, fly | Pressure, osmolarity & shear force |
| TRPML3 | TRPM | Mammals, worm, fly | Audition |

function mutations in organisms ranging from invertebrates to zebra fish, and from mice and humans (Christensen and Corey 2007; Eijkelkamp et al. 2013) .

## 7.3.1 TRPA1

The ankyrin-repeat channel TRPA1 is strongly conserved in the animal kingdom and it is found in many vertebrates and invertebrates. The *C elegans* TRPA1 is activated by mechanical stimulus, suggesting a role for TRPA1 in mechanosensation (Kindt et al. 2007). Indeed, TRPA1 is required for normal responses to nose-touch, and for a specific foraging behaviour of the worm in the presence of food that consists of high frequency and local exploratory movements of the head. In *Drosophila* larvae that lack *Painless*, the invertebrate orthologue of TRPA1, mechanical nociception is dampened (Tracey et al. 2003). It has been suggested that distinct isoforms of *painless* are responsible for specific sensory modalities that require its function. Moreover, the function of *painless* in noxious mechanosensation is independent of its ankyrin repeats as this phenotype is reverted after the introduction of a short isoform of the *painless* gene in mutant flies (Hwang et al. 2012).

In mammals, TRPA1 is expressed in sensory neurons of the dorsal root, trigeminal and nodose ganglia, and in many organs and tissues, including the brain, inner ear, smooth and skeletal muscle, and pancreas (Nilius et al. 2012). TRPA1 was initially a strong candidate to act as the hair cell transduction channel in vertebrates (Corey et al. 2004) on the basis of three main observations: (i) TRPA1 is expressed in the hair cells of both the cochlea and the vestibular system; (ii) TRPA1 messenger RNA transcripts appear on embryonic day 17, coinciding with the onset of mechanotransduction; and most importantly, (iii) disruption of TRPA1 expression in zebra fish with morpholino oligonucleotides, and in mice with small-interference RNA, strongly inhibits hair cell mechanotransduction. TRPA1 was also found to be expressed in the free nerve endings and in the bundles of stereocilia, leading to the proposal that it fulfils a role in both nociceptive and auditory cell function (Nagata et al. 2005). However, subsequent studies in zebrafish larvae lacking the orthologues of mammalian TRPA1 exhibited normal mechanosensory hair cell function (Prober et al. 2008). In addition, hearing and vestibular function is normal in two different TRPA1$^{-/-}$ mouse lines (Kwan et al. 2006; Bautista et al. 2006), although these two lines have a conflicting nociceptive responses. One of these lines exhibited pain hypersensitivity (Kwan et al. 2006), TRPA1$^{-/-}$ mice displaying a higher mechanosensory pain threshold than their TRPA1$^{+/+}$ littermates as well as a weaker response to supra-threshold stimuli. By contrast, no difference in the mechanical threshold was detected between TRPA1$^{-/-}$ and wild type animals in the other line (Bautista et al. 2006).

More evidence of a role for TRPA1 in sensing mechanical stimuli has been obtained through recordings in the skin-nerve preparation from TRPA1$^{-/-}$ (Kwan et al. 2009). In the absence of TRPA1 both C and AM fibre nociceptors had a lower firing rate at all force intensities and for noxious force, respectively. TRPA1 was

expressed in many medium to large DRG somata and on large-calibre axons associated to Aβ-fibres, and hence it was concluded that TRPA1 reduced the slow adaptation to sustained force in Aβ-fibres but increased the firing of D-hair and RA Aβ-fibres (Kwan et al. 2009). Moreover, pharmacological inhibition of TRPA1 using the selective antagonist HC-030031 and genetic ablation has shown that cutaneous C fibres require TRPA1 to respond to noxious stimulus evoked by formalin application, as well as to high intensity mechanical forces. However, HC-030031 had no effect on mechanical firing in nociceptive Aδ fibres (Kerstein et al. 2009).

The contribution of TRPA1 to mechanical sensitivity was also assessed by studying the mechanically-gated currents in cultured DRG neurons induced by applying an electrically driven mechanical probe to the cell membrane. TRPA1 deletion in knockout mice significantly reduces the maximum IA currents in small-diameter neurons, producing no effect on the RA and SA currents in small and large neurons. Moreover, the inhibitor HC-030031 significantly decreases IA current amplitude in wild type mice activated by the TRPA1 agonist AITC (Brierley et al. 2011). Similarly, SA currents were absent in IB4 negative neurons from TRPA1$^{-/-}$ mice and the amplitude of RA and IA currents in IB4 positive neurons from TRPA1$^{-/-}$ mice was reduced by over the 60 %. Moreover, HC-030031 was only seen to dampen SA currents wild type mice (Vilceanu and Stucky 2010). Together, it seems that TRPA1 mainly participates in SA and IA currents.

So far, direct evidence of TRPA1 activation by mechanical forces has only been obtained in HEK cells transiently expressing TRPA1, and only in response to a hyperosmotic solution but not to a hypoosmotic solution (Zhang et al. 2008). By contrast, TRPA1 does contribute to the $Ca^{2+}$ influx evoked by hypoosmotic stimulation-induced plasma membrane stretching in Merkel cells from hamster buccal mucosa (Soya et al. 2014). TRPA1 also plays a role in the mechanical hyperalgesia and allodynia induced by the gasotransmitter hydrogen sulphide in mice (Okubo et al. 2012) and in the mechanical hyperalgesia caused by a deep-tissue incision in the rat hind paw (Wei et al. 2012). Mechanical hyperalgesia induced by Freund's adjuvant in wild type mice was strongly reduced by blocking TRPA1 with the small molecule, AP18. However, the fact that AP18 does not prevent Freund's adjuvant-induced mechanical hyperalgesia in TRPA1$^{-/-}$ mice may suggest that TRPA1 is involved in the maintenance of mechanical hyperalgesia rather than its generation (Petrus et al. 2007).

Several studies point to a role of TRPA1 in visceral mechanotransduction. TRPA1 is expressed in the rodent and human bladder, and activation of TRPA1 by agonists or changes in its expression is associated with bladder dysfunction (Du et al. 2007, 2008; Streng et al. 2008). A role for TRPA1 in noxious colonic distension was also reported (Brierley et al. 2009).

Together, these results suggest that TRPA1 plays a role in mechanosensation although it remains to be determined whether it acts as a mechanical sensor or if it indirectly participates in mechanosensation by amplifying or modulating the signal from the transduction channel.

## 7.3.2  TRPC

Examining the mechanosensitivity of TRP channels in heterologous system has provided conflicting data in some instances. This is certainly the case of **TRPC1** which was first considered to be a mechanosensitive non-selective cation channel (MscCa) given that application of positive and negative pressure resulted in a large increase in current that can be attributed to MscCa in *Xenopus* oocytes and in CHO-K1 cells transfected with human TRPC1 (Maroto et al. 2005). However, a study published 3 years later showed the difficulties of testing mechanosensitivity in heterologous systems due to the background mechanical activity observed in cell lines (Gottlieb et al. 2008).

To date, the only proven role of TRPC1 in mechanosensation was described by studying the recordings of the afferent terminals that innervate the hairy skin of TRPC1$^{-/-}$ mice (Garrison et al. 2012). In these animals there was an ~40% reduction in action potential firing of SA-Aβ fibres in response to forces at intensities lower than 4–200 mN yet not in the RA-Aβ fibres. A reduction of 50% in the discharges was observed in the D-hair Aδ fibres, whereas C-fibres and nociceptive AM fibres innervating hairy skin responded normally to noxious mechanical stimulation in TRPC1$^{-/-}$ mice, meaning that TRPC1 does not play significant role in cutaneous mechanical nociception. However, in a behavioural light-touch test a significant decrease in mechanical sensitivity was evident in TRPC1 deficient mice compared to wild type mice (Garrison et al. 2012). More recent findings indicate a reduced static firing rate of SA-Aδ fibres and a moderate decrease in the behavioural response to light touch in an epidermal piezo2 knockout mice (Maksimovic et al. 2014). These latter data might suggest that TRPC1 and piezo2 mediate mechanotransduction in Merkel cells.

Within the cardiovascular system, pressure-induced constriction of cerebral arteries in smooth muscle cells is unaffected in TRPC1 knock-out mice, indicating that TRPC1 is not an obligatory component of stretch-activated ion channel complexes in vascular smooth muscle (Dietrich et al. 2007).

**TRPC3** has been implicated in the kinetics of mechanical activated currents, given that the proportion of sensory neurons that display IA currents increased in TRPC3$^{-/-}$ mice while those responding with RA currents decreased (Quick et al. 2012). Interestingly, TRPC3 was also attributed a role in the detection of light touch when it forms a complex with TRPC6. Indeed, there were deficits in innocuous mechanosensation in the TRPC3 and TRPC6double knockout mice but not in the single KO mice. There was also a significant decrease in the proportion of neurons displaying RA currents in these double KO animals, and elimination of TRPC3 and TRPC6 also produced hearing deficits (Quick et al. 2012).

Mechanical activation of **TRPC6** has been addressed, and it was reported that osmotic and pressure-induced membrane stretch directly activates the TRPC6 channel expressed in heterologous systems. The fact that TRPC6 is strongly expressed in vascular smooth muscle cells made it a candidate mechanotransducer in smooth muscle (Spassova et al. 2006). However, later studies demonstrated the activation

of TRPC6 through a Gq/11-coupled protein receptor (Schnitzler et al. 2008; Inoue et al. 2009; Sharif-Naeini et al. 2010). TRPC6 has also been involved in kidney regulation via podocin modulation, a protein involved in the function of the filtration barrier in the mammalian kidney. However, the implication of podocin in mechanosensation is in any case speculative, such that the participation of TRPC6 and other members of the TRPC subfamily is probably indirect (Huber et al. 2006).

**TRPC5** has been proposed to act as a direct sensor of lysophospholipids (Flemming et al. 2006), suggesting that this channel is sensitive to the structure of the lipid bilayer.We characterized the activation of **TRPC5** in response to hypoosmotic stimulation and positive pressure in a heterologous system expressing TRPC5. This activation is blocked by the tarantula peptide GsMTx-4, a specific inhibitor of stretch activated channels, and it is independent of PLC activation (Gomis et al. 2008). Interestingly TRPC5 is also activated by applying force to the cell's surface via a glass pipette controlled by a piezo-electric system, provoking currents with RA kinetics (unpublished data). TRPC5 channels are expressed in trigeminal and DRG neurons, suggesting a possible role in mechanotransduction, although their physiological role in mechanotransduction and osmotic regulation remains to be clarified.

### 7.3.3   TRPV

Several TRPV channels have been described to be sensitive to mechanical stimulus or volume/osmotic change. **TRPV1** is required for osmosensory transduction in the organumvasculosum lamina terminalis, a primary osmosensor nucleus in the brain (Ciura and Bourque 2006; Ciura et al. 2011). Although controversial, the TRPV1 channel has been implicated in mechanical hypersensitivity as a consequence of inflammation, heat injury or nerve ligation (Honore et al. 2005; Bolcskei et al. 2005). The reason for the discrepancies observed is not clear but it is possible that TRPV1 may be involved in cutanous mechanical hyperalgesia through an indirect mechanism rather than as a direct noxoius mechanical sensor. The involvement of TRPV1 in mechanical hyperalgesia is more obvious in deeper tissues than in cutanous pain.

**TRPV2** is expressed in mesensteric and basilar arterial myocytes and it is activated by membrane stretch in TRPV2-CHO cells. Therefore, it would seem that TRPV2 can function as a stretch-activated channel in vascular smooth muscle (Muraki et al. 2003), although studies in intact arteries are still needed to confirm the physiological role of TRPV2. Studies in somatosensory systems indicated that TRPV2 is not essential in mechanical nociception (Park et al. 2011).

**TRPV4** was first reported as an osmotically activated channel over a decade ago, when it was shown that the osmotic stimulus activates the TRPV4 (previously known as VR-OAC or OTRPC4) expressed in HEK and in CHO cells (Liedtke et al. 2000; Strotmann et al. 2000; Wissenbach et al. 2000). However, a subsequent study failed to find significant activation of TRPV4 expressed in CHO cells by hy-

poosmotic stimulation (Suzuki et al. 2003), while the activation of TRPV4 by cell swelling was seen to occur through the PLA2-dependent formation of arachidonic acid and its subsequent metabolism to 5',6'-epoxyeicosatrienoic acid (Vriens et al. 2004). The contribution of TRPV4 *in vivo* was studied by expressing the mammalian TRPV4 in *C elegans* sensory neurons and using TRPV4$^{-/-}$ mice. TRPV4 is required for nose touch avoidance in *C elegans* (Liedtke et al. 2003) and its loss markedly reduced the sensitivity of the mouse tail to pressure (Suzuki et al. 2003). Hypotonic solutions activate 54% of C-fibres in rats and the effect of hypoosmotic stimulation is more effective in inflammation states, suggesting that TRPV4 plays an important role in mechanical hyperalgesia (Alessandri-Haber et al. 2003; Alessandri-Haber et al. 2006). Moreover, proteases generated during inflammation cause mechanical hyperalgesia through TRPV4 sensitisation (Grant et al. 2007). Interestingly, interactions between different TRP channels, such as TRPC1, TRPC6 and TRPV4 contribute to the development of mechanical hyperalgesia, although they may fulfil different roles (Alessandri-Haber et al. 2009).

TRPV4 is expressed in hair cells and thus, the role of TRPV4 in the transduction of acoustic stimuli has also been studied. The cochlea of TRPV4$^{-/-}$ mice has a normal morphology but these animals develop late-onset hearing loss, which is similar to the autosomal dominant non-syndromic hearing loss in humans, and loss of TRPV4 makes the cochlea vulnerable to acoustic injury (Tabuchi et al. 2005). There is also evidence of a possible role for TRPV4 in skeletal muscle fibres. Recordings of single channel activity showed that hypoosmotic solutions activate mechanosensory channels and the absence of mechanosensory activity in the muscle of TRPV4$^{-/-}$ mice (Ho et al. 2012). However, the implication of other TRP channels forming heteromeric proteins with TRPV4 cannot be ruled out.

### 7.3.4   TRPM

Three members of the TRPM subfamily have been implicated in osmosensation: the **TRPM3** channel that is expressed in the odontoblast (Son et al. 2009) and kidney (Grimm et al. 2003); **TRPM4** in blood vessels (Morita et al. 2007) and that has been implicated in cerebral blood flow regulation (Reading and Brayden 2007); and **TRPM7** that is expressed in human epithelial HeLa cells and is thought to be involved in regulation associated with a volume decrease (Numata et al. 2007). Although these data imply an inherent stretch or mechanosensitivity of these channels, further studies are necessary to define the functional role of these channels in mechanotransduction.

### 7.3.5   TRPN1

The *nompC* gene encodes the **TRPN1** channel in *Drosophila melanogaster* and it is involved in touch, hearing and proprioception. Mutations, in this gene result in de-

ficiencies in bristle mechanotransduction (Kernan et al. 1994; Walker et al. 2000). However, while TRPN1 is an excellent candidate mechanotransduction channel in flies and fish, *nompC* homologues have not been found in the mammalian genome (Sidi et al. 2003; Shin et al. 2005; Li et al. 2006).

## 7.4   Concluding Remarks

Since their discovery three decades ago, TRP channels have been shown to participate in a number of different sensory processes. Still, our understanding of the functional roles of this ion channel superfamily is limited in comparison to what we know about those of ligand- and voltage-activated channels. Progress included the discovery of the involvement of some of the TRP channels in the detection of mechanical forces, although as discussed previously in this chapter, the activation mechanisms and functional significance of TRP channel's contribution to mechanotransduction is still under discussion. This is not surprising, considering that, as occurs in other cell types, diverse members of the TRP superfamily responding to mechanical energy are expressed by sensory neurons. Moreover, TRP proteins may interact forming heteromultimeric complexes. The expected functional redundancy of TRP channels participating in mechanosensation complicates the definition of the individual functional role of each channel in mechanical stimulus detection.

The identification of the molecules and/or transduction mechanisms that allow sensory neurons to diferentiate stimuli of low and high intensity *in vivo* is still an important unanswered question in mechanotransduction. It is possible that non-nociceptive and nociceptive neurons express different ion channels, or the same channels but with different density.

Other factors aside from neuron sensitivity may also determine its ability to detect stimuli of different intensity, as for example a filtering of the stimulus by perireceptor structures, which could distort the efficiency of final transmission of mechanical force to the channel.

This chapter has offered a brief overview of the potential contribution of various members of the TRP channel superfamily to mechanical transduction in the somatosensory system, which leads ultimately to mechanosensation. It is evident that further work is required to fully understand the molecular and cellular processes underlying the different modalities of mechanosensation evoked by activation of the various functional classes of mechanosensitive cells, and the contribution to these processes of TRP channels.

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