Mini Review

Putative mechanoproteins in vertebrate cutaneous mechanoreceptors—are they at the basis of the mechanotransduction?

Abstract

The mammalian skin contains sensory structures (mechanoreceptors) that are responsible for different modalities of mechanosensitivity like touch, vibration and pressure sensation. These specialized sensory organs are anatomically and functionally connected to mechanosensory neurons which electrophysiologically correspond with Aβ fibers. The process of mechanosensitivity requires the conversion of a mechanical stimulus into an electrical signal (mechanotransduction) through the activation of ion channels that gate in response to mechanical stimuli originating actions potential potentials. The ion channels that are putatively mechanotransducer belong primarily to the families of acid-sensing ion channels, transient receptor potential potential channels, and Piezo2. This short review compiles the current knowledge on the occurrence of putative mechanoproteins mechanoreceptors, and therefore the involvement of these proteins on the biology of touch.

Keywords: touch, mechanoreceptors, mechanoproteins, acid-sensing ion channels, transient receptor potential potential channels, piezo2

Introduction

In mammals the cutaneous mechanosensitive structures that are responsible for light brush, touch, pressure sensation, stretch, and vibration are special sensory organs known collectively as cutaneous mechanoreceptors.1,2 All these modalities of mechanosensitivity are mediated by Aβ and Aδ nerve fibers (the speed of action-potential propagation, myelin thickness) with low mechanical thresholds originating from intermediate- or large-sized mechanosensory neurons.3,4 The peripheral process of the mechanosensory axons contact in the skin with specialized cells like Merkel cells, or form a part of sensory organs like Meissner corpuscles, Ruffini’s corpuscles, hair follicle-associated sensory nerve endings, Pacinian corpuscles.5–8

Mechanotransduction can be defined as the conversion of a mechanical stimulus into an electrical signal. The molecular mechanisms underlying this complex process still remains poorly understood, but electrophysiological studies suggest that it occurs through the activation of ion channels.9–13 The first step of mechanotransduction occurs in the mechanoreceptors,14–17 and involves the activation of the peripheral branch of the pseudo-unipolar primary mechanosensory neurons14,18 and the sensory corpuscles connected to them.14–17

For a long time, the genesis of the action potential in mechanoreceptors was explained by the mechanical properties of the capsule and the periaxonic cells. Then, the discovery that some kinds of ion channels are gated by mechanical forces did suggest that the mystery of the genesis of the sense of touch was discovered. However, almost twenty years later the problem is unsolved. It is generally assumed that deformations in the membrane of the different cells that form the mechanoreceptors (axons, Schwann-related cells, fibroblast-like cells) trigger the opening of mechanosensitive ion channels that transduce mechanical energy into electrical activity. Thus, the cells forming the mechanoreceptors are thought to express ion channels activated by force or displacement to act as mechanodetectors and/or mechanotransducers. Probably these ion channels correspond to two different categories: mechanically gated channels that act as force sensor themselves, and mechanically sensitive channels that are activated by second messengers of the true force sensors.

The present review is a compilation of the current knowledge of the relationships among mechanoreceptors and putative mechanoproteins, especially their localizations in human mechanoreceptors, and overview the sensory phenotype of mice genetically modified for these proteins.

Putative mechanoproteins in the cutaneous mechanoreceptors

To be a candidate for transducing the mechanical stimulus, ion channels must be present in the right location and must be necessary for mechanotransduction. Thus, it must be expressed and located at the site of mechanical transduction, and its blocking should block the mechanically activated conductance. Nevertheless, even if expressed properly in time and place, the putative mechaprotein could be an accessory protein for the channel and not part of the ion channel.

Members of the degenerin/epithelial sodium channels (DEG/ENaC) super family, the transient receptor potential potential (TRP) ion channels families, the two-pore domain potassium (K2p) channels family, and the Piezo1 and Piezo2 proteins are considered as putative mechanotransducer channels.1,9,11,19–21 However, only a few of them have proved to show mechanotransducer properties in vertebrates.21,23 But unfortunately, the sensory phenotypes of mice deficient for these proteins do not support always a key role in mechanotransduction.

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Transient receptor potential ion channels (TRP) super family

Members of the TRP superfamily are integral membrane proteins that function as ion channels. They consist of seven subfamilies, and at least 28 different TRP subunits have been identified in mammals. Nearly all TRP families have members which could be mechanosensors. In particular, TRP canonical 6 (TRPC6) is a candidate for mechanosensing which is widely distributed in mammalian tissues including DRG neurons; consistently deletion of TRPC6 causes deficits in light touch. Recently, Sexton et al. have demonstrated, using quadruple TRPC1, 3, 5 and 6 knockout mice that all these channels contribute to cutaneous mechanosensation in a combinatorial manner.

On the other hand, TRP vanilloid 4 (TRPV4) can work as a mechanosensor. TRPV4 was located in the axons innervating murine Meissner corpuscles, Merkel cells, penicillate nerve endings and intraepidermal terminals, but not in hair follicle palisades, and immunoreactivity for this protein was also detected in Merkel cells, or in avian mechanoreceptors. TRPV4 deficient mice show decreased responsiveness to sensation of noxious mechanical stimuli and human TRPV4 mutations cause peripheral neuropathies.

Recently we demonstrated TRPC6 in the axon of human Meissner corpuscles (Figure 1A-1C), whereas TRPV4 was detected in the axon (Figure 1D-1F) and also in the lamellar cells; and TRPV4 and TRPC6 were co-localized in the axon. TRPC6 co-operates with TRPV4 to mechanical hyperalgesia presumably as part of a mechanoreceptor signaling complex, and messenger RNAs for TRPV4 and TRPC6 are frequently co-expressed in sensory neurons. A suspected role in mechanosensing has been also suggested for TRPV2, and TRP Ankyrin 1.

Two-pore-domain potassium (K+) ion channels (K2P) family

Two-pore-domain potassium (K+) ion channels (K2P) form a family within the superfamily of K+-selective channel subunits. There are six K2P channel subfamilies, consisting of 15 distinct mammalian genes. TREK-1 and TRAAK channels belonging to this family are among the few channels for which a direct mechanical gating by membrane stretch has been shown, but is presence in mechanoreceptors has been never reported.

Acid-sensing ion channels

Acid-sensing ion channels (ASICs) are a group of H+-gated voltage-insensitive amiloride-sensitive cation channels included in the degenerin/epithelial Na+ channel (DEG/ENaC) superfamily. At present six ASIC proteins, subunits, encoded by four genes, have been identified: ASIC1a, ASIC1b, ASIC2a, ASIC2b, ASIC3, and ASIC4 that may function as mechanosensors or are required for mechanosensation. ASIC2 and ASIC3 were found in the axons supplying mammalian Meissner corpuscles, Merkel disks, and Pacinian corpuscles, and ASIC1 was detected in human Pacinian corpuscles, and avian Herbst corpuscles display ASIC2 immunoreactivity. We have recently detected the occurrence of ASIC1 plus ASIC2, and ASIC2 alone in human cutaneous Merkel and Meissner corpuscles, respectively, as well as in Merkel cell neurite complexes. In the murine Pacinian corpuscles also the inner core cells were ASIC2 positive, and the lamellar cells of some human Meissner and Pacinian corpuscles as well.

Figure 1 Double immunofluorescence for TRPC6 (A), TRPV4 (D) and NFP (neurofilament proteins, B, E) in human digital Meissner corpuscles. Both ion channels are localized in the axons supplying these corpuscles (C and F). The Merkel cells identified because display cytokeratin 20 (CK20, H) express Piezo2 (G and I).

Objective 40x/1.25 Oil; pinhole airy 1, XY resolution 156nm and Z resolution 334nm.
**Piezo2**

Piezo2 is a vertebrate stretch-gated multipass transmembrane protein required for nonselective cationic mechanosensitive channels in mammalian cells. In the peripheral nervous system it has been detected in dorsal root ganglia neurons, Merkel discs (consisting of Merkel cells and Aδ-afferent nerve endings) and isolated Merkel cells, low-threshold mechanoreceptors that innervate both hairy and glabrous skin including Meissner corpuscles and lanceolate nerve endings. Consistently animals deficient in Piezo2 show an almost complete deficit in light-touch sensation and proprioception without affecting other somatosensory functions. In human patients carrying mutations in Piezo2 show an almost complete deficit in light-touch sensation and proprioception.  

**Only mechanoproteins?**

In summarizing the current knowledge, the ion channels can be gated by three mechanisms:

A. They can be opened by modifications of the cell membrane in the vicinity of the channels;

B. The intra- and extra-cytoplasmic domains of ion channels are bound to the proteins of the cytoskeleton and the extracellular matrix, respectively, and the tension of these proteins can produce the opening of ion channels; and

C. That the channels are coupled to mechanosensory proteins through intermediaries of signaling. Therefore, any of the three previous theories should be at the basis of mechanotransduction in the mechanoreceptors. The involvement of these putative mechanoproteins in mechanosensing is now universally accepted, and cannot explain alone the compels mechanotransduction process. In fact, the disruption of cytoskeletal proteins in cultured sensory neurons results in the disappearance of the action potential induced by mechanical stimulation. Likely when ion channels like TRP or ASIC are blocked the mechanical stimulation of cells results in no changes in the action potential with respect to the cells without blocking. These experiments clearly suggest that there is something more than the mechanoproteins in the genesis of the mechanotransduction and that sensory nerve terminals have a specific mechanosensitive response that is related to cell architecture.

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**Conflict of interest**

Author declares that there is no conflict of interest.

**References**


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