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David P. Corey

J. Physiol. 2006;576;23-28; originally published online Aug 10, 2006;

DOI: 10.1113/jphysiol.2006.116582

Topical Review

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David P. Corey

Howard Hughes Medical Institute and Department of Neurobiology, Harvard Medical School, 220 Longwood Avenue, Boston, MA 02115, USA

In contrast to nearly all other sensory systems, the mechanically sensitive ion channel carrying the receptor current into hair cells of the inner ear has not been identified in molecular terms. A number of candidates from at least two different ion channel families have been considered: these include the epithelial sodium channel (ENaC) and acid-sensing ion channel (ASIC) members of the DEG/ENaC superfamily of amiloride-sensitive sodium channels, as well as the TRP channels TRPN1, TRPV4, TRPML3 and TRPA1. For each, initial supportive results were followed by further studies that cast doubts on their involvement. No promising candidates have recently emerged, but the TRP family continues to be attractive in general.

(Received 5 July 2006; accepted after revision 8 August 2006; first published online 10 August 2006)
Corresponding author D. P. Corey: Howard Hughes Medical Institute and Department of Neurobiology, Harvard Medical School, 220 Longwood Avenue, Boston, MA 02115, USA. Email: dcorey@hms.harvard.edu

The ion channels carrying the stimulus-activated receptor current in sensory neurons have been identified and the mechanism of their activation elucidated, for a variety of sensory systems and for species ranging from worms and flies to humans. In striking contrast are those mediating hearing and balance in vertebrates – the hair-cell transduction channels. Hypothesized as a distinct class of ion channel and characterized biophysically more than 20 years ago (Corey & Hudspeth, 1983), they have been the object of a continuous quest since then. In the past 10 years, a variety of candidates have appeared, only to disappear, wraith-like, in the clear light of further experiments. At the present time we do not know the molecular identity of the transduction channel, but these previous apparitions are bringing us closer to an answer.

We know very well what the hair cell transduction channel should look like, in physiological terms. It is a non-selective cation channel that is permeable to all the alkali cations and to many divalent cations (Corey & Hudspeth, 1979; Ohmori, 1985). The channel has a particularly high calcium permeability, passing Ca^{2+} at least 10 times better than Na^{+} (Lumpkin *et al.* 1997; Ricci & Fettiplace, 1998); at the same time, Ca^{2+} in millimolar concentrations acts as a partial blocker, inhibiting current by monovalent ions. Remarkably, the channel is also permeable to small organic cations, even fluorescent styryl dyes like FM1-43 of molecular weight > 450 Da (Corey & Hudspeth, 1979; Gale *et al.* 2001; Meyers *et al.* 2003; Farris *et al.* 2004). There are no highly specific blockers: amiloride and its analogues, as well as aminoglycosides, block at low micromolar concentrations in a voltage-dependent manner. The block is relieved at more negative potentials (Jorgensen & Ohmori, 1988; Kroese *et al.* 1989; Rusch *et al.* 1994) suggesting that these charged compounds can be driven through the channel by voltage (Marcotti *et al.* 2005). A systematic study of blockers indicated that the pore is ∼1.3 nm in diameter at its narrowest, with a larger vestibule extending ∼1.5 nm in from the outside (Farris *et al.* 2004). Perhaps consistent with the lack of selectivity, the conductance of the channel is large, ranging from 100 to 300 pS or more (Crawford *et al.* 1991; Geleoc *et al.* 1997; Ricci *et al.* 2003). That the conductance can vary by 3-fold or more in different hair cells from a single organ (Ricci *et al.* 2003) was quite unexpected, but it puts further constraints on prospective candidates.

As there are no high-affinity ligands for the transduction channel (and probably not enough channel protein in the tissue to sequence even if it could be affinity purified), a variety of indirect strategies have been used to search for the transduction channel. These include searches for genes that cause deafness when mutated, searches for channels related to mechanosensory channels in other organs, and searches for channels with similar selectivity and permeability.

Amiloride-sensitive sodium channels

Following initial observations that amiloride reduced the sensitivity of lateral line hair cells, Jorgensen & Ohmori (1988) used single-cell recordings to show that amiloride blocks the channel in a voltage-dependent manner. The half-blocking concentration is nearly 100-fold higher for hair cells than for the amiloride-sensitive sodium channels of transporting epithelia (the ENaC channels);

 DOI: 10.1113/jphysiol.2006.116582

nevertheless this raised interest in ENaCs as candidates for the transduction channels. Hackney *et al.* (1992) used an antiserum raised against a biochemically purified ENaC for immunogold labelling of stereocilia, and found the highest density of immunoreactivity at the point of closest apposition between adjacent stereocilia. With electron microscopy, this could be distinguished from the location of the tip links (just above the apposition), where channels are thought to be located (Pickles *et al.* 1984).

Interest in the ENaC family of channels was raised considerably when Rossier and colleagues cloned the α, β and δ subunits of the ENaC channel from rat colon (Canessa *et al.* 1993, 1994), and recognized that they were part of a gene family that also included two proteins, MEC-4 and MEC-10, which are defective in mechanosensation mutants of the nematode *C. elegans* (Chalfie & Sulston, 1981; Chalfie & Au, 1989). A related protein, DEG-1, causes degenerative neuronal death when certain residues are mutated, conferring the name 'degenerins' or DEGs to this channel family in worms (Chalfie & Wolinsky, 1990) and contributing to the rather cumbersome name DEG/ENaC for the channel superfamily (Corey & García-Añoveros, 1996). Chalfie *et al.* (1993) revealed more extensive sequence similarity between the two channel groups, and suggested in addition that the hair cell transduction channel might be an ENaC.

Several groups then searched for ENaCs or related channels in mammalian tissues, leading to the discovery of αENaC isoforms in the chick cochlea (Killick & Richardson, 1997), and to the discovery of another branch of the DEG/ENaC family in mammals, now termed the ASICs (Price *et al.* 1996; Waldmann *et al.* 1996; García-Añoveros *et al.* 1997). A number of the ASIC channel subunits are expressed by mechanosensory neurons of the dorsal root and trigeminal ganglia and are transported to the sensory endings in skin (e.g. García-Añoveros *et al.* 2001), suggesting that they may constitute mechanically activated ion channels.

Despite these intriguing findings, problems soon arose that cast doubt on the involvement of DEG/ENaCs in hair-cell transduction. First, the DEG/ENaC channels have too low a conductance (10–15 pS), too high a Na^+ selectivity ($P_{Na}/P_K = 5$–100), and too low a Ca^{2+} permeability ($P_{Ca}/P_K < 0.4$) (Kellenberger & Schild, 2002) to be consistent with the hair cell transduction channel. In addition, knockout mice seem to have normal inner ear function. Rusch & Hummler (1999) found that αENaC knockout mice had normal vestibular behaviour, and normal receptor currents in cochlear outer hair cells. ASIC2 knockouts have normal hearing, as measured by the auditory brainstem-evoked response (ABR) (Peng *et al.* 2004; Roza *et al.* 2004), and ASIC1 and ASIC3 knockouts have no reported auditory or vestibular deficit (Xie *et al.* 2003). At this point, there is no support for involvement of the DEG/ENaCs in hair cell transduction.

NOMPC (TRPN1)

A genetic screen for mechanosensation genes in *Drosophila* revealed another candidate ion channel family. Kernan *et al.* (1994) found five '*nomp*' genes whose mutation caused *no m*echanoreceptor *p*otential in the bristle organs. One of them, *nompC*, was found to encode a protein homologous to members of the transient receptor potential (or TRP) family of ion channels (Walker *et al.* 2000), a group of channels typified by a large conductance and a high Ca^{2+} permeability appropriate for the hair cell channel (Owsianik *et al.* 2006). *nompC* is expressed in the sensory bristle complexes in *Drosophila* and a homolog is in mechanosensory neurons in *C. elegans*. Three *nompC* alleles had nonsense mutations; in those the large, transient part of the mechanoreceptor potential is absent. A fourth had a missense mutation that causes the transient to be faster, suggesting that nompC is itself a mechanically gated ion channel or is intimately associated with it (Walker *et al.* 2000). While there is presently no additional evidence for the function of nompC in bristle mechanotransduction, the involvement of a TRP channel in a ciliated mechanosensory organ not unlike a hair cell focused new attention on the TRP channel family.

Although the nompC (now TRPN1) channel was initially thought to be restricted to invertebrate animals, Sidi *et al.* (2003) found an ortholog in the zebrafish genome. *In situ* hybridization showed weak expression in inner ear hair cells by 48 h post-fertilization, when hair cells begin to show mechanosensitivity in zebrafish. To inhibit normal expression of zebrafish TRPN1, Sidi *et al.* injected fertilized eggs with morpholino oligonucleotides targeting the splice donor site of exon 28, so that missplicing would delete the transmembrane domains. Successful disruption of the mRNA in morphant fish was detected by PCR. Morphants lacked an 'acoustic' startle response elicited by tapping the dish, and they swam in circles or sideways suggesting vestibular dysfunction. In fish that lacked the startle response, hair cells of the lateral line neuromast organs did not accumulate the fluorescent dye FM1-43, a marker of functional transduction channels, and they did not generate a microphonic potential when stimulated with sinusoidal fluid flow. In these experiments, however, relatively large amounts of morpholino were injected, and although the fish studied had no visible morphogenic defects there may have been off-target effects that were undetected and that non-specifically affected hair cell function.

TRPN1 has also been detected in two frog species: *Xenopus laevis* (Shin *et al.* 2005) and *Rana catesbeiana* (D. Tamasauskas, K. Y. Kwan and D. P. Corey, unpublished observation). A good antibody to the *Xenopus* TRPN1 labelled the lateral line hair cells of stage 48 embryos and saccular hair cells of adult *Xenopus*. However, the label was detected in the kinocilia, but not in the stereocilia

of saccular hair cells where the most or all of the transduction channels are located (Shin *et al.* 2005). Another class of ciliated epidermal cells was strongly labelled in *Xenopus*, supporting the association of TRPN1 with microtubule-based cilia. Perhaps TRPN1 in kinocilia is somehow involved in the mechanical coupling of the mechanical stimulus to the stereocilia bundle, which could explain a hearing deficit in morphant zebrafish.

Whatever the role of TRPN1 in fish and frogs, it cannot be part of the transduction channel in all vertebrates. The TRPN1 gene is entirely absent (and not simply a pseudogene) in mammals and birds, and is also missing in some other fishes (the pufferfishes *Fugu rubripes* and *Tetraodon nigroviridis*).

TRPV4

A genetic screen in *C. elegans* for genes involved in osmotic sensation revealed a new TRP channel, Osm-9, related to the vertebrate capsaicin receptor, TRPV1. Heller and colleagues (Liedtke *et al.* 2000), then screened a chicken inner ear library and mammalian brain and kidney libraries for additional homologs of Osm-9 and TRPV1. They discovered (simultaneously with three other groups) a channel now known as TRPV4. TRPV4 is expressed in most cells lining the endolymphatic duct of the mouse ear, including the hair cells and the marginal cells of the stria vascularis (Liedtke *et al.* 2000; Shen *et al.* 2006). TRPV4 is mechanically sensitive, in that it is activated by osmotic cell swelling and by fluid flow. It is also activated by heat and by phorbol esters (see O'Neil & Heller, 2005 for review). Like the hair cell transduction channel, it has a high Ca^{2+} permeability and a conductance of about 90 pS (Owsianik *et al.* 2006). Finally, TRPV4 knockout mice have a hearing deficit (Tabuchi *et al.* 2005).

While TRPV4 was an intriguing possibility, there was doubt about its role in transduction from the beginning (Liedtke *et al.* 2000). The strongest expression in the cochlea is not in hair cells but in the stria, which is a transporting epithelium and where an osmoregulatory role makes sense. Its activation by mechanical stimuli is slow, suggestive of a second messenger intermediate and inconsistent with transduction (O'Neil & Heller, 2005). Also the deficit in the mouse knockout only appears at several months of age, and represents no more than about 20 dB of threshold shift (Tabuchi *et al.* 2005).

TRPML3

A large number of mutant mice exhibit hearing loss, sometimes in combination with other deficits, and some of the affected genes have been identified. For instance, Varitint waddler mutant mice have pigmentation defects, and also show deafness and circling behaviour that is attributable to progressive cytoplasmic pathology of the hair cells and disorganization of hair cell stereocilia in the cochlea (Cable & Steel, 1998; Di Palma *et al.* 2002). Both alleles of Varitint waddler (Va and Va^J) act in a semi-dominant manner, with hearing loss and stereocilia disorganization in heterozygotes; Va homozygotes are usually lethal but Va^J homozygotes are not. The mutated gene is most probably that encoding another TRP channel, TRPML3 or mucolipin-3 (Di Palma *et al.* 2002). The more severe Va allele has a single amino acid substitution (A419P) near the cytoplasmic end of the putative fifth transmembrane domain, likely to contribute to the ion conduction pathway; this would explain a dominant phenotype, since one mutant subunit could block conduction in a multimeric channel. The less severe Va^J allele has, in addition, a substitution between the putative third and fourth transmembrane domain (I362T), which apparently compensates in part for the A419P mutation.

There are two other members of the TRPML subfamily in mammals. Both TRPML1 and TRPML2 are associated with the lysosomal compartment of cells and TRPML1 is important for lysosome acidification. Fluorescence resonant energy transfer experiments show that all three TRPML proteins associate with one another, and coexpression of TRPML3 with either of the others localizes it to lysosomes in cultured cells (Venkatachalam *et al.* 2006). Indeed, in hair cells, antibody labelling of TRPML3 showed it to be primarily in organelles in the cell body, albeit with faint label in stereocilia (Di Palma *et al.* 2002). Thus it seems that TRPML3 is primarily in cytoplasmic organelles and not the plasma membrane, and that the deafness arises not from mutation of a transduction channel but from indirect effects of abnormal organelle trafficking. While TRPML3 cannot be ruled out as a transduction channel candidate, it seems unlikely.

TRPA1

A growing number of other TRP channels have been implicated in mechanosensation, in both vertebrates and invertebrates (Sukharev & Corey, 2004; Lin & Corey, 2005). In addition, the TRP family is attractive for its generally high conductance, low selectivity and high Ca^{2+} permeability (Owsianik *et al.* 2006). These led Corey *et al.* (2004) to screen all 33 mouse TRP channels, using *in situ* hybridization. Several TRPs were found to be expressed in hair cells (including TRPML3), but a particularly good candidate was TRPA1. First, TRPA1 is first expressed in the sensory epithelium of the mouse utricle (based on quantitative RT-PCR) at embryonic day 17, the same time during development that these hair cells become mechanically sensitive (Geleoc & Holt, 2003). An affinity-purified antibody to a C-terminal fragment of TRPA1 labelled the tips of stereocilia in bullfrog

and mouse vestibular hair cells. Label was weaker but present in cochlear hair cells. Label in bullfrog hair cells was nearly eliminated by brief treatment with BAPTA or La^{3+}, which cuts the tip links and is thought to promote recycling of transduction components from the stereocilia (Siemens *et al.* 2004). In the zebrafish genome, two TRPA1 orthologs were discovered. Injection of eggs with morpholino oligonucleotides targeting TRPA1a but not TRPA1b caused diminished FM1-43 loading of both lateral line and inner ear hair cells (at 50–60 h post-fertilization), and caused smaller microphonic potentials in the inner ear in response to vibratory stimulation of the body. The mouse genome harbours a single TRPA gene, whose expression was inhibited with siRNAs. Hair cells in utricules cultured from embryonic day (E) 15 mice – chosen because the mRNA has not appeared at that point – were infected at E16 with adenoviruses encoding one of two siRNAs to TRPA1 and were tested physiologically at E17–E18. Infected cells (identified by the GFP also encoded in the virus) had little or no transduction current and only slight loading with FM1-43. A control adenovirus encoding only GFP did not reduce the transduction current (Corey *et al.* 2004). Together, this evidence strongly supported TRPA1 as a candidate for the channel.

TRPA1 was additionally attractive because it is unique among mammalian TRPs in having a large number (17) of ankyrin repeats in its extended N-terminus. The alpha helices of polyankyrin domains pack into a curved structure, which was shown by both steered molecular dynamics and atomic force microscopy to have an elasticity nearly the same as that measured for the hair cell 'gating spring' (Sotomayor *et al.* 2005; Lee *et al.* 2006). Moreover, the only other TRP channel with a large number of ankyrin repeats is TRPN1, also thought to be a mechanosensitive channel. The intriguing possibility arose that TRPA1 has both a mechanically sensitive channel domain and an elastic domain that pulls the channel open (Howard & Bechstedt, 2004; Corey & Sotomayor, 2004).

Trouble with the hypothesis appeared almost immediately. Hair cell transduction is not affected by allyl isothiocyanate (M. A. Vollrath and D. P. Corey, unpublished observations), a known activator of TRPA1 (Jordt *et al.* 2004). The transduction channel has a sensitivity to blockers mostly like that of TRPA1, but the transduction channel is 10–20 times more sensitive to amiloride than is TRPA1 (Nagata *et al.* 2005), and is 100 times less sensitive to Gd^{3+} than is TRPA1. TRPA1 is thought to be activated by intracellular Ca^{2+} (Jordt *et al.* 2004), but Ca^{2+} inhibits the transduction channel (Howard & Hudspeth, 1988; Cheung & Corey, 2006). However, all of these differences could be attributed to the possibility that TRPA1 *in vivo* assembles in a multimeric channel with other subunits, which alter its pharmacology.

To further test its function, both Bautista *et al.* 2006 and Kwan *et al.* (2006) deleted critical exons from the mouse TRPA1. Although the mice showed the expected deficits in cutaneous pain sensation, consistent with the known expression of TRPA1 in small diameter neurons of the dorsal root and trigeminal ganglia, they were not deaf. A detailed evaluation showed normal acoustic startle reflex and vestibular behaviour, normal ABR, and normal transduction and adaptation in the receptor currents of single utricular hair cells (Kwan *et al.* 2006). These results are difficult to reconcile with the idea of TRPA1 as the transduction channel.

What went wrong? There are two classes of explanation. It might be, on the one hand, that the absence of TRPA1 throughout hair cell development causes the up-regulation of another (TRP?) channel to compensate. Compensation is a common story in knockout mice; however, if the polyankyrin domain is important for function, there is no other mammalian TRP that could compensate. It might be that TRPA1 is a subunit of one group of transduction channels, for instance at the lower end of each tip link, while other proteins constitute channels at the upper end. Deletion of half might not produce deafness. However, the total transduction current was not smaller in the knockout mice (Kwan *et al.* 2006) and in any case there is no kinetic or pharmacologic evidence for two distinct mechanically activated conductances in hair cells. On the other hand, it might be that each experiment supporting TRPA1 was somehow flawed: Even affinity-purified antibodies can bind to other proteins, perhaps even proteins of the transduction complex. Morpholinos can disrupt development non-specifically, and the inhibition of hair cell function with TRPA1 morpholinos was 50–70% at best. Even though the adenovirus was not toxic to mouse hair cells, siRNAs can have off-target effects. A variety of further tests, no doubt underway in several laboratories, should distinguish these possibilities.

Conclusions

What, then, is the hair cell transduction channel? TRPA1 is still an attractive candidate, but only if another TRP channel could compensate for it in knockout mice. TRP channels in general are enticing, for their high single-channel conductance, their non-selective pore with high Ca^{2+} permeability, and for their association with sensory transduction and mechanosensation in a variety of other tissues (Clapham, 2003; Lin & Corey, 2005; Owsianik *et al.* 2006). Since most TRP channels were identified by sequence similarity rather than by functional or positional cloning, functions are not well understood for the majority of the 30-odd TRPs in mammalian genomes. Most remain potential candidates. Some other channel classes have high conductance and/or non-selective pores; these include acetylcholine receptors, glutamate receptors,

cyclic-nucleotide-gated channels, the P2X ATP-gated channels, and connexin hemichannels. Yet without more systematic search strategies, there may be more phantoms to chase before we have the real channel in hand.

References

Bautista DM, Jordt SE, Nikai T, Tsuruda PR, Read AJ, Poblete J, Yamoah EN, Basbaum AI & Julius D (2006). TRPA1 mediates the inflammatory actions of environmental irritants and proalgesic agents. *Cell* **124**, 1269–1282.

Cable J & Steel KP (1998). Combined cochleo-saccular and neuroepithelial abnormalities in the varitint-waddler-j (vaj) mouse. *Hear Res* **123**, 125–136.

Canessa CM, Horisberger JD & Rossier BC (1993). Epithelial sodium channel related to proteins involved in neurodegeneration. *Nature* **361**, 467–470.

Canessa CM, Schild L, Buell G, Thorens B, Gautschi I, Horisberger JD & Rossier BC (1994). Amiloride-sensitive epithelial Na^+ channel is made of three homologous subunits. *Nature* **367**, 463–467.

Chalfie M & Au M (1989). Genetic control of differentiation of the *Caenorhabditis elegans* touch receptor neurons. *Science* **243**, 1027–1033.

Chalfie M, Driscoll M & Huang M (1993). Degenerin similarities. *Nature* **361**, 504.

Chalfie M & Sulston J (1981). Developmental genetics of the mechanosensory neurons of *Caenorhabditis elegans*. *Dev Biol* **82**, 358–370.

Chalfie M & Wolinsky E (1990). The identification and suppression of inherited neurodegeneration in *Caenorhabditis elegans*. *Nature* **345**, 410–415.

Cheung EL & Corey DP (2006). Ca^{2+} changes the force sensitivity of the hair-cell transduction channel. *Biophys J* **90**, 124–139.

Clapham DE (2003). TRP channels as cellular sensors. *Nature* **426**, 517–524.

Corey DP & García-Añoveros J (1996). Mechanosensation and the DEG/ENaC ion channels. *Science* **273**, 323–324.

Corey DP, García-Añoveros J, Holt JR, Kwan KY, Lin SY, Vollrath MA *et al.* (2004). TRPA1 is a candidate for the mechanosensitive transduction channel of vertebrate hair cells. *Nature* **432**, 723–730.

Corey DP & Hudspeth AJ (1979). Ionic basis of the receptor potential in a vertebrate hair cell. *Nature* **281**, 675–677.

Corey DP & Hudspeth AJ (1983). Analysis of the microphonic potential of the bullfrog's sacculus. *J Neurosci* **3**, 942–961.

Corey DP & Sotomayor M (2004). Hearing: tightrope act. *Nature* **428**, 901–903.

Crawford AC, Evans MG & Fettiplace R (1991). The actions of calcium on the mechano-electrical transducer current of turtle hair cells. *J Physiol (Lond)* **434**, 369–398.

Di Palma F, Belyantseva IA, Kim HJ, Vogt TF, Kachar B & Noben-Trauth K (2002). Mutations in Mcoln3 associated with deafness and pigmentation defects in varitint-waddler (Va) mice. *Proc Natl Acad Sci U S A* **99**, 14994–14999.

Farris HE, Leblanc CL, Goswami J & Ricci AJ (2004). Probing the pore of the auditory hair cell mechanotransducer channel in turtle. *J Physiol* **558**, 769–792.

Gale JE, Marcotti W, Kennedy HJ, Kros CJ & Richardson GP (2001). FM1-43 dye behaves as a permeant blocker of the hair-cell mechanotransducer channel. *J Neurosci* **21**, 7013–7025.

García-Añoveros J, Derfler B, Neville-Golden J, Hyman BT & Corey DP (1997). BNaC1 and BNaC2 constitute a new family of human neuronal sodium channels related to degenerins and epithelial sodium channels. *Proc Natl Acad Sci, USA* **94**, 1459–1464.

García-Añoveros J, Samad TA, Zuvela-Jelaska L, Woolf CJ & Corey DP (2001). Transport and localization of the DEG/ENaC ion channel BNaC1α to peripheral mechanosensory terminals of dorsal root ganglia neurons. *J Neurosci* **21**, 2678–2686.

Geleoc GS & Holt JR (2003). Developmental acquisition of sensory transduction in hair cells of the mouse inner ear. *Nat Neurosci* **6**, 1019–1020.

Geleoc GS, Lennan GW, Richardson GP & Kros CJ (1997). A quantitative comparison of mechanoelectrical transduction in vestibular and auditory hair cells of neonatal mice. *Proc R Soc Lond B Biol Sci* **264**, 611–621.

Hackney CM, Furness DN, Benos DJ, Woodley JF & Barratt J (1992). Putative immunolocalization of the mechanoelectrical transduction channels in mammalian cochlear hair cells. *Proc Biol Sci* **248**, 215–221.

Howard J & Bechstedt S (2004). Hypothesis: a helix of ankyrin repeats of the NOMPC-TRP ion channel is the gating spring of mechanoreceptors. *Curr Biol* **14**, R224–R226.

Howard J & Hudspeth AJ (1988). Compliance of the hair bundle associated with gating of mechanoelectrical transduction channels in the bullfrog's saccular hair cell. *Neuron* **1**, 189–199.

Jordt SE, Bautista DM, Chuang HH, Mckemy DD, Zygmunt PM, Hogestatt ED, Meng ID & Julius D (2004). Mustard oils and cannabinoids excite sensory nerve fibres through the TRP channel ANKTM1. *Nature* **427**, 260–265.

Jorgensen F & Ohmori H (1988). Amiloride blocks the mechano-electrical transduction channel of hair cells of the chick. *J Physiol* **403**, 577–588.

Kellenberger S & Schild L (2002). Epithelial sodium channel/degenerin family of ion channels: a variety of functions for a shared structure. *Physiol Rev* **82**, 735–767.

Kernan M, Cowan D & Zuker C (1994). Genetic dissection of mechanosensory transduction: Mechanoreception-defective mutations of *Drosophila*. *Neuron* **12**, 1195–1206.

Killick R & Richardson G (1997). Isolation of chicken α ENaC splice variants from a cochlear cDNA library. *Biochim Biophys Acta* **1350**, 33–37.

Kroese AB, Das A & Hudspeth AJ (1989). Blockage of the transduction channels of hair cells in the bullfrog's sacculus by aminoglycoside antibiotics. *Hear Res* **37**, 203–217.

Kwan KY, Allchorne AJ, Vollrath MA, Christensen AP, Zhang DS, Woolf CJ & Corey DP (2006). TRPA1 contributes to cold, mechanical, and chemical nociception but is not essential for hair-cell transduction. *Neuron* **50**, 277–289.

Lee G, Abdi K, Jiang Y, Michaely P, Bennett V & Marszalek PE (2006). Nanospring behaviour of ankyrin repeats. *Nature* **440**, 246–249.

Liedtke W, Choe Y, Marti-Renom MA, Bell AM, Denis CS, Sali A, Hudspeth AJ, Friedman JM & Heller S (2000). Vanilloid receptor-related osmotically activated channel (VR-OAC), a candidate vertebrate osmoreceptor. *Cell* **103**, 525–535.

Lin SY & Corey DP (2005). Trp channels in mechanosensation. *Curr Opin Neurobiol* **15**, 350–357.

Lumpkin EA, Marquis RE & Hudspeth AJ (1997). The selectivity of the hair cell's mechanoelectrical-transduction channel promotes Ca^{2+} flux at low Ca^{2+} concentrations. *Proc Natl Acad Sci U S A* **94**, 10997–11002.

Marcotti W, Van Netten SM & Kros CJ (2005). The aminoglycoside antibiotic dihydrostreptomycin rapidly enters mouse outer hair cells through the mechano-electrical transducer channels. *J Physiol* **567**, 505–521.

Meyers JR, Macdonald RB, Duggan A, Lenzi D, Standaert DG, Corwin JT & Corey DP (2003). Lighting up the senses: FM1-43 loading of sensory cells through nonselective ion channels. *J Neurosci* **23**, 4054–4065.

Nagata K, Duggan A, Kumar G & Garcia-Anoveros J (2005). Nociceptor and hair cell transducer properties of TRPA1, a channel for pain and hearing. *J Neurosci* **25**, 4052–4061.

Ohmori H (1985). Mechanoelectrical transduction currents in isolated vestibular hair cells of the chick. *J Physiol* **359**, 189–217.

O'Neil RG & Heller S (2005). The mechanosensitive nature of TRPV channels. *Pflugers Arch* **451**, 193–203.

Owsianik G, Talavera K, Voets T & Nilius B (2006). Permeation and selectivity of TRP channels. *Annu Rev Physiol* **68**, 685–717.

Peng BG, Ahmad S, Chen S, Chen P, Price MP & Lin X (2004). Acid-sensing ion channel 2 contributes a major component to acid-evoked excitatory responses in spiral ganglion neurons and plays a role in noise susceptibility of mice. *J Neurosci* **24**, 10167–10175.

Pickles JO, Comis SD & Osborne MP (1984). Cross-links between stereocilia in the guinea pig organ of Corti, and their possible relation to sensory transduction. *Hearing Res* **15**, 103–112.

Price M, Snyder P & Welsh MJ (1996). Cloning and expression of a novel human brain Na^+ channel. *J Biol Chem* **271**, 7879–7882.

Ricci AJ & Fettiplace R (1998). Calcium permeation of the turtle hair cell mechanotransducer channel and its relation to the composition of endolymph. *J Physiol* **506**, 159–173.

Ricci AJ, Crawford AC & Fettiplace R (2003). Tonotopic variation in the conductance of the hair cell mechanotransducer channel. *Neuron* **40**, 983–990.

Roza C, Puel JL, Kress M, Baron A, Diochot S, Lazdunski M & Waldmann R (2004). Knockout of the ASIC2 channel in mice does not impair cutaneous mechanosensation, visceral mechanonociception and hearing. *J Physiol* **558**, 659–669.

Rusch A & Hummler E (1999). Mechano-electrical transduction in mice lacking the α-subunit of the epithelial sodium channel. *Hear Res* **131**, 170–176.

Rusch A, Kros CJ & Richardson GP (1994). Block by amiloride and its derivatives of mechano-electrical transduction in outer hair cells of mouse cochlear cultures. *J Physiol* **474**, 75–86.

Shen J, Harada N, Kubo N, Liu B, Mizuno A, Suzuki M & Yamashita T (2006). Functional expression of transient receptor potential vanilloid 4 in the mouse cochlea. *Neuroreport* **17**, 135–139.

Shin JB, Adams D, Paukert M, Siba M, Sidi S, Levin M, Gillespie PG & Grunder S (2005). *Xenopus* TRPN1 (NOMPC) localizes to microtubule-based cilia in epithelial cells, including inner-ear hair cells. *Proc Natl Acad Sci U S A* **102**, 12572–12577.

Sidi S, Friedrich RW & Nicolson T (2003). NompC TRP channel required for vertebrate sensory hair cell mechanotransduction. *Science* **301**, 96–99.

Siemens J, Lillo C, Dumont RA, Reynolds A, Williams DS, Gillespie PG & Muller U (2004). Cadherin 23 is a component of the tip link in hair-cell stereocilia. *Nature* **428**, 950–955.

Sotomayor M, Corey DP & Schulten K (2005). In search of the hair-cell gating spring: Elastic properties of ankyrin and cadherin repeats. *Structure* **13**, 669–682.

Sukharev S & Corey DP (2004). Mechanosensitive channels: Multiplicity of families and gating paradigms. *Sci STKE* **219**, re4.

Tabuchi K, Suzuki M, Mizuno A & Hara A (2005). Hearing impairment in TRPV4 knockout mice. *Neurosci Lett* **382**, 304–308.

Venkatachalam K, Hofmann T & Montell C (2006). Lysosomal localization of TRPML3 depends on TRPML2 and the mucolipidosis-associated protein TRPML1. *J Biol Chem* **281**, 17517–17527.

Waldmann R, Champigny G, Voilley N, Lauritzen I & Lazdunski M (1996). The mammalian degenerin MDEG, an amiloride-sensitive cation channel activated by mutations causing neurodegeneration in *Caenorhabditis elegans*. *J Biol Chem* **271**, 10433–10436.

Walker RG, Willingham a T & Zuker CS (2000). A *Drosophila* mechanosensory transduction channel. *Science* **287**, 2229–2234.

Xie J, Price MP, Wemmie JA, Askwith CC & Welsh MJ (2003). ASIC3 and ASIC1 mediate FMRFamide-related peptide enhancement of H^+-gated currents in cultured dorsal root ganglion neurons. *J Neurophysiol* **89**, 2459–2465.

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David P. Corey

J. Physiol. 2006;576;23-28; originally published online Aug 10, 2006;

DOI: 10.1113/jphysiol.2006.116582