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might not be able to recycle back to the plasma membrane.

How the insulin pathway is regulated remains unclear, as both protein kinase[1] and phosphatase[2] inhibitors seem to inhibit insulin-mediated glutamate receptor internalization. One possible explanation could be that cycles of phosphorylation and dephosphorylation are involved in the insulin pathway or that multiple components mediate internalization, of which some must be phosphorylated and others dephosphorylated for activation. This second possibility seems less likely in view of studies on synaptic vesicle recycling in the presynaptic nerve terminal, where many of the endocytotic components seem to be in the same (dephosphorylated) state[13]. More work is needed to sort out the mechanistic differences and fine details of this signaling pathway. The most intriguing observation is the differential subcellular distribution of internalized receptors depending on the stimulus. Insulin-triggered AMPAR endocytosis preferentially occurs in the cell soma and, in contrast to the AMPAR- and NMDAR-mediated pathways, does not seem to lead to recycling of receptors to the surface. It is therefore tempting to speculate that AMPA and NMDA mimic physiological responses regulating synaptic plasticity phenomena such as LTD, which happen on a time scale of minutes, whereas the insulin cascade could cause long-term modulation of the relative rates of exo- and endocytosis via irreversible redistribution of AMPARs to late endosomal compartments[14].

In spite of all the excitement, many unanswered questions remain: how is spatial regulation achieved between discrete portions of the neuron and how are these pathways interconnected? How exactly is the insulin signal transduced? Do all of these pathways eventually converge or are there specific proteins that confer unique properties onto a given pathway? Given the rapid pace of progress in this field, it is likely that we will not have to wait long before the answers to these questions emerge.

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Closing in on a mammalian touch receptor

Monica Driscoll and Nektarios Tavernarakis

A recent ***Nature*** paper on mice lacking the Na^+ channel BNC1 shows that this channel is essential for neuronal touch receptor function and may be part of a mechanosensory complex.

Touch receptors are critical in nearly everything we do to interact with the world—tying shoelaces, pouring coffee, moving cursors. Touch-transducing molecules also contribute fundamentally to biology in less obvious ways. For example, fly mutants defective in larval touch sensation are essentially inviable[1]. Despite its importance, however, our understanding of the sense of touch remains incomplete.

A variety of morphologically and electrophysiologically distinct mechanoreceptor neurons are dispersed in mammalian skin, often intimately tethered to surrounding tissue or structures such as sensory hair follicles. Specialized mechanically gated ion channels that are located in these neurons are critical in transduction, but for years these channels eluded cloning efforts because of their relatively low density in the skin, the lack of biochemical reagents that avidly and specifically bind them, and the extreme difficulty of assaying for mechanical gating in heterologous expression systems. Genetic dissection of touch sensation in *C. elegans* came to the rescue, yielding the first candidate molecules for metazoan mechanosensory channels (reviewed in ref. 2). Price and colleagues now report the first evidence that the related mammalian channel subunit BNC1 is required for proper function of specific classes of mammalian mechanoreceptor neurons[3].

In the nematode *C. elegans*, touch to the body is sensed by six mechanosensory neurons that are intimately associated with the cuticle[4]. A genetic screen identified a number of touch-insensitive mutants[4,5], analysis of which defined a dozen genes specifically needed for body touch sensation. Two genes from this screen encode channel subunits MEC-4 and MEC-10, which are related to the epithelial amiloride-sensitive sodium channel (ENaC) superfamily[6] and are expressed nearly exclusively in touch receptor neurons. The nematode channel subunits were named 'degenerins' (DEG) because channel-hyperactivating amino-acid substitutions can induce neuronal degeneration. Importantly, additional channel subunits of the 21-member *C. elegans* degenerin family have been implicated in mechanical signaling involving other sensory neurons. At least two degenerins are required for nose-touch sensation mediated by head mechanosensory neurons (our unpublished observations), and the UNC-8 degenerin is required for normal locomotion, which seems to depend on stretch-sensitive neuronal signaling, analogous to proprioception[7].

How might degenerin channels sense and transduce mechanical stimuli? The best-developed model is for the MEC-4/MEC-10 touch receptor channel complex[2,8] (Fig. 1). MEC-4 and MEC-10 are postulated to form a heteromultimeric channel in which extracellular domains interact with proteins situated in a specialized extracellular matrix that encircles the touch receptor neurons. Likewise, the channel intracellular domains may be tied

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to a unique microtubule network assembled in the touch receptor neurons. When a mechanical force is applied, the contacts outside and inside the cell relay gating tension on the MEC-4/MEC-10 channel. As a consequence the channel opens, allowing inward cation flow that depolarizes the neuron.

This is an attractive model, but electrophysiological confirmation has been stonewalled by the technical challenge of stimulating and recording directly from the *C. elegans* touch receptor neurons, which are tiny (soma on the order of 1 μm) and closely tied to the cuticle. Furthermore, reconstitution and assay of the mechanotransducing complex in a heterologous expression system is likely to be extremely difficult because success will probably require not only channel expression, but also regeneration of channel gating contacts provided by additional proteins in their physiological contexts. Thus, researchers in the field have looked forward to testing of mammalian degenerin homologs, which, by analogy, are candidate participants in touch-transducing channels.

To date, mammalian members of the ENaC superfamily fall into two subfamilies that are expressed in either epithelia (ENaCs) or neurons (ASICs, acid-sensing ion channels[9]). The neuronally expressed family members share the interesting property that they can be gated by H^+ *in vitro*. These acid-sensitive gating properties underlie speculation that the ASIC channels could be activated in response to the local acidosis that occurs in injured or inflamed tissue, thereby being important in pain perception[10]. Among the ASIC channels, BNC1 (ref. 11; also known as MDEG, ref. 10; BNaC1, ref. 12; ASIC2, ref. 9) emerged as a reasonable candidate for a mechanosensory channel because it is the ASIC family member most similar in amino-acid sequence to nematode MEC-10, and it can be mutated analogously to create a hyperactivated channel[10]. Price and colleagues[3] now show that BNC1 immunoreactivity is concentrated in a specific subdomain of mechanosensory nerve terminals that innervate the guard hair follicle in mouse hairy skin, a location well suited for sensation of hair movement. More specifically, BNC1 is present in palisades of the lanceolate nerve terminals, fine parallel processes projected in the hair follicle[3] (Fig. 2 a and b). These nerve terminals house one type of rapidly adapting mechanoreceptor.

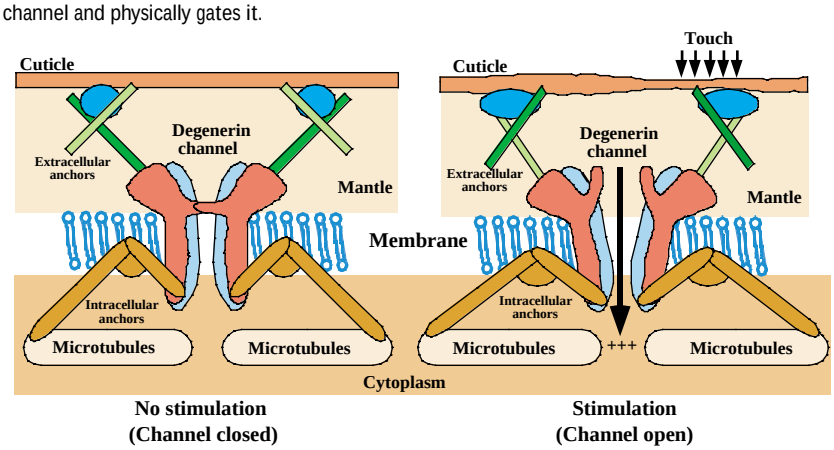
Is BNC1 involved in mechanosensation or nociception? Either (or both) is plausible because BNC1 is detectable in both large-diameter neurons (mostly mechanosensitive neurons) and small-diameter neurons (mostly nociceptors) of the dorsal root ganglion (DRG)[3]. By generating a BNC1 null mutant mouse[3], Price and colleagues tested both of these possibilities. At a gross level, the BNC1 null mice appeared generally normal in development, size, fertility and behavior. To address a potential function for BNC1 in mechanotransduction, the authors used a skin–nerve preparation, in which nerve terminals are tested for responses to applied displacement force. This preparation includes specialized nerve terminals that can be classified into five mechanoreceptor types based on electrophysiological properties: rapidly adapting (RA) low-threshold mechanoreceptors, slowly adapting (SA) low-threshold mechanoreceptors, D-hair mechanoreceptors, A-fiber mechanonociceptors and polymodal C-fiber mechanonociceptors.

Price and collaborators noted some important similarities and exciting differences when they compared the electrophysiological properties of single nerve fibers of these mechanoreceptor classes from skin of $BNC1^{-/-}$ mutants with wild type. There was no change in the stimulus–response curves or the median force required to activate D-hair mechanoreceptors, A-fiber mechanonociceptors or C-fiber mechanonociceptors. Likewise, all efforts to test for changes in acid-induced responses and nociception in DRG neurons and polymodal C fibers (which included assay of H^+-gated currents, determination of channel pH sensitivity, evaluation of pharmacological properties and assays for heat nociception) failed to indicate an essential role for BNC1 in modulating H^+-gated currents or in nociception executed by DRG neurons or polymodal C fibers. Thus, there was no evidence for a critical function of the BNC1 subunit in H^+-mediated responses to tissue acidosis.

In contrast, the authors uncovered a striking change in the function of RA and SA low-threshold mechanoreceptors in the BNC1 null mutant. Although the minimal detectable force for activation of these mechanoreceptors remained the same, the stimulus–response curve for RA (and to a lesser extent SA) neurons from mutant mice was significantly altered (Fig. 2c and d). Mutant neurons still responded to displacement force, but produced fewer action potentials over a comparable range of stimuli. Interestingly, the altered response did not seem to result from developmental defects in the neurons involved, as no differences in the absolute number and proportion of RA and SA fibers were detected. Further tests showed that the deficit was likely to be in the actual generation of a mechanically induced depolarizing potential (as opposed to a defect in the capacity to generate action potentials, for example), consistent with the hypothesis that BNC1 participates directly in a mechanosensitive channel.

The consequences of the BNC1 channel deficiency, although somewhat modest at first glance, may be of profound biological importance, because in humans the dynamic sensitivity of RA and SA receptors is thought to be critical for perception and discrimination of touch sensation. Moreover, the work of Price and colleagues provides the first direct data in support of the hypothesis that the molec-

Fig. 1. A molecular model of a touch-transducing complex in *C. elegans* mechanosensory touch receptor neurons, based on genetic and molecular studies. Protein contacts in a specialized extracellular matrix (called the mantle) and in the cytoskeleton are postulated to exert tension on the MEC-4/MEC-10 degenerin ion channel. The mechanical force of a touch to the cuticle pulls on the channel and physically gates it.



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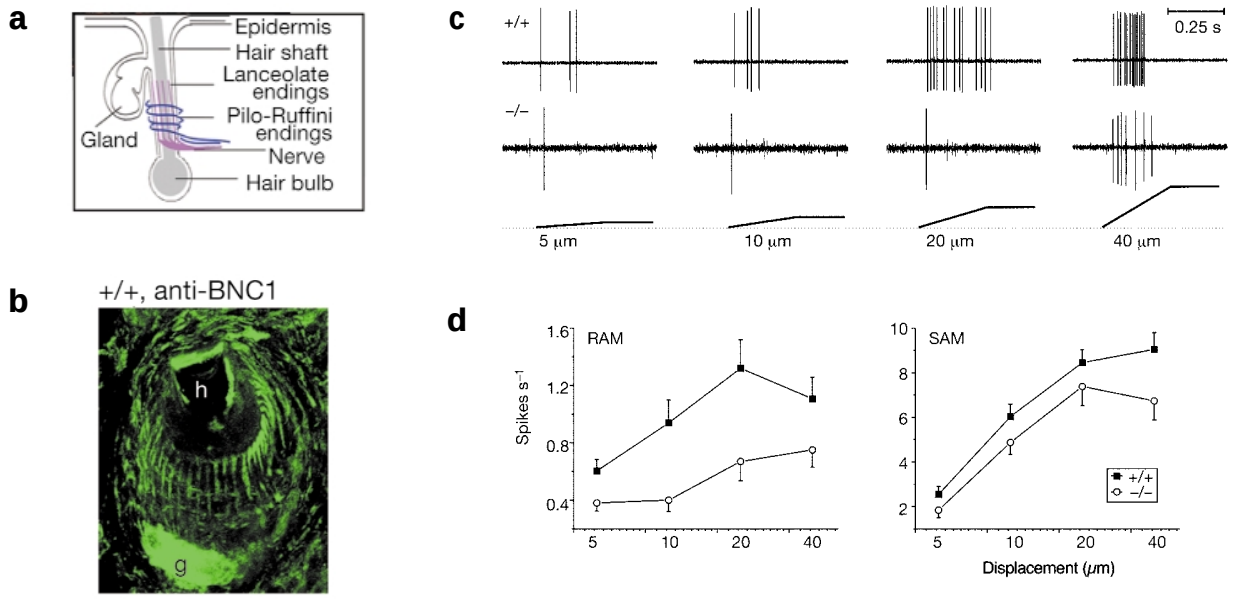

Fig 2. Immunostaining of BNC1 around hair follicles in wild-type mice and comparison of mechanosensory responses. (**a**) The anatomy of a hair follicle. (**b**) Confocal image of an oblique section through a hair follicle showing concentrated staining in lanceolate endings. h, hair follicle, g, sebaceous gland. (**c**) Comparison of RA mechanoreceptor responses from wild-type mice and BCN1$^{-/-}$ mutants. Wild-type RA mechanoreceptors elicit action potentials only in response to initial rapid displacement of the skin. RA neurons from the BNC1$^{-/-}$ mouse failed to increase action potential discharges in the lowest displacement stimulus range. (**d**) Comparison of stimulus–response curves for RA and SA mechanoreceptors in wild-type mice and BCN1$^{-/-}$ mutants. Reprinted by permission from *Nature* (ref. 3), copyright (2000) Macmillan Magazines Ltd.

ular mechanisms of touch transduction may be conserved from invertebrates to mammals. Why might the response be modified rather than eliminated in mechanosensitive neurons of the BNC1 knockout? One plausible idea is that DEG/ENaC channels are most often heteromultimeric, and BNC1 might act more as an auxilliary subunit than as the core of a mechanotransducing complex, much as β and γENaC are less critical than αENaC function in kidney epithelia[6]. Alternatively, different DEG/ENaC channels (or other types of channels) may have redundant functions in the same neurons. Consistent with this possibility, ENaC subunits have been detected in palisades of mechanosensory lanceolate nerve terminals in the rat vibrissal sinus complex[13] and in baroreceptor nerve terminals that sense blood pressure[14], suggesting that ENaC family subunits could be components of neuronal mechanotransducing channels as well. Characterization of expression patterns of all ASIC and ENaC family members and genetic knockouts of candidate mechanotransducer channels will be required to address the question of functional redundancy. Such studies should also reveal whether other DEG/ENaC family members are needed for the function of other mechanoreceptors or nociceptors in mouse skin.

It is important to note that work on the BNC1 null mutant does not definitively prove that the BNC1-containing channel is a mechanically gated sensory channel, although it comes close. These data cannot rule out the possibility that BNC1 might form or influence an auxiliary channel that facilitates the function of the actual mechanotransducing channel. (This alternative hypothesis is equally applicable to the case of the *C. elegans* degenerin channels.) Recently, another candidate mechanosensory channel, NompC, was identified in *Drosophila*[15]. The NompC (no mechanoreceptor potential) channel is a member of the TRP channel family (unrelated in amino-acid sequence to DEG/ENaC channels), and it is required for normal mechanosensitive currents in fly hair bristles. The roles of mammalian NompC homologs in mechanical signaling and the potential interactions of DEG/ENaC and NompC channels will need to be investigated for a clear understanding of the relationship between mammalian and invertebrate mechanotransduction. Likewise, the identities and properties of force-generating tethers in touch-transducing complexes will need to be determined. Still, given concrete hypotheses to pursue and complete gene sequences on the horizon, we can be optimistic about understanding how we feel touch in the foreseeable future. The work of Price and collaborators is an exciting step in that direction.

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