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Review

Forcing open TRP channels: Mechanical gating as a unifying activation mechanism

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ABSTRACT

Transient receptor potential (TRP) proteins are cation channels that comprise a superfamily of molecular sensors that enable animals to detect a wide variety of environmental stimuli. This versatility enables vertebrate and invertebrate TRP channels to function in a diversity of senses, ranging from vision to taste, smell, touch, hearing, proprioception and thermosensation. Moreover, many individual TRP channels are activated through a surprising range of sensory stimuli. The multitasking nature of TRP channels raises the question as to whether seemingly disparate activators gate TRPs through common strategies. In this regard, a recent major advance is the discovery that a phospholipase C (PLC)-dependent signaling cascade activates the TRP channels in Drosophila photoreceptor cells through generation of force in the lipid-bilayer. The premise of this review is that mechanical force is a unifying, common strategy for gating TRP channels. In addition to several TRP channels that function in mechanosensation and are gated by force applied to the cells, changes in temperature or alterations in the concentration of lipophilic second messengers through stimulation of signaling cascades, cause architectural modifications of the cell membrane, which in turn activate TRP channels through mechanical force. Consequently, TRPs are capable of functioning as stretch-activated channels, even in cases in which the stimuli that initiate the signaling cascades are not mechanical. We propose that most TRPs are actually mechanosensitive channels (MSCs), which undergo conformational changes in response to tension imposed on the lipid bilayer, resulting in channel gating.

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1. Introduction

The founding member of the TRP family of cation channels was identified nearly 30 years ago in Drosophila [1,2]. We now know that this group of proteins is conserved from worms to humans [3], and consists of between 13 and 28 members depending on the species [4–6]. The TRPs are subdivided into seven subfamilies based on sequence homology (TRPC, TRPV, TRPM, TRPA, TRPN, TRPML and TRPP) [7], and include the common features of six transmembrane segments and permeability to cations. TRPs serve as sensors for a broad spectrum of stimuli, including light [2,8,9], odors [10–12], tastants [13,14], acids [15,16], temperature [17,18], gravity [19], auditory stimuli [20,21], as well as mild and noxious mechanical forces [22–24]. These channels not only promote the perception of the external environment, they allow individual cells in animals to sample and respond to internal stimuli. One example is TRPP2 (Polycystin2), which is proposed to sense fluid flow in renal tubules [25]. Mutations in the genes encoding TRPP2 and a related protein with 11 predicted transmembrane segments, TRPP1 (Polycystin1), are the major causes of autosomal dominant polycystic kidney disease [26–28].

The stimuli that activate TRPs do so either through multistep signaling cascades, or through a single step, that does not depend on production of second messengers. Examples of multistep mechanisms are the cascades in fly photoreceptor cells and mammalian intrinsically photosensitive retinal ganglion cells, which are initiated by light-activation of rhodopsins [29,30]. These classical G-protein coupled receptors (GPCRs) engage heterotrimeric G-proteins that stimulate PLC, which in turn activate TRPC channels [2,8,9,31,32]. Similar signaling cascades function in a variety of other cell types such as mammalian taste receptor cells [13]. In contrast to these multistep mechanisms, TRP channels also appear to be gated in a single step by changes in force, binding of chemicals and shifts in temperature [4–6,33,34].

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Strikingly, many individual TRP channels are activated through a range of stimuli. A notable illustration of this polymodal feature of TRPs is activation of TRPV1 by capsaicin (the active ingredient of chili peppers) [17], allyl isothiocyanate (AITC, component of mustard and wasabi that is responsible for their pungent taste) [35], resiniferatoxin (a toxin found in a cactus-type plant) [36], noxious heat [17], acidic pH [17], and N-acyl amide [37].

How do TRP channels respond to such broad arrays of stimuli? A breakthrough in our understanding of the mechanisms underlying channel gating emerged from the recent high-resolution structure of TRPV1, which was solved by cryo-electron microscopy [38,39]. Using peptide toxin and small vanilloid agonists, it now appears that opening of the channel pore results from a dual gate that involves structural changes in the outer pore domain and lower gate. Not all stimuli may contribute to channel opening through precisely the same biophysical mechanism, since different stimuli may act on one or the other portions of the dual gate, and then the effects are coupled allosterically. The dual-gating of TRPV1 explains why various chemical agonists promote channel gating. However, without obtaining "snapshots" of the channel at different temperatures, we still do not know how TRPV1 is thermally activated.

In this review, we posit that most TRPs are mechanosensitive channels (MSCs). In some instances, mechanical gating of TRP channels occurs by stimuli that activate TRPs through a single step, without employment of a signaling cascade. In other cases, even when the initial stimulus is not mechanical (e.g. light, chemicals or changes in temperature), TRPs are mechanically-gated through signaling cascades that alter the lipid composition of the membrane, change the conformation of the plasma membrane, and gate the TRPs through membrane stretch. Thus, even if activation of a TRP channel is coupled to a signaling cascade, and the initial stimulus is not mechanical force, the TRP can still be activated directly by force.

2. Direct mechanical gating of TRP channels in one step

Most TRP channels are situated in the plasma membrane and as a result, force from an extracellular source could potentially modulate the open probability of the channels, without the contribution of a signaling cascade (Fig. 1). A mechanical stimulus could exert its influence on a TRP channel directly. Alternatively, mechanical force could alter the curvature of the lipid-bilayer, which in turn creates a tension that opens the channel. We also view this latter mechanism as direct mechanical activation, since the architectural modifications in the lipid bilayer provide the force that provokes opening of the channels.

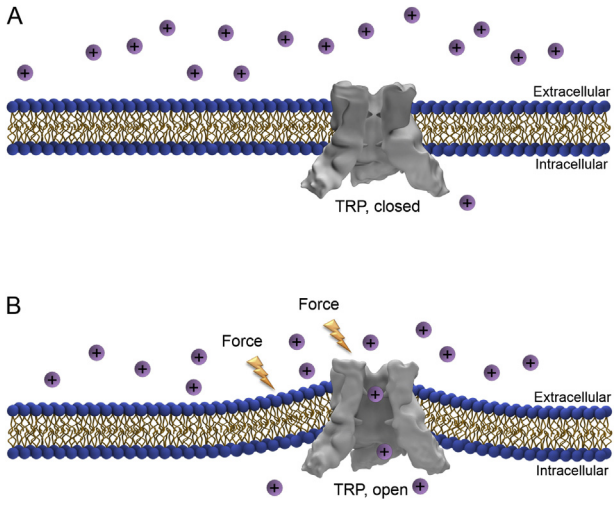

Fig. 1. Model of direct force-activation of TRP channels without a signaling cascade. (A) The TRP channel is closed prior to the mechanical stimulus. (B) The TRP channel opens in response to application of external force to the plasma membrane and/or the TRP channel. No signaling cascade is involved in this process.

If a TRP is directly activated by force, without the contribution of a signal cascade, then the activation should be very rapid. Currently, the fastest known sensory signaling cascade is fly phototransduction. In Drosophila photoreceptor cells, some TRP and TRPL channel open within a couple of milliseconds of light exposure, and response is maximal within 10–20 ms [40,41]. Thus, if mechanical activation occurs in less than ~2 ms, then it is likely to be independent of a signaling cascade.

The *Caenorhabditis elegans* TRPN channel, TRP-4 is required for force-induced conductance in the ciliated mechanosensory cephalic neuron, and is directly mechanically gated *in vivo*, as it is activated in less than 1 ms [42]. The founding TRPN channel, Drosophila NOMPC, is required for touch sensing in adult flies [24], and for detecting gentle touch in larvae [22]. Upon introduction into a heterologous cell expression system, NOMPC responds to mechanical stimuli within a 1–2 ms range, indicating that it is also likely to be directly gated by force [22].

In order to transmit force to the pore region, an elastic structure induces a conformational change, leading to pore opening. A feature of many TRP channels is a tandem array of N-terminal ankyrin repeats, the longest of which is a record-breaking set of 29 in TRPN channels [24]. This cluster of ankyrin repeats is proposed to function as a "gating spring," enabling external force to be conveyed to the channel pore [43]. The model is supported by molecular dynamic simulations, suggesting that the extension and stiffness of the structure match those predicted by the gating spring model [44]. Using atomic force microscopy, ankyrin repeats appear to unfold under force, and this process generates a refolding force, which is consistent with the hypothesis that ankyrin repeats act as gating springs [45]. TRPA1 also includes an impressive array of 14 N-terminal ankyrin repeats [46], and amphipathic molecules that cause mechanical stress to the lipid bilayer activate this channel, indicating that it is a MSC [47]. Therefore, some TRP channels may be force-activated through a mechanical mechanism involving ankyrin repeats.

3. Direct mechanical gating of TRP channels via a multistep cascade

The title of this section might seem counterintuitive. How can a TRP channel be directly mechanically gated if it is coupled to a signaling pathway? In fact, there is compelling evidence from Drosophila visual transduction that a non-mechanical stimulus (light) triggers a signaling cascade that generates force on the lipid-bilayer, which then serves as the trigger that opens the stretch-activated TRP channels [48]. In fly photoreceptor cells, a single photon is captured by rhodopsin, and the signal is amplified through a pathway that employs a heterotrimeric G-protein and activation of PLC [29,49] (Fig. 2). The PLC cleaves a minor phospholipid component of the plasma membrane, phosphatidylinositol 4, 5-bisphosphate (PIP_2), leading to the production of inositol 1,4,5-trisphosphate (IP_3), diacylglycerol (DAG) and a proton (H^+). The removal of the bulky inositol head group from PIP_2, resulting in the production of DAG, causes contractions of the microvilli membrane [48]. This "photomechanical response" affecting photoreceptor cells, which is detectable by light microscopy and quantifiable by atomic force microscopy, generates sufficient mechanical force to open the TRP and TRPL channels. The conclusion that light produces mechanical force is further substantiated by

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