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Neuronal stretch reception – Making sense of the mechanosense

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ABSTRACT

The sensation of mechanical force underlies many of our daily activities. As the sense of touch determines the quality of life, the subconscious sense of proprioception and visceral mechanosensation is indispensible for survival. Many internal organs change shape, either as an active part of their physiology or passively due to body movements. Importantly, these shape changes need to be sensed and balanced properly to prevent organ failure and dysfunction. Consequently, a failure to properly sense volume changes of internal organs has a huge clinical relevance, manifested by a plethora of congenital and age-related diseases. Here we review novel data on mammalian stretch reception as well as classical studies from insect and nematode proprioceptors with the aim to highlight the missing link between organ-level deformation and mechanosensing on the molecular level.

1. Neuronal mechanosensation in peripheral neurons and beyond

Mechanosensation has a dual role in our lives, an overt and a concealed one. Brain neurons, for example, preferentially elongate their processes into regions of defined rigidity [1] – a mechanosensitive process that evades our attention and we are unaware of. On the other hand, everyone experiences movements of internal organs, in a pleasant or unpleasant way. In our body, many visceral organs in our body generate and respond to mechanical forces and consequently are subjected to repetitive cycles of stretch and compression. The most prominent of these organs is the heart and muscles (Fig. 1), less prominent but equally important are the lungs, the bladder, and the gastrointestinal tract (reviewed in [2]). Both, the generation and the response need to be tightly regulated, in order to ensure life-long function without mechanical failure. These different organs are innervated by specialized sensory neurons [3] that express and utilize specialized molecular sensors that are embedded in the plasma membrane of the neuron to sense the mechanical deformation. In most cases, these sensors are mechano-electrical transduction channels which open or close upon the application of mechanical stress [4], ultimately leading to a change in neuronal activity. The nature and identity of these molecular mechanosensors have been long known in *C. elegans* touch receptor neurons involved in sensing gentle body touch [5], but have remained largely elusive for decades in mammals and humans until the discovery of the Piezo ion channel family in 2010 [6]. Soon after their discovery the mystery of the sense of touch [7–9], proprioception [7] and the control of visceral reflexes [10,11], seemed solved. However, the unusual size and domain organization of the PIEZO proteins raised several questions about how these proteins sense mechanical force, a question that has driven the field for the past 35 years since the initial discovery of mechanically gated ion channels [12]. In the past few years, we saw an explosion of stunning Piezo structures (reviewed in [13]), fueled by the development of new cryo-EM detectors, generating new exciting hypotheses about their gating mechanism [14]. A closer look, however, warrants additional concepts to be considered and we thus would like to paint a dialectic picture of how neuronal stretch reception during organ level deformation is coupled to molecular movement of individual ion channels. As important as the nature of the channel and its location within the neuron, is the question of how the stress reaches it. A critical part of this process is inherent to the organization of the neurons and their surrounding as well as the material they are made of. We thus pay particular attention to the mechanical properties of neurons, their cytoskeleton and how impinging stresses change neuronal morphologies related to mechanosensation.

At large, the specialization of the neuronal substrates involved in mechanical somatosensation in vertebrates is very complex and situations in which sensory cells and neurons participate in the same function is not uncommon [8]. Likewise, the same behaviors and functions are driven by a set of mechanosensitive channels with overlapping but not redundant functions. Amiloride-sensitive [15,16] and Piezo2 driven

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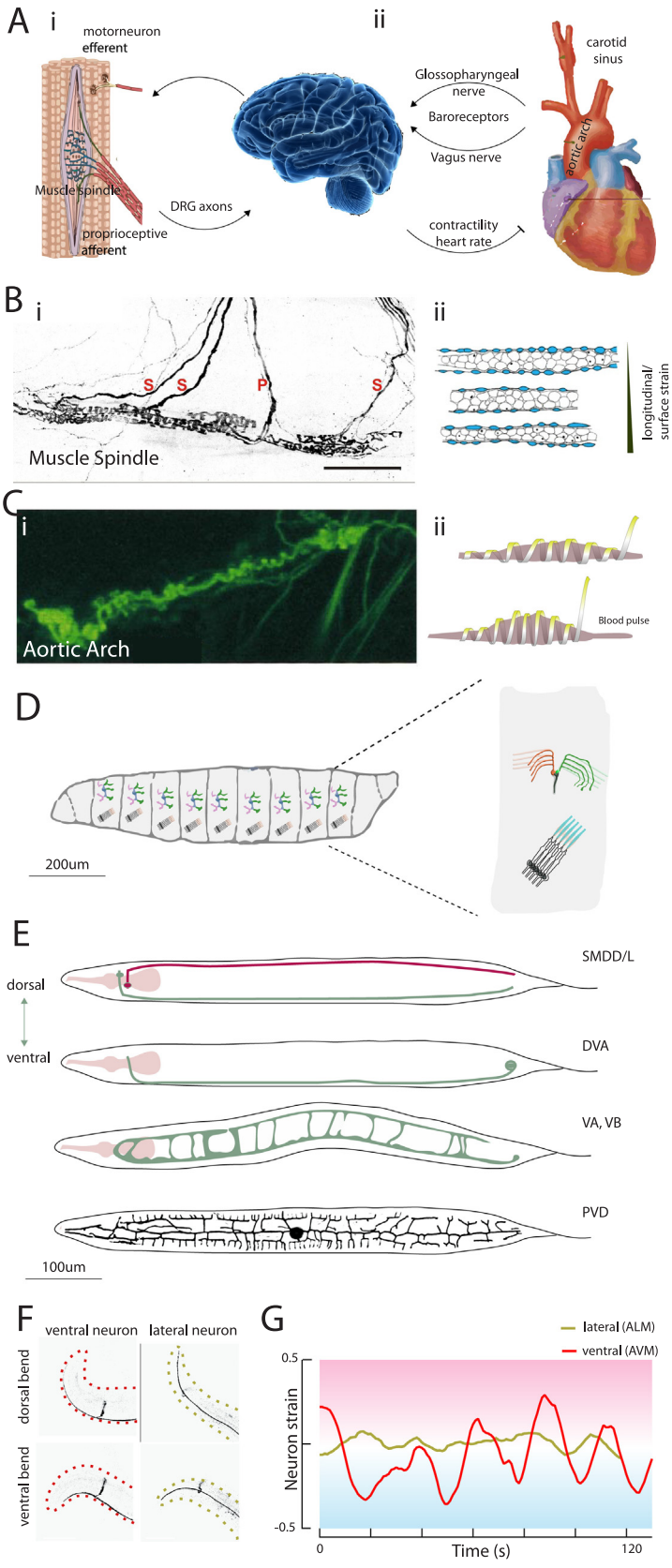

Fig. 1. Brain-body feedback loops initiated by mechanical stretch receptors A) Schematic representation of the two peripheral neuronal pathways connecting the central nervous system with muscles and the blood vessels. **i** Proprioceptive sensory afferent of the dorsal root ganglion neurons innervate muscle spindles and golgi tendon organs (not shown) embedded in skeletal muscle. The afferent form annulospiral sensory terminals, which wrap around the intrafusal muscle fibers become compressed during muscle tension, which is hypothesized to activate embedded mechanoreceptors [15]. **ii** Specialized mechanosensitive baroreceptors of the carotid sinus travel within the glossopharyngeal while aortic arch baroreceptors go via the vagus nerve and become activated by increased blood pressure, which signal to the brainstem. This leads to an inhibition of the sympathetic nervous system and a reduction in blood pressure, heart rate and arterial vasoconstriction [34]. B) Representative morphologies of mechanosensors innervating the **i** proprioceptors of the mouse muscle spindle (Photograph reproduced from [27] under CC-BT-04), and **ii**, their schematic change in dimensions. Note the flattening of the terminals (blue) and separation with longitudinal strain (with permission from [29]). C) Representative morphologies of mechanosensors innvervating the **i** aortic arch (with permission from [33]), and **ii** the hypothetical deformation by increased blood pressure/flow. D) Location and schematic morphology of fly larval md and chordotonal neurons. E) Location and morphology of proposed proprioceptors in *C. elegans*. In total four SMD neurons have their cell bodies in the head and extend two long processes on the ventral and dorsal side respectively. DVA interneuron is located ventrally and are subjected to repeated elongation and contraction cycles during locomotion (unpublished), similar to the ventral touch receptor neurons [68]. A, B and D-type motorneurons innervate ventral and dorsal side and are subjected to similar stresses during locomotion. Only A and B-type motorneurons have asynaptic processes implicated in proprioception. PVD extends elaborate dendritic processes between the sarcomeres of body wall muscles. Their location between the muscles and hypodermis is ideally placed for muscular strain measurements. F) Snaphots of ventral and lateral neurons (ALM and AVM) in animals with ventral and dorsal body bends. (Figure adapted from [68]) G) Possible deformation of ventral proprioceptors as a function of body bending (unpublished). Proprioceptors located at the ventral and dorsal side experience cyclic compressive and tensile strains due to body movement, whereas lateral neurons solely experience bending. Note, lateral neurons close to the midline do not experience any contraction/elongation cycles (like ALM, [68]).

currents [7] are responsible, at least partially, for mediating proprioceptive stretch-evoked currents in muscle-nerve explants, but respond to different mechanical stimuli, while TRP, ASIC, DEG/ENaC and Piezo channels have been related to barosensation [17,18]. The nature of the channel, the direction and moiety of ion flow strongly depends on the system studied and the gating probability on the force vector applied [19]. Despite these wildly differing physiological functions and ion channels they employ, it is plausible that these mechanoreceptors share

a common principle of mechanosensation, by sensing the change in dimension of the structure they innervate. Because the neurons hosting the mechanosensors are made of elastic proteins and membranes, the changes in length, width, radius or volume create a stress on the mechanosensors which subsequently changes the physiological states by modulating ion channel function. Underlining these fundamental principles in mechanosensitive stretch sensation is subject of this review.

Whereas the mechanical and physiological principles of the sense of touch, hearing and mechanical nociception have recently been summarized in various excellent reviews [3,20–24], here we highlight current findings in proprioception and visceral mechanosensation.

2. Proprioception

Locomotion requires the interplay of the central nervous system (CNS), muscles, and the peripheral nervous system (PNS). Sensory feedback from the mechanosensory neurons of the PNS provides moment-by-moment adjustments to the pattern, and locomotion critically depends on this adaptive motor control. Sensory neurons innervating the specialized mechanoreceptors in the muscles and tendons become stretched or otherwise deformed from their equilibrium position and sense muscle tension changes, joint angle and tendon length [7,15], to initiate an action potential. This `6th senses of our own bodies', has the peculiar property that we just become aware of it when something has gone wrong: The lack of proprioception for example, is known to everyone upon a squeezed nerve, which could numb the entire limb. Less common is the so-called phantom pain after limb amputation, which has been associated to proprioceptive nerve functions, that can be minimized by coupling the terminal amputated nerve to existing muscles [25].

Proprioceptive stretch sensation is probably the best characterized stretch sense in mammals on the morphological and circuit levels and has been extensively reviewed in [15,26]. The basic feedback loop consists of sensory neurons that measure the change in muscle mechanics and adjusts the contraction via signaling through motoneurons (Fig. 1A). Axons emanating from the dorsal root ganglion innervate specialized sensory receptors in the skeletal muscles, commonly summarized as muscle spindles and Golgi tendon organs. Muscle spindles are located inside the muscles and are positioned parallel with the contractile muscle fibers, making them most sensitive to length changes during contraction. They are supplied by two types of sensory afferents, each of which encode a different mechanoresponse: Afferent type 1 are most sensitive to strain rate and the movement will go undetected if it is too slow [26], while type 2 signal sustained muscle activity. However, it is not known whether or not the two types of afferents use different combinations of mechanosensitive ion channels to differentiate between the differential and the sustain stimulus, or if it is an emergent property of their morphology. At this end, both groups and nerves innervating Golgi tendon organs express Piezo2 channels [7]. In both cases, however, we can find the sensory terminal of the afferents are neatly positioned to sense changes in muscle length and tension by wrapping around the muscle spindle in spiraling rings, giving them the name annulospiral sensory endings [7,27]. In semi-isolated muscles, mechanical stretch of the spindles causes a measureable extension of the sensory region that is accompanied by an increase in the spacing between the turns of the annulospirals [28] and a flatting of the terminals themselves [29] (Fig. 1B).

At least two different mechanosensitive ion channels have been implied in murine proprioceptor function, ASIC3 [16] and PIEZO2 [7]. Patients with a mutation in Piezo2 have substantial defect in touch sensation but also movement control and posture, indicative of a defect in mechanical stretch receptions [30]. In general, Piezo proteins are responsible for mediating wildly differing behaviors, begging for the answer how they sense force during touch, proprioception, pain, osmosis, blood flow etc. (for a review on Piezo proteins see [31]). The data from mouse suggests that ASIC3 and Piezo2 respond to different stimuli: Force application with a mechanical probe directly to the soma or neurite primarily activated Piezo2 dependent current [7] while substrate stretch primarily activated ASIC3 dependent currents [16]. Intriguingly, ASIC3 knockout had no effect on directly stimulated neurons, but eliminated substrate-stretch evoked current. Whether or not ASIC3 is a mechanoelectrical transduction channel itself or assisting other transducer like Piezo2, remains to be tested in an heterologous system. Along those lines, Piezo1 has also been shown to be sensitive to the direction of the force vector, being more sensitive to pulling than to indenting stresses [19].

In summary, experiments on mammalian proprioceptors show that mechanoreceptor activation depends on the force-vector applied, highlighting the need to understand the mechanics of mechanoreceptor system in question.

3. Baroreflex

The so-called baroreceptors (pressure sensor) are stretch-sensitive neurons of the vagus or glossopharyngeal nerve that innervate the carotid and aortic arch arteries and respond to mechanical dilatation of blood vessel walls during increased blood pressure and stress (Fig. 1A). They signal blood pressure changes to the brain stem and provide a rapid negative feedback loop in which an elevated blood pressure obligatorily causes the heart rate and accordingly blood pressure to decrease. These vital functions are reflected in the huge medical literature and anatomical classification available. Unfortunately, our mechanistic and molecular understanding, of how individual baroreceptors and their ion channels sense mechanical arterial stretch, severely lacks behind the clinical importance of the baroreflex [32]. Recent studies, however, have begun to shed light on the mechanism of baroreception [11]. The morphology of the afferents form extensively coiled, annulospiral morphologies [33], similar to proprioceptive endings in intrafusal muscle fibers (see Fig. 1C and [15,27]), that are consistent with the hypothesis that arterial baroreceptors sense strain and not pressure [34]. Whether or not these morphologies are tied to neuronal activation, remains to be established experimentally by correlating their activity to cellular strain, but it is tempting to speculate that these highly spiraling, spring-like morphologies naturally exist in a slackened state, while becoming stretched out during aortic distension [35].

The molecules converting arterial stretch into a biochemical signals are still a matter of debate. Aortic arch and carotid sinus baroreceptors of the rat nodose ganglia express mechanosensitive ion channels at their nerve terminals innervating the blood vessels [33]. Those proposed mechanosensors included Piezo [11], yENaC [33], ASIC2 [36] and TRPC5 [37] ion channels, but their direct role in this context is unclear and currently disputed [38–40]. Recent data shows that both, Piezo1 and Piezo2 act redundantly in nodose and petrosal ganglia of the vagal nerves to regulate the baroreflex [11].

Alterations in baroreceptor sensitivity has a tremendous clinical relevance and is implicated in a variety of cardiovascular diseases and hypertension [41,42]. A big role in the disease process plays the elasticity of the innervated vascular wall [43,44], as well the mechanics of the nerve itself [45]. A recent computational model emphasizes that baroreceptor signaling is sensitive to changes in mechanical strain of the aortic walls, where the changes in arterial compliance is positively related with a decline in baroreceptor sensitivity [46]. Taken together, the baroreceptor measures the changes in dimensions of the innervated vessel, which deforms according to their wall tensions and intraluminal pressure. This in turn can be affected by aberrant elasticity of the vessel wall and/or neuronal cell mechanical properties.

4. Insights from non-vertebrate model organisms

As in other animals, the locomotory gait of the popular non-vertebrate models *Caenorhabditis elegans* and *Drosophila melanogaster* is

regulated by stretch-activated mechanoreceptors innervating their body walls and segments at all stages during their lives [47,48]. At least three different neuronal sensory organs have been related to proprioceptive feedback control in wandering fly larvae (Fig. 1D) – multidendritic (md) neurons, chordotonal organ and campaniform sensillae (since the major function of this organ is to sense cuticle strain and flight control in adult flies, we refer to Refs. 49,50).

In the fly larvae, locomotion occurs by peristaltic extensions and contractions of the individual body segments, such that during each wave a segment experiences a cycle of tension and relaxation. The individual proprioceptors are positioned to ensures direction-specific sensing during forward and backward locomotion [51]. This information is carried back to the central nervous system by proprioceptive feedback from the bipolar dendrite and class I md neurons (Fig. 1D), which lie just under the cuticle and based on their morphology and data from different insect species, are thought to be stretch sensitive cells. This proprioceptive feedback is critical for coordinating the rapid muscle contractions of a peristaltic wave [51]. The ion channels mediating this response are the transient receptor potential homolog NOMPC [52] and transmembrane channel like proteins of the TMC family [53], while the fly Piezo protein has been implicated in bd neuron stretch responses [54]. Employing high-speed confocal scanning microscopy it could be shown that the deformation pattern in md neurons during forward and backward locomotion and found that curling of the dendrites correlated with the strength of direction sensitive calcium transients [55] in moving animals (Fig. 1D). How channel activation is related to cellular deformation of these dendrites in freely locomoting larvae is still an outstanding question, even less is known about the mechanical properties relating the deformation to mechanosensation.

The mechanics and molecules of proprioception are better defined in the larval chordotonal organs (Fig. 1D), which are ciliated stretch receptors that increase their firing rate in response to substrate vibrations and act as low-frequency stretch receptors [49]. Since in-situ imaging of larval crawling is missing, we do not know how the ChO deforms during locomotion and how it sense stretch. However, it was shown that under tensile, mechanical stresses to the cap cell, the dendritic cilia start to bend, which has been suggested to cause mechanoreceptor activation [56]. How a mechanical stretch can cause bending of the cilia is a mystery, but active motility was suggested to cause lateral deflection of the ciliary microtubules [56]. Laser cutting of the ChO suggest that the sensory and support cells are under constitutive mechanical tension [57]. Direct mechanical deformation also suggest that the bending stiffness of the organs is relatively low compared to its stretch stiffness, consistent with chord held under tension. The molecules and structures supporting this pre-tension are not known, but due to the abundance of myosin in the cap cells, it is likely that it plays a prominent role in cell mechanics [57]. The ECM seems to play a special role in cell mechanics and force transfer. The leucine-rich repeat protein Artichoke localizes to the dendritic tips and thus along similar anatomical regions as NOMPC. Loss of function in this protein leads to cilia disorganization reminiscent of a loss in mechanical stretch [58].

What might be the significance this tension? Similar to *C. elegans* touch receptor neurons [20] and the hair-cell transduction apparatus [59,60], this mechanical tension is hypothesized to be critical for maximizing the sensitivity of mechanotransduction channels through keeping their open probability at rest at a value, where small mechanical stimuli would cause the maximal open probability change [61]. In other words, even a low number of channels can cause a graded response since the current flow is proportional to the open probability. Picturing the energy landscape in Fig. 2A, the channel would not reside in its local minimum, but on the time average slightly closer to the energy barrier (equivalent to a lower barrier height). Putting the channel under a constitutive tension also could set the direction in which the channel moves within the higher dimensional energy landscape (Fig. 2B), such that different states become populated. The bearing of the pre-stress is likely mediated by cytoskeletal elements, e.g. the spectrin cytoskeleton [62] rather the lipid bilayer, although membranes of several cell types have been proposed to resist flow during timescales that are important for mechanosignaling [63].

Like in bd neurons, the mechanoreceptor in chordotonal organs is NOMPC [52] but its function, however, is not cell-autonomous. Unexpectedly, mechanotransduction of gentle touch, sound, and proprioceptive feedback during larval locomotion requires the adhesion-type GPCR latrophilin (dCirl) [64] as disrupting its function impaired larval locomotion and body contraction amplitudes. Furthermore, dCirl is specific for mechanosensation, as latrophilin mutants fail to increase the spike rate in chordotonal organs in response to mechanical stimuli [65,66]. Superresolution imaging showed that dCirl colocalizes to region with the mechanosensitive channel where it suppresses cAMP levels and increases excitability of ChOs. The location of the receptor is thus in accordance with the sites of ionotropic mechanotransduction, which is present in the dendritic membrane and the single cilium of ChO neurons. The classical concept of GPCRs as sensors of chemical compounds has been changing and the notion that GPCRs detect and transduce physical modalities, such as, membrane stretch and osmolarity, has been getting traction and opened a new yet crucial avenue of research in the field of neuronal [64,66] and non-neuronal mechanobiology [67].

Likewise, the visual opsins NINAe and Rh6 are primarily expressed in the chordotonal organs and require all-trans retinal as a cofactor, but act independent of temperature, light and vision [65]. They have an indirect effect on the expression and localization of mechanosensitive TRP channels such as NOMPC, Nanchung and Inactive and its mutations lead to defect in locomotion and neuronal firing upon stretch. Interestingly, the opsins also seem to have a neuroprotective function, as dendrites lacking NINAE and Rh6 are more flaccid, disorganized and showed increased membrane blebbing than in wildtype flies [65]. These phenotypes are similar to neuromechanical defects seen in *C. elegans* mechanosensors [68] and it is interesting to speculate whether or not the mechanical pre-stress seen in chordotonal organs [57] depends on opsin function is necessary for sensory function.

Proprioceptive coordination of locomotion in *C. elegans* is similarly complex as in *Drosophila*. At least five different neuron classes have been implicated, PVD multimodal neurons [69], TRN mechanosensors [70], DVA interneurons [48,71,72], the SMD neurons [73] and VA, VB motoneurons [74,75] (Fig. 1E). Motoneurons, PVD and DVA have been directly shown to be activated by body bending, either in microfluidic devices [75] or microcapillaries [48,69], although the contribution of DVA activity in flexural control of freely behaving animals needs further studies [71]. In particular, the cholinergic motor neurons have long undifferentiated processes that extend along the nerve cords without forming any synapses. Intriguingly, in the B-type motor neurons, these long asynaptic processes extend past posteriorly than their neuromuscular junctions. These asynaptic processes are hypothesized to be proprioceptive sensors of these motorneurons([75] and references therein).

On one hand there is considerable data on the mechanical properties for *C. elegans* TRNs, which have been shown to be under constitutive, spectrin-dependent mechanical tension of a ~15 μN/m [62] with an average elasticity [68] of ~6 kPa, but on the other hand almost no mechanical information is available for *C. elegans* proprioceptors. However, in the current `mission accomplished' model for *C. elegans* proprioception [75], the cellular and molecular mechanics are hypothesized to play an important role. In this model, muscle contraction causes a bending strain which generates a stress in the proprioceptors [48] dependent on the neuron's elasticity. Our own data derived from animals expressing a spectrin-tension sensors in candidate proprioceptors like DVA or DA9 show that these neurons experience a similar mechanical pre-stress as TRNs (Das et al., in preparation), indicative that tension is an emergent property of the spectrin cytoskeleton. Whether or not this tension in proprioceptors has a role in locomotion

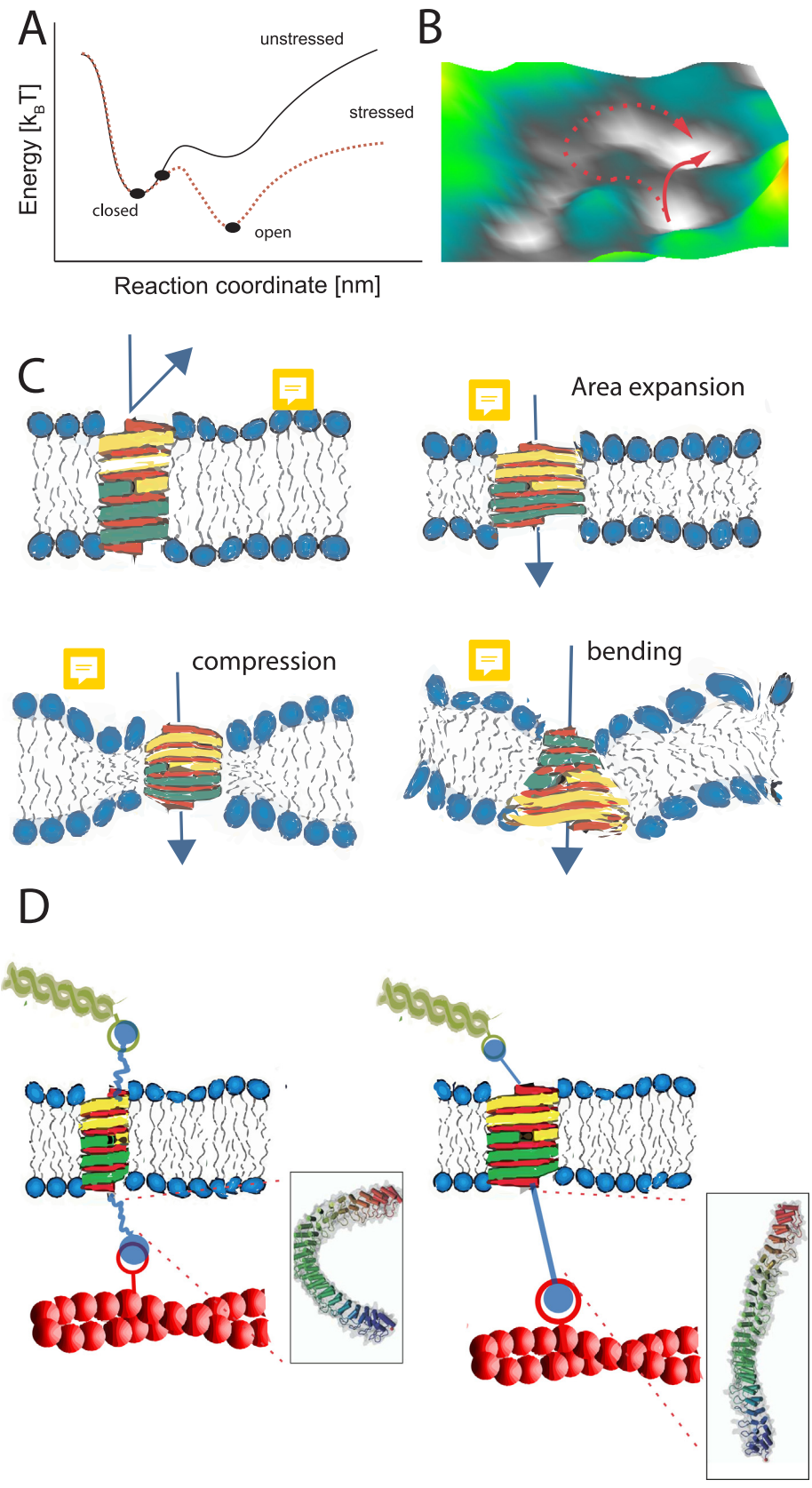

Fig. 2. Potential force transmission pathways in mechanosensitive ion channels. A: Sketch of a hypothetical 1D energy landscape of a mechanosensitive ion channel subjected to stress. The force tilts the energy landscape leading to an effective lowering of the barrier separating the closed and open state. A pre-stressed channel will not reside in the deepest portion of the well, but will be statistically be more likely closer to the barrier apex. Black ovals indicate positions of the ion channel state. B: Two-dimensional representation of the energy landscape. A mechanical pre-stress could prescribe a preferred reaction coordinate [107] during application of mechanical stress and thus define the opening mechanism. C: Schematic scenarios of the force-from-lipid principle. **i** unstressed state, closed. **ii** membrane under mechanical tension with thinning bilayer leading to hydrophobic mismatch. **iii** local membrane deformation due to local phase separation by increased membrane tension [95]. **iv** increased membrane tension due to membrane bending [31]. D: Schematic representation of the force from filament principle, in which an ion channel interacts with an ECM protein (green triple helix) and/or an intracellular tether to the cytoskeleton. Force application will stretch the tether and cause a conformational change independent of an area increase. The inset shows a hypothesized gating tether composed of 24 ankyrin repeats subjected to a terminal force of 50 pN [108]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article)

remains to be tested. The morphological changes associated with signaling in proprioceptors of *C. elegans* are also ill-defined. However, we can speculate that in SMDD, DVA and motoneurons body posture sensing is coupled to compression and extension of their processes, similar to the morphological changes that happen in ventral TRNs during body bending (Fig. 1F, G and ref 62). In contrast to the lateral neurons, ventrally and dorsally located neurites are perfectly positioned to receive the maximum amount of stress per change in body posture.

Likewise, the most distal dendrites in PVD might experience lateral movement, and thus shares significant similarity with mammalian muscle spindles, such that the sensory terminals are oriented perpendicular to the long-axis of the sarcomeres, an arrangement that might maximize strain sensitivity.

The channels mediating the mechanical activation are less well defined and each of these neurons expresses multiple sets of potentially mechanosensitive ion channels. DEG/ENaC channels are implicated in the response to mechanical bending in PVD and the motorneurons. UNC-8 and DEL-1 are putative pore-forming subunits expressed in VA and VB motoneurons and are expected to localize to specialized undifferentiated processes in the VA neurons proposed as stretch receptors that do not form neuromuscular junctions [76]. However, precise localization of these channels has not been determined and mutations therein only result in subtle uncoordination and reduced sinusoidal amplitude during locomotion [74], suggesting that proprioception is mediated by other yet to be identified channels [76]. MEC-10 is a pore-forming subunit of the mechanosensory channel in PVD and TRNs and its mutations lead to a reduction in bending evoked calcium transients in PVD [69]. It localizes to the dendrites consistent with its function in sensing muscle tension [77].

Channels of the TRP family have been proposed to act as mechanosensors in SMD and DVA neurons. Mutations in TRP-4 lead to an increase in body curvature while ablation of DVA decreases body bending, consistent with their function in proprioceptive mechanosensation. Although it could be shown that TRP-4 is a mechanosensitive pore-forming channel subunit [48,72], mechanosensitivity for TRP-1 and TRP-2 in a heterologous system still needs to be determined [73].

How TRNs are involved in proprioception is not completely understood. Mutations in the mechanosensitive ion channel MEC-4 that lead to TRN degeneration as well as targeted laser ablation of anterior and posterior TRNs also lead to changes in swimming locomotion [70]. However, MEC-4 expressing neurons are not sensitive to mechanical stimulations delivered in the low frequency range that occurs during locomotion, but only at higher > 5 Hz frequencies [78,79], making it unlikely that TRNs sense body deformations. MEC-4 might sense viscosity of the surrounding medium by measuring the load on the body wall which is then involved in gait adaptation [70].

Despite all of these neurons are activated by changes in body posture, it is not clear whether or not these neurons act directly as a cell autonomous stretch receptor or if they respond to an upstream sensory factor. The central question remains to be answered, how bending radii of the body in the order of 25–50 μm are sensed on the molecular scale by ion channels that are more than 3 orders of magnitude smaller. But, even if we knew the mechanosensitive ion channel and the sole mechanoreceptor neurons, it remains unclear how cellular deformation is coupled to mechanoreceptor activation.

5. How do proprioceptors sense organ and muscle stretch?

Several mechanisms have been proposed to govern mechanosensitive ion channel opening, all of which can be classified under two general, not necessarily mutually exclusive, scenarios, independent of the exact nature of the channel and its environment. The two paradigms at play have been dubbed the force-from-lipid [80–82] and force-from-filament principles [20,83], according to the dominant force transmission pathway through the membrane or some protein connection, respectively. In either case, the force applied to the mechanosensitive channel will tilt its energy landscape and thus alter the probabilities whether or not it is found in the open or closed conformation. The work done by the force needs to be larger than the surrounding thermal energy (on the order of $1k_bT$) such that the molecular sensor can differentiate between stochastic thermal fluctuations and a deterministic, mechanical signal [84]. For example, 1 kbT is the work required for stretching a molecular spring with a spring constant of 8 pN/nm by 1 nm. In terms of a planar lipid bilayer, 1 kbT corresponds to an area fluctuation of 200 nm^2 (0.00001% of cell surface) for a eukaryotic cell of size 20 μm with a typical neuronal membrane tension of about 20 μN/m [85,86], or ~ 10 nm2 for bacterial membrane tension of 1 mN/m [87].

The force from lipid principle dates back more than 40 years and has received much theoretical attention. According to this principle, mechanosensitive ion channels are sensitive to changes in plasma membrane bilayer mechanics, notably membrane tension and/or membrane bending [17] (Fig. 2C). The importance is evident since all ion channels are embedded into a cell membrane and thus must comply, one way or another, to changes in lipid bilayer mechanics. Second, the unique pressure profile in biomembranes is well suited to exert directed forces on the molecular scale [88].

This is a consequence of the fact that membranes have a large elastic area expansion modulus endowing the bilayer will little area elasticity. Thus, without a membrane reservoir, little increase in surface area by a mechanical forces must rapidly elevate in-plane membrane stress, which is accompanied by thinning of the membrane. This membrane thinning generates an energetically unfavorable hydrophobic mismatch between the trans-membrane segments of the embedded proteins and the fatty acid core of the lipid molecules, to which the conformationally flexible channels respond by tilting their TMDs to reduce this mismatch such that the free energy of the membrane protein/lipid system is minimized [89]. This tilting is observed in molecular dynamics simulation and crystal structures of plant and bacterial mechanosensitive channel of large and small conductance (MscL/S; reviewed in [87,90,91]). This associated conformational change is coupled to pore opening and the predicted area expansion of ~20nm2, necessary to traverse the energy barrier. Further evidence for the FFL principle comes from reconstitution of mechanosensitive ion channels TREK, TRAAK and Piezo in heterologous systems and lipid vesicles, in which high enough membrane stretch easily occurs due to the lack of an extensive membrane reservoir [92]. However, the questions of how these proteins are gated in eukaryotic cells remains an interesting intellectual challenge. Piezo ion channels for example, are humongous protein complexes curving the membrane into a cup-like structure [93], which could lead to a channel opening by coupling changes in membrane tension to changes in curvature and bending [94]. Despite these unusual structural organization and doming, Piezo1 gates at unphysiological membrane tensions of 1–5 mN/m [31], levels that lead to phase transitions in model membranes [95] and are two or three order of magnitude of what is normally fond in neurons [62,86].

As noted by Howard and colleagues [14], the little changes in membrane tension in eukaryotic cells might not be sufficient to cause an expansion of ~100nm2 necessary to gate ion channels such as Deg/ENaCs, Asics or TRPs due to the small area change associated to their conformational change. Whether or not membrane tension is the primary gating mechanism employed in neurons, remains challenging to probe, but the possibility exists that a physical interaction between channel and the cytoskeleton is involved in force transfer to stabilize the open conformation and permit ion flux.

This so-called force-from-filament principle (FFF, Fig. 2D, [83]), postulates an interaction of the ion channel with a `tether' on the intracellular (e.g. to the cytoskeleton) and/or the extracellular side (e.g. the ECM). Whereas it is undisputable that an ion channel interacts with the membrane, the quest for intra- and extracellular interaction partners has been notoriously difficult [20]. A genetic interaction between the stomatin protein MEC-2 and microtubules in *C. elegans* was long time the basis for proposed a tethering mechanism [96], a line of thought that was abandoned based on results from structural and functional experiments [97,98]. Recent data, however, highlight the importance of the mammalian MEC-2 homolog STOML3 for Piezo1 mediated mechanoreceptor currents in cultured dorsal root ganglion (DRG) neurons [99,100] that are involved in the sense of touch and proprioception. It has been suggested that STOML3 facilitates force

transfer to ion channels and the observation that this protein was targeted specifically to neuron - substrate adhesion domains emphasizes the potential role of extracellular tethering [101]. In *C. elegans*, several extracellular matrix proteins are required for proper touch sensation (reviewed in [20]), but the role of ECM in proprioception remains to be determined.

Strong candidates for the FFF principles is NOMPC (or TRPN, similar to TRP-4 in *C. elegans*), the Drosophila TRP channel homolog responsible for proprioceptive functions in md neurons, neurons of the campaniform sensillae and chordotonal organs. NOMPC molecules have a large, helical intracellullar domain containing 29 ankyrin repeats implicated in force transfer from the cytoskeleton to the channel gate [102]. Molecular dynamics simulation of the ankyrin from erythrocyte Ankyrin-R domain reveals an enormous flexibility and the capability to buffer stresses by eventually unfolding and refolding. The repeats extend far into the cytoplasm and make contacts to microtubules – an interaction that is critical for proper physiological function. Strikingly, transplanting the MT-binding domain to voltage gated potassium channels (Kv2.1) confers mechanosensitivity to otherwise non-mechanosensitive channels, presumably by acting as a gating tether and transferring stretch from the microtubule network to stabilize the open conformation [103].

Another mechanism of channel gating has been proposed for osmosensory neurons of the brain. During cell shrinkage, the plasmamembrane collapses, creating negative tensions differentials and collides with the underlying microtubules network visible as microtubule buckling mechanism [104]. This generates pushing forces from the cortical microtubule cytoskeleton to activate TRPV1 ion channels in ONs and signal plasma hypertonicity to command thirst during dehydration. The interaction between the channel and the microtubules is likely direct, as TRPV1 has two microtubule binding sites at the C-terminus [104] leading to very fast activation within 4 ms of force application. Taken together, new methods and experimental strategies will reveal the natural stimulus and how different mechanosensitive ion channel are gated by mechanical stresses within their native environment.

6. Future perspectives, potentials and open questions

Although we just concentrated on mechanical signaling by neuronal stretch receptors, without comprehensive discussion of the sense of touch, hearing, pain and most visceral mechanosensation processes, the picture is already very complex. In order to build predictive models, we need a better understanding of how mechanoreceptor morphology enables mechanical signaling and how the shapes of their sensory terminals changes upon stretch. This alone is not sufficient to estimate the stresses during signaling, we also need information about their mechanical properties. This change in geometry together with information about the mechanical properties of the constituent cell types, will allow us to quantify the mechanical stresses involved in mechanical signal. We thus need to deploy techniques that allows us to visualize the distribution of stresses along and within mechanoreceptors and gain insights into the force transmission pathway. We will also need single molecule techniques to identify energy barriers and the force associated with gating to map the kinetics to structural changes. But how can small model organism help us to gain a better understanding of the fundamental processes, even though they lack lungs and blood vessels?

Strikingly, the deformation frequencies and strain rates that the vagal sensory afferents experience during breathing and arterial dilation are very similar to the deformation rates that proprioceptive neurons experience during *C. elegans* and *Drosophila* larval locomotion. Both processes involve the repetitive mechanical deformation in the range of 0.6–1.5 Hz (heart beat and breathing frequency [105]) that is sensed by specialized mechanoreceptors, while the limit cycle of *C. elegans* and *Drosophila* locomotion behavior repeats every 0.5–1 s [106]. Thus, *C. elegans* sensory neurons and vagal afferent experience similar stresses during mechanosensation and, as postmitotic and terminally differentiated cells need to be functional and sensitive for their entire life span. This has dramatic demands on to their mechanostability and how they achieve their resilience is yet to be explored. Thus, *C. elegans* and *Drosophila* remain excellent models to explore the mechanics of MS channel gating and mechanical stability under continuous mechanical stresses. Since the ion channels involved and the components of the load bearing cytoskeleton are highly conserved in worms and humans and ubiquitous components of all neurons, the findings may have direct implications on mammalian systems. Despite the mind-boggling progress made in the field of mechanosensory transduction in the last 10 years, several fundamental questions remain open: Do cells sense stress or strain? Is the major mechanotransduction pathway along the membrane or the cytoskeleton? The future promises answers combining high-resolution force spectroscopy with new imaging modalities to probe functional mechanics in mechanical stretch reception.

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