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REVIEW ARTICLE
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Functional biology of ion channels: a review

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Abstract

Over the past few decades, a great deal of attention has been focused on discovering the protein partners that form mechano-electrical transduction (MeT) channels in somatic mechanoreceptors. Two classes of ion channel proteins are leading candidates: amiloride-sensitive channel (ASCs) and transient receptor potential (TRP) channel proteins. Here, we surveyed the literature to establish that most, if not all mechanoreceptor neurons in mice express multiple ASC and TRP channel proteins. But, the landscape of ion channel co-expression in mechanoreceptor neurons is only beginning to be mapped. Future work aimed at refining such maps for mammalian mechanoreceptor neurons will be critical for deeper understanding. Also, each of these potential MeT channel subunits operates within a large company of other ion channel actors that increase the complexity, flexibility, and robustness of somatosensory neuron function. Recently, two additional classes of membrane proteins (Piezo and TMC) have been linked to mechano-transduction. This situation is likely to exist in other mechanoreceptor neurons, including those responsible for touch and pain sensation in mammals.

Keywords: amiloride-sensitive channels (ASCs), mechano-electrical transduction (MeT) channels, mechanoreceptor neuron, somatosensory neuron, transient receptor potential (TRP) channels.

Introduction

All sensory neurons are alike. Each sensory neuron detects a physical stimulus and produces an electrical signal that gives rise to behavioural responses, conscious perceptions, or both. Many operate near the physical limits of detection and operate over a dynamic range of several orders of magnitude. These properties suggest that they are endowed with a detector, an amplifier, and mechanisms for gain control. One of the most striking and well understood examples is the ability of photoreceptors to detect single photons while retaining sensitivity to light intensities that vary by nine orders of magnitude [1].

Nociception is a physiological process which involves transduction, transmission, modulation and perception of the noxious stimuli. Chemical mediators are important components of the nociceptive reflex and offer a target of pharmacologic modulation [2]. Nociceptors are specialized nerve fibres that have their dendritic endings in peripheral tissue, with several different subtypes identified. The fastest of the nerve fibres are the large diameter myelinated A-α sensory fibers which are involved with the sensations of touch, pressure, etc. Somewhat slower are the thinly myelinated A-α fibres which are involved in sharp physiologic and acute pain. C-fibres have small diameter, are unmyelinated and, are very slow conductors of nociception and are involved in dull, aching chronic pain. Chemical modulation of pain transmission occurs via several neurotransmitter-receptor systems that have been shown to affect the spinal processing of nociceptive input. Excitatory neurotransmitters (e.g., substance P), are active in spinal cord and enhance pain transmission. The inhibitory elements are the opioids, the α2-adrenergic fibres, serotoninergic and adenosinergic receptors. Endogenous neurotransmitters work on dorsal horn neurons to inhibit excitatory transmitter release and consequently to decrease pain and perception.

The skin is the largest sensory surface, extending nearly two square meters on an average. Mechanoreceptor neurons are principal actors in this theatre. They are responsible not only for detecting mechanical cues, but also for encoding and transmitting all relevant information to the central nervous system. Every moment of every day, our skin and its embedded sensory neurons are bombarded with mechanical cues that we experience as pleasant or painful. Knowing the difference between innocuous and noxious mechanical stimuli is critical for survival and relies on the function of mechanoreceptor neurons that vary in their size, shape, and sensitivity [3]. Their performance is shaped by ion channels that include, but are not limited to, sensory transduction channels. Agents that activate or inhibit mechanoreceptor neurons can exert their influence by acting on channels other than transduction channels. For example, naked mole rats are insensitive to the persistent skin acidification that is a feature of their environment. These animals have acid-gated ion channels (ASICs) with a similar sensitivity to protons (H^+) as those found in mice. However, the voltage-gated Na^+ channels expressed in their C-fibre noci-ceptors are hypersensitive to inhibition by protons and this inhibition

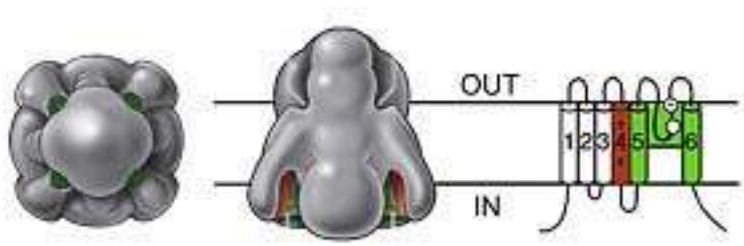

Figure-1. A low-resolution electron microscopic image of a purified Na+ channel (Sato et al,2001)

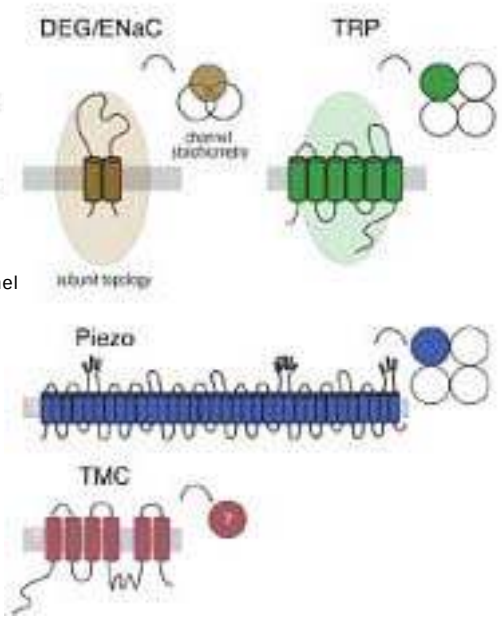

Figure-2. Topology and stoichiometry of proteins proposed to form MeT channels in animals

counterbalances the excitation due to ASIC activation, rendering animals insensitive to acidifi-cation [4]. Thus, the difference in nociceptor sensitivity arises from variation in voltage-gated Na^+ sodium channels that are essential for action potential generation rather than any variation in sensory trans-duction.

Studies on ion channels

Electrical signalling in biology depends on the rapid, highly sensitive response of voltage-gated ion channels to small changes in membrane potential. Voltage-gated ion channels derive their steep voltage dependence of activation from electrically driven movement of positively charged amino acid residues outward across the membrane in response to depolarization. Voltage-gated ion channels generate electrical signals in species from bacteria to human being. Their voltage-sensing modules are responsible for initiation of action potentials and graded membrane potential changes in response to synaptic input and other physiological stimuli [5]. In their landmark papers on voltage-clamp analysis of Na^+ currents in the squid giant axon, Hodgkin and Huxley predicted that activation of the Na^+ conductance must involve movement of charged particles, now termed "gating charges," across the membrane electrical field [6]. The gating charge movements' estimates indicate movement of 12–16 positive charges outward across the electric field during gating of Na^+ or K^+ channels [7].

Discovery of the voltage sensors and gating charges of ion channels: Biochemical studies using neurotoxins as molecular probes led to discovery of the voltage-gated Na^+ channel protein and reconstitution of its voltage-dependent gating and ion conductance from purified protein and phospholipid components. Determination of the primary structure of the voltage-gated Na^+ channel from *Electrophorus electricus* electroplax revealed a protein of more than 1800 amino acid residues in length, arranged in four repeated domains (I–IV). These four domains are arrayed around a central pore, as observed in more recent cryo-electron microscopic images (Fig.1) [8].

Phospholipids and voltage sensor function: An essential role for phospholipids in the structure and function of voltage-gated Na^+ channels was suggested by early biochemical experiments in which specific phospholipid combinations were required for reconstitution of ion conductance, voltage-dependent toxin binding, and voltage-dependent gating of purified Na^+ channels. Consistent with this requirement for specific lipids, the high-resolution structure of a KV1.2/2.1 chimera revealed intrinsically bound phospholipid molecules [9]. These bound phospholipids are seen around the waist of the protein where it contacts the phospholipid bilayer and also in the internal and external vestibules in the voltage sensor [9]. The phospholipid head groups are in position to serve as ion pair partners of gating charges at the intracellular and extracellular surfaces of the membrane, but not within the core of the voltage-sensing module. Evidence that phospholipid head groups can affect voltage-dependent gating supports an important role for these bound lipids in voltage sensor function [10, 11].

Studies on mechanoreceptor neurons

Though mechanoreceptor neurons were first studied more than 75 years ago [12], the events that link sensory stimulation to neuronal activation are only beginning to be understood. Genetic screens for animals defective in touch sensation have revealed critical roles for genes encoding TRP channels and ASCs in behavioural responses to mechanical inputs (Fig.2). We review data demonstrating that TRP

channels and ASCs are widely distributed in the sensory neurons of vertebrates and examine the idea that these channels have conserved, but distinct functions.

Sensing with ion channels: For several decades, attention has been focused on the idea that mechano-electrical transduction (MeT) channels are formed by proteins enriched in mechanoreceptor neurons and required for their function. The mec-4 ASC and osm-9 TRP channel genes were the first candidates identified from classical genetic screens. The ASC genes are conserved in animals, but absent from plants, bacteria, and fungi [13] and encode proteins with two trans-membrane domains and a large extracellular domain. As revealed in high resolution crystal structures [14, 15], three ASC proteins assemble to form an ion channel. Both homomeric and heteromeric channels have been observed [16-18]. The TRP channel genes comprise a large superfamily conserved in eukaryotes and encode proteins predicted to have six trans-membrane domains. Four TRP channel proteins assemble into homomeric or heteromeric ion channels [19]. Recently, two additional classes of membrane proteins (Piezo and TMC) have been linked to mechano-transduction (Fig.2) [20-23]. Both TRPs and ASCs are broadly expressed in somatosensory neurons. Several mechanoreceptor neurons are known to co express multiple TRPs and multiple ASC channels.

Conclusion

There exists a fundamental block to progress in understanding how mechanoreceptor neurons function. The studies related to stimulus-initiated behaviour, action potential generation, or intracellular calcium dynamics do not allow researchers to separate the initial step of mechano-transduction from amplification, gain control, and transmission. Behaviour, spikes and calcium dynamics depend on the action of all of the ion channels expressed by sensory neurons. These channels are interconnected in feedback loops regulated by a common control variable-membrane potential.

Authors' contributions

SS is behind the concept of this review article and also prepared the initial version of the article. APKM helped in preparation of the final version of this article with necessary corrections. AKK and SM made live discussion on the topic and the work of the authors easier.

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Competing interests

The authors declare that they have no competing interests.

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