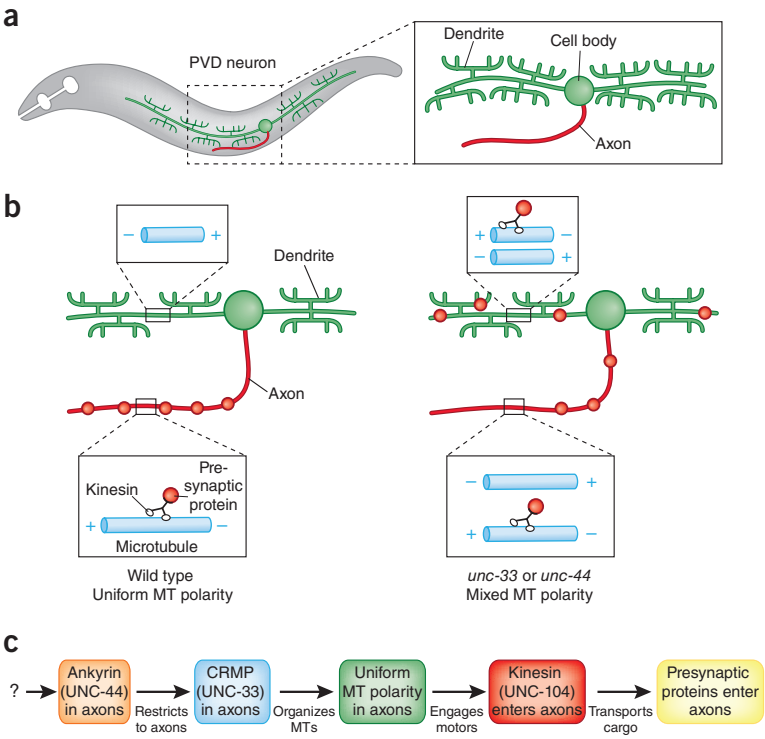

Figure 1 Model for establishment of neuronal polarity in *C. elegans*. (**a**) Morphology of the PVD sensory neuron in *C. elegans*. (**b**) Wild-type PVD neurons have uniform plus-end-distal microtubule (MT) polarity in axons and minus-end-distal polarity in dendrites. Presynaptic proteins RAB-3 and SAD-1 are delivered to axons and not dendrites through UNC-104/KIF1A-mediated transport. *unc-33*/CRMP and unc-44/ankyrin mutants have mixed MT polarity resulting in UNC-104/KIF1A-mediated transport of presynaptic proteins into both axons and dendrites. (**c**) Chain of events for axonal determination and protein sorting suggested by the study of Maniar *et al.*[8]. After UNC-44/ankyrin is localized to the initial segment of the incipient axon, it restricts the location of the MT-binding protein UNC-33/CRMP to these processes. CRMP then organizes the developing MT array into the characteristic plus-end-distal arrangement seen in axons. This allows UNC-104/kinesin-3 motors to engage with the MT array and transport axon-specific cargo, such as the presynaptic proteins RAB-3 and SAD-1.

questions. (i) What mechanism targets UNC-44/ankyrin to the axonal initial segment in the first place? (ii) Does a similar CRMP-dependent mechanism define microtubule organization in axons and dendrites of higher organisms? In cultured rodent hippocampal neurons, for example, axons show uniform plus-end-distal microtubule polarity, whereas dendrites show mixed polarity[13]. (iii) Do *C. elegans* dendrites generally have their microtubule minus ends oriented toward the growth cone, as reported for various *Drosophila* neurons[14], or is this property confined to these chemosensory neurons? In this respect, it would also be interesting to know the microtubule polarity of the more complex dendritic structures in PVD neurons. (iv) If UNC-44/ankyrin's main function is to prevent diffusion of UNC-33/CRMP from axonal to dendritic compartment, what directs UNC-33/CRMP to dendrites in the strong *unc-44* mutants? (v) What are the roles of the shorter UNC-33 isoforms that did not rescue *unc-33* polarity defects? (vi) How is preferential minus-end-distal polarity achieved in dendrites of the wild-type sensory neurons in which EB1 tracking was performed? Answers to these questions are likely to bring us closer to a more complete understanding of how axonal and dendritic proteins get on the right track.

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Tune in to KCNQ

Clare H Munns & Michael J Caterina

A study finds that the voltage-gated K^+ channel KCNQ4 is expressed in a subset of rapidly adapting, low-threshold mechanoreceptors, where it shapes the response profile to dynamic tactile stimuli.

Our ability to sense and discriminate diverse mechanical stimuli is determined by the expression and function of specialized mechanoreceptors in the skin. Although intense mechanical stimuli are detected by the free nerve endings of mechano-nociceptive neurons, nonpainful stimuli are detected by a host of low-threshold mechanoreceptors (LTMRs). The precise stimulus-response characteristics of the diverse array of LTMR types are critical to our ability to perform sensory tasks, such as tactile recognition of complex objects, reading braille, feeling the buzz of a cellphone or appreciating a caress. However, the molecular basis of LTMR functional diversity remains poorly understood. In this issue of *Nature Neuroscience*, Heidenreich *et al.*[1] demonstrate that the voltage-gated K^+ channel KCNQ4 is crucial for setting the velocity and frequency preference of a subpopulation of rapidly adapting mechanoreceptors in both mice and humans.

Clare H. Munns and Michael J. Caterina are in the Departments of Biological Chemistry and Neuroscience, Center for Sensory Biology, Johns Hopkins School of Medicine, Baltimore, Maryland, USA.
e-mail: caterina@jhmi.edu

The five members of the KCNQ subfamily of voltage-gated K^+ channels form functional homo- or heterotetrameric channels that underlie the low-threshold voltage-activated M current[2]. The specific properties of KCNQ-mediated currents, most notably activation at subthreshold potentials and slow inactivation, have led to the suggestion that these channels are involved in the regulation of resting membrane potential, action potential threshold and repetitive firing behavior. Disruption of KCNQ function has been linked to multiple diseases, including cardiac arrhythmias and epilepsy. In the auditory system, KCNQ channels are expressed in spiral ganglion neurons and cochlear hair cells[3]. Mutations in KCNQ1 and KCNQ4 have been associated with two forms of hereditary deafness, Jervell and Lange-Nielsen syndrome[4], and nonsyndromic sensorineural deafness type 2 (DFNA2)[5], respectively. Disease-associated KCNQ4 mutants exhibit impaired channel function and reduced membrane trafficking and, when co-expressed with wild-type channels, exert a dominant-negative effect[5–8]. Different hypotheses have been proposed to explain how K^+ channel dysfunction can result in deafness, including an imbalance in endolymph homeostasis and a disruption of calcium signaling in spiral ganglion neurons, leading to excitotoxicity and cell death[9]. Mice deficient in KCNQ4, or expressing a human DFNA2 mutation, faithfully recapitulate the deafness phenotype observed in individuals with DFNA2 (ref. 3). In these mice, age-dependent loss of cochlear outer hair cells, coupled with attenuated receptor potential amplification, were attributed to chronic depolarization of the outer hair cell as a result of reduced KCNQ4 function.

Expression of KCNQ2, KCNQ3 and KCNQ5 has also been reported in dorsal root ganglion (DRG) neurons that innervate the skin and other peripheral targets[10]. M currents exhibiting the expected profile of responses to pharmacological KCNQ modulators were recorded from isolated DRG neurons and potentiation of KCNQ activity suppressed signaling to the spinal cord dorsal horn after tissue inflammation. These findings have suggested that KCNQ channels are involved in nociception and hyperalgesia. In these early studies, *Kcnq4* mRNA detected in DRG was attributed to non-neuronal cells. However, Heidenreich *et al.*[1] find that KCNQ4 is indeed expressed in approximately 10% of DRG neurons and that staining for this particular subunit overlaps with markers of myelinated LTMRs. Additional characterization revealed that KCNQ4 is present in the nerve terminals of two different Aβ rapidly adapting LTMR populations in the skin: those contributing to Meissner's corpuscles and a subset of those forming lanceolate endings around hair follicles. In both structures, KCNQ4 is localized near presumed sites of mechanotransduction. Furthermore, this expression pattern is highly specific in that no KCNQ4 expression was observed in anatomically defined rapidly adapting (Pacinian corpuscles) or slowly adapting (Merkel cell-neurite complexes) LTMR subtypes.

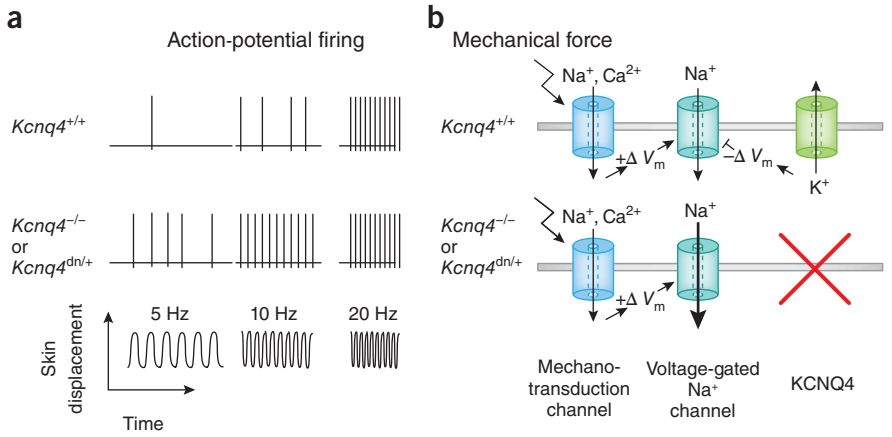

Figure 1 KCNQ4 shapes Aβ rapidly adapting LTMR tuning to dynamic mechanical stimuli. (**a**) Action-potential firing in wild-type (*Kcnq4*$^{+/+}$) and KCNQ4-deficient Aβ rapidly adapting LTMRs during stimulation with sinusoidal skin indentation. At low amplitude, the wild-type LTMR firing rate encodes stimulus frequency poorly at <20 Hz. In the absence of functional KCNQ4 (*Kcnq4*$^{-/-}$) or in the presence of dominant-negative KCNQ4 (*Kcnq4*$^{dn/+}$), the LTMR firing rate tracks stimulus frequency over an expanded frequency range. (**b**) Proposed mechanism of KCNQ4 suppression of Aβ rapidly adapting LTMR excitability. Top, in LTMRs from wild-type mice, tonic KCNQ4 activity hyperpolarizes the resting membrane potential ($-\Delta V_m$), antagonizing the generator potential ($+\Delta V_m$) produced by mechanically gated cation channels, thereby making it more difficult to activate voltage-gated Na^+ channels and reach action potential threshold. Bottom, in KCNQ4-deficient mice, mechanotransduction current is unopposed, making firing threshold easier to reach.

Armed with this information, Heidenreich *et al.*[1] subsequently performed an extremely thorough investigation of the contribution of KCNQ channels to LTMR function using an *in vitro* hairy skin–nerve preparation. They found that pharmacological blockade of all KCNQ currents with linopirdine increased the response to a ramp-and-hold mechanical stimulus in both Aβ rapidly adapting LTMRs and Aδ D-hair LTMRs, but did not affect slowly adapting LTMR responses. Gene knockout of KCNQ4 abolished the linopirdine-mediated effect only in the Aβ rapidly adapting LTMRs. The specific augmentation of mechanical responsiveness in Aβ rapidly adapting LTMRs was reproduced in skin-nerve preparations from mice deficient in KCNQ4 and from heterozygous knock-in mice harboring a single allele of the dominant-negative DFNA2 KCNQ4 mutation. Aβ rapidly adapting LTMRs are tuned to best detect and encode sinusoidal skin deformation in the range of 20–50 Hz, and have been proposed to mediate the perception of 'flutter vibration'[11]. This is in contrast with Pacinian corpuscles, which best encode higher frequencies (100–300 Hz), or slowly adapting LTMRs, which exhibit a flatter tuning curve. By systematically varying the timing and amplitude of the mechanical stimulus, Heidenreich *et al.*[1] very nicely demonstrated that, in the absence of functional KCNQ4, the enhancement of Aβ rapidly adapting LTMR responsiveness is confined to situations in which mechanical stimuli are applied either slowly or at low frequency (**Fig. 1a**). As a result, the optimal frequency range for these neurons to encode dynamic stimulation is broadened in mutant mice to include lower frequencies and slower displacement velocities. Thus, KCNQ4 appears to restrict the lower frequency limit of Aβ rapidly adapting LTMR coding. Heidenreich *et al.*[1] speculate that KCNQ4 might do so by virtue of its tonic hyperpolarization of the membrane potential (**Fig. 1b**) and that the frequency dependence of this effect is likely a consequence of conductive, rather than capacitative, shunting. Although plausible, this explanation will require confirmation using intracellular recordings from LTMR terminals.

To explore the functional importance of the neurophysiological phenotype described above, Heidenreich *et al.*[1] employed a behavioral assay of texture exploration. DFNA2 mutant mice on a mixed genetic background exhibited a hint of augmented exploratory behavior in this assay. However, the results were not statistically different between genotypes and were not recapitulated using

Kcnq4$^{-/-}$ mice on a more uniform genetic background. More convincing evidence for a higher level mechanosensory consequence of KCNQ4 loss of function, however, came from the analysis of human subjects with DFNA2. Compared with healthy, age-matched controls, these individuals demonstrated a significantly increased ability to detect low-frequency vibrotactile stimuli applied to the skin, with no differences at higher frequencies. This gain of function provides strong support for a conserved role of KCNQ4 in shaping the low-frequency limit of the rapidly adapting mechanoreceptor tuning curve.

In contrast with the situation for hair cells and spiral ganglion neurons[3], no degeneration of Aβ rapidly adapting LTMRs was observed in DFNA2 knock-in mice[1]. This apparent protection from cytotoxicity might result from the rapid adaptation of mechanosensory signaling in the LTMRs (whose mechanism remains to be determined), a more robust capacity to handle calcium influx or the fact that LTMRs are exposed only intermittently to stimuli adequate for their activation. Indeed, persistent limb vibration can cause peripheral nerve injury[12]. It would therefore be interesting to examine the mechanosensory and anatomical phenotype of DFNA2 knock-in or *Kcnq4*$^{-/-}$ mice at different ages or following persistent exposure to low-frequency vibratory stimuli.

In hippocampal neurons, KCNQ2 and KCNQ3 channels colocalize with voltage-gated Na^+ channels to regulate action potential threshold[13]. Thus, the localization of KCNQ4 at the mechanosensory end organ in both Meissner's corpuscles and hair follicles[1] not only places the channel in an optimal position to shape excitability, but also raises the possibility that the KCNQ channels may form a complex with mechanotransduction channels or with voltage-gated Na^+ channels that initiate action potential firing. If such complexes are shown to exist, they might not only help to explain the precise kinetics of mechanoreceptor tuning, but might also provide a means of identifying the elusive mechanotransduction channels.

The current study also raises an interesting question: which channels mediate KCNQ4-like functions in the other rapidly adapting LTMR cell types? Heidenreich *et al.*'s pharmacological data[1] suggest the involvement of another KCNQ subtype in D hairs. Given the fact that Pacinian corpuscles, which are tuned to higher frequencies than Meissner's corpuscles and hair follicle LTMRs, do not express KCNQ4, it will be interesting to determine what mechanisms shape the lower frequency limits of their tuning curves. It should also be emphasized that Heidenreich *et al.*'s mouse neurophysiological recordings[1] were confined to hairy skin. Thus, although their human experiments implicate KCNQ4 in Meissner corpuscle tuning, recordings from glabrous skin are warranted to explicitly analyze this issue in mice.

Although human subjects expressing the DFNA2-associated mutation display a sensory phenotype detectable under psychophysical testing conditions, it is unclear whether these individuals are cognizant of this heightened sensitivity to vibratory stimuli. It will be interesting to determine whether this apparent gain of function is associated with negative consequences, such as a compromise in their abilities to resolve subtly different tactile stimuli. Regardless, the findings of Heidenreich *et al.*[1] provide exciting new insights into the ionic mechanisms that shape our mechanosensory abilities and reveal that at least some of these mechanisms are intrinsic to the mechanoreceptive neurons themselves.

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What's primary about primary olfactory cortex?

Tali Weiss & Noam Sobel

Learned odor discrimination and generalization are reflected in patterns of ensemble activity in anterior piriform cortex, where learned discrimination between two odors reduces the correlation between their induced patterns.

We can all name single odor objects, such as coffee, red wine and rose. Each of these objects, however, is in fact a mixture that is often composed of hundreds of different odor molecules that we can also detect on their own. Where in the brain are these individual representations combined into a unified object? Moreover, the brain may either generalize or separate the perceptual representation of physicochemically similar mixtures. For example, two different oranges may share 98% of their physicochemical odorous components, and the brain may generalize or 'complete' these two patterns into one perceptual object: orange. In turn, two different oranges may also share 98% of their physicochemical odorous components, yet the brain may separate them into two distinct perceptual objects: orange and rotten orange. The olfactory system must conduct a balancing act between generalizations of similar stimuli, such that not all experience will be unique, while allowing discrimination between other similar stimuli when such separation is beneficial for the organism. In this issue of *Nature Neuroscience*, Chapuis and Wilson[1] provide experimental evidence that suggests such pattern separation and completion is first evident in anterior piriform cortex (APC), a portion of olfactory cortex.

The mammalian olfactory system is stereotypically structured. Following odorant transduction at the olfactory epithelium in the nose, the neural signal projects via the olfactory nerve to the olfactory bulb in the brain, where odorants drive spatiotemporal patterns of activity. Olfactory bulb output is projected via the olfactory tract to several ventral cortical targets, most prominently piriform cortex. Currently, all cortical targets of the olfactory bulb are referred to as primary olfactory cortex[2]. Although much is known regarding odor response organization in

Tali Weiss and Noam Sobel are in the Department of Neurobiology, Weizmann Institute of Science, Rehovot, Israel.
e-mail: tali.weiss@weizmann.ac.il or noam.sobel@weizmann.ac.il