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Review article

Modulation of TRPV4 by diverse mechanisms

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ABSTRACT

Transient receptor potential ion channels (TRP) are a superfamily of non-selective ion channels which are opened in response to a diverse range of stimuli. The TRP vanilloid 4 (TRPV4) ion channel is opened in response to heat, mechanical stimuli, hypo-osmolarity and arachidonic acid metabolites. However, recently TRPV4 has been identified as an ion channel that is modulated by, and opened by intracellular signalling cascades from other receptors and signalling pathways. Although TRPV4 knockout mice show relatively mild phenotypes, some mutations in TRPV4 cause severe developmental abnormalities, such as the skeletal dyplasia and arthropathy. Regulated TRPV4 function is also essential for healthy cardiovascular system function as a potent agonist compromises endothelial cell function, leading to vascular collapse. A better understanding of the signalling mechanisms that modulate TRPV4 function is necessary to understand its physiological roles. Post translational modification of TRPV4 by kinases and other signalling molecules can modulate TRPV4 opening in response to stimuli such as mechanical and hyposmolarity and there is an emerging area of research implicating TRPV4 as a transducer of these signals as opposed to a direct sensor of the stimuli. Due to its wide expression profile, TRPV4 is implicated in multiple pathophysiological states. TRPV4 contributes to the sensation of pain due to hypo-osmotic stimuli and inflammatory mechanical hyperalsgesia, where TRPV4 sensitizaton by intracellular signalling leads to pain behaviors in mice. In the vasculature, TRPV4 is a regulator of vessel tone and is implicated in hypertension and diabetes due to endothelial dysfunction. TRPV4 is a key regulator of epithelial and endothelial barrier function and signalling to and opening of TRPV4 can disrupt these critical protective barriers. In respiratory function, TRPV4 is involved in cystic fibrosis, cilary beat frequency, bronchoconstriction, chronic obstructive pulmonary disease, pulmonary hypertension, acute lung injury, acute respiratory distress syndrome and cough.In this review we highlight how modulation of TRPV4 opening is a vital signalling component in a range of tissues and why understanding of TRPV4 regulation in the body may lead to novel therapeutic approaches to treating a range of disease states.

Contents

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1. Introduction

The physiological mechanisms for opening of Transient Receptor Potential (TRP) ion channels is an area of intense study. TRP ion channel vanilloid type 4 (TRPV4) is a particularly interesting case because it appears to be involved in a wide range of physiological responses and it is activated my many stimuli. The dysfunction of TRPV4 is liked to numerous pathophysiological states, indicating an important role in many vital physiological responses. This review summarizes the current understanding of the way in which the TRPV4 ion channel responds to different stimuli, to act as an integrator of diverse signalling pathways. We focus on sensitization and opening of the TRPV4's ion channel by distinct receptors and signalling mechanisms. The structure and function of TRPV4 has been recently extensively reviewed (White et al., 2016).

Experiments with TRPV4 knockout mice show that TRPV4 is involved in many processes, both physiological and in disease states. However, the mechanism of TRPV4 involvement in these states is poorly understood. While the activation of TRPV4 by its synthetic agonists has been assessed in many tissues, the physiologically relevant regulators are still poorly characterized. Understanding the signalling to open or sensitize TRPV4, is likely to identify new targets for novel therapeutics that can modulate TRPV4 activation as an alternative to the potentially dangerous use of TRPV4 agonists or antagonists.

1.1. Transient receptor potential ion channels

The first of the Transient Receptor Potential (TRP) ion channel was discovered in a mutant of the *Drosophila melanogaster* fly that was unable to respond to repeated or constant bright light stimulation (Cosens and Manning, 1969). The *trp* mutation was in a gene encoding an integral membrane protein with six trans-membrane domains (Wong et al., 1989). Electrophysiological analysis revealed that it was a calcium-permeable, non-selective cation channel that opens in response to signalling from activated rhodopsin (Hardie and Minke, 1992). TRP channel opening was shown to be due to phospholipase C (PLC) activation by rhodopsin, resulting in the hydrolysis of phosphoinositol 4,5 bisphosphate (PIP_2) to generate inositol trisphophate (IP_3) and diacylglycerol, which alters the physical composition of the membrane. The resulting rapid physical changes in the lipid bilayer leads to movement of the rabdomere microvilli, mechanically opening TRP (and the related TRPL) ion channels (Hardie and Franze, 2012).

1.2. Mammalian TRPs

The number of human TRP ion channel homologues identified has increased since the discovery of TRPC1A (Zitt et al., 1996). There are currently 28 known mammalian TRP channels, divided into 6 subfamilies: canonical (TRPC), vanilloid (TRPV), melastatin (TRPM), mucolipin (TRPML), polycystic (TRPP) and ankyrin (TRPA), based on sequence homology. TRP channels are tetrameric proteins with subunits having six transmembrane domains and cytoplasmic C- and N-terminal tails, Most TRPs are non-selective cation channels with a high permeability for sodium, chloride, potassium and calcium, but each has unique characteristics for ion permeability, conductance, voltage dependence, and gating; and is activated by different ligands or physiological stimuli.

Many TRP channels open in response to physical stimuli including: temperature, pH, shear stress and other mechanical forces such as stretch and hypoosmolarity. Moreover, there are many TRP channels which are ligand-gated and voltage sensitive. For example TRPV1 is opened by temperatures greater than 42 °C and capsaicin, the hot component of chilli peppers (Caterina et al., 1997). Conversely, TRPM8 is opened by temperatures below 23 °C (Peier et al., 2002) and by the cooling agents, menthol and icillin. Low temperature and icillin can potentiate each other and hence TRPM8 acts as a coincidence detector for these stimuli (Chuang et al., 2004). However, menthol, icillin and capsaicin are not endogenous compounds, and the physiological mechanisms of activation of TRPM8 and TRPV1 are only partially understood. TRPV4 is also a polymodal ion channel that can be activated and sensitized *via* diverse agonists and signalling pathways. The following sections will focus on the current knowledge of TRPV4 gating and its relevance to physiological and pathological states.

1.3. TRPV4 expression

TRPV4 was discovered by cloning cDNAs with homology to the conserved coding regions of mammalian TRPV1 and TRPV2 and *Osm-9 the osmosenssor* from *C. elegans* (Liedtke et al., 2000) and