

Interaction between TRP and Ca²⁺-activated chloride channels

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The transient receptor potential (TRP) channel superfamily includes a large number of proteins that constitute 7 subfamilies (TRPC, TRPV, TRPM, TRPML, TRPN, TRPA and TRPP). These channels have been strongly conserved evolutionarily. The family was first cloned from a mutant *Drosophila* strain in which receptor potentials in the eye were transient upon light stimulation.¹ There are 27 known channels in the 6 subfamilies, excluding TRPN in humans. Some of the TRP channels respond to a wide variety of sensory stimuli, including chemicals and temperature changes. Thus, they are termed “thermosensitive” TRP channels. Three in particular (TRPV1, a capsaicin receptor, TRPA1, a receptor for mustard oil, and TRPM8, a menthol receptor) are involved in temperature sensation in sensory neurons.² The structure of TRPV1 was recently solved at a 3.4 Å level using a single particle analysis with cryo-electron microscopy.³

One of the key characteristics of thermosensitive TRP channels is their high Ca²⁺ permeability that is more than 5 times larger than that of sodium. Therefore, thermosensitive TRP channels might well play important roles involving Ca²⁺. There are many Ca²⁺ binding proteins in the cytosol that contribute to tight regulation of intracellular Ca²⁺ concentrations. Nonetheless, upon entering the cells through TRP channels, Ca²⁺ is certainly involved in mediating various intracellular events. Indeed, TRPV4, a thermosensitive TRP channel (reportedly an osmo- or mechano-sensor,⁴ and anoctamin 1 (TMEM16A; a Ca²⁺-activated chloride channel⁵), functionally

interact in choroid plexus epithelial cells in the brain.⁶ Upon entering choroid plexus epithelial cells, Ca²⁺ activates anoctamin 1, leading to chloride efflux because the chloride equilibrium potential in choroid plexus epithelial cells is smaller than the resting membrane potentials due to relatively high intracellular chloride concentrations. The chloride efflux could drive water movement from the choroid plexus epithelial cells to ventricles, a process that could be viewed as a mechanism for release of cerebrospinal fluid from the choroid plexus.

Aquaporin (AQP) 1 and AQP4 water channels are well-expressed in choroid plexus epithelial cells, and TRPV4 directly interacts with AQP4. Activation of anoctamin 1 was also observed downstream of Gq-coupled receptor activation that can increase intracellular Ca²⁺ concentrations though Ca²⁺ release from intracellular Ca²⁺ stores by Ins(1,4,5) P₃ receptor activation. However, activation of anoctamin 1 was not frequently observed following a simple increase in intracellular Ca²⁺ concentration compared with that seen after TRP channel activation.⁶ This result indicated that Ca²⁺ entering the cells through Ca²⁺-permeable channels activated anoctamin 1 more effectively. In fact, co-immunoprecipitation studies showed that TRPV4 physically interacted with anoctamin 1,⁶ suggesting that co-localization of the 2 proteins is important. The findings presented in the work illustrate the significance of TRPV4 in choroid plexus epithelial cells and emphasize the importance of the interaction between Ca²⁺-permeable channels and Ca²⁺-activated proteins

Keywords: TRP channels, Ca²⁺, Ca²⁺-activated chloride channels, TMEM16A (anoctamin 1), choroid plexus

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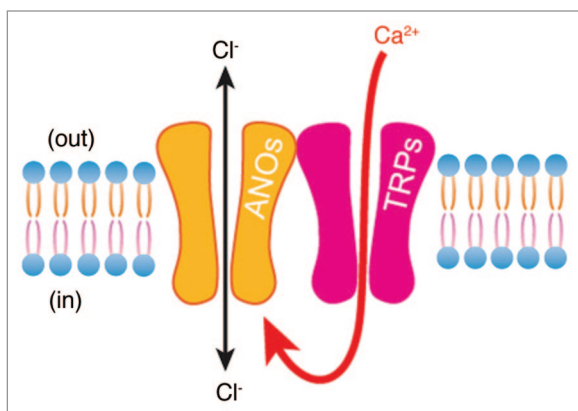


Figure 1. A schematic model for chloride movement. TRP channels, characterized by high Ca^{2+} permeability, permit Ca^{2+} entry, leading to activation of chloride channels (anoctamins; ANOs). The direction of chloride movement can be determined by the chloride equilibrium potentials.

on the plasma membrane as well as the importance of nano-domains where Ca^{2+} concentrations could be highly increased.

Ca^{2+} -activated chloride channels, especially anoctamins (anoctamin 1 to anoctamin 10) are expressed in many cells, suggesting that similar interactions between TRP channels with high Ca^{2+} permeability and anoctamins could be involved in numerous physiological functions in a wide range of cells, from epithelial cells to neurons. Because anoctamin 1 has the highest Ca^{2+} sensitivity, participation of anoctamin 1 in the interactions would be most likely. The direction of chloride movement can be determined simply by the relationship between chloride equilibrium potentials and membrane potentials depending on the intracellular chloride concentrations. In the case of choroid plexus epithelial cells, chloride can move outward because of the high intracellular chloride concentrations that drive water efflux. In neurons, chloride is generally believed

to move inward upon activation of chloride channels, such as the activation of GABA or glycine receptors that causes hyperpolarization. This mechanism is involved in the inhibition of neural activities by GABA or glycine. However, in spinal cord neurons, chloride concentrations can be changed dynamically depending on tissue conditions such as injury or inflammation that reduce the expression of chloride transporters, including *KCC2*.⁷ Intracellular chloride concentrations in neurons are also known to be high in early developmental stages when GABA may excite neurons.⁸ Under those conditions, Ca^{2+} influx through TRP channel activation might induce chloride efflux, leading to depolarization. Thus, it is intriguing to speculate that functional interaction between TRP channels with high Ca^{2+} permeability and Ca^{2+} -activated chloride channels with or without physical binding could be involved in various cellular functions depending on the intracellular chloride concentrations (Figure 1).

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