Activation Mechanism and Physiological Implications of Anoctamin 1

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Ca\(^{2+}\)-activated chloride channels (CaCCs) mediate numerous physiological functions such as movement of Cl\(^{-}\) and fluid through transport epithelia and regulation of sensory transduction. Despite their physiological significance, a molecular species that defines endogenous CaCCs has not been disclosed.

Anoctamin 1 (ANO1 or TMEM16A) was cloned to be a candidate for CaCC. ANO1 is activated by intracellular Ca\(^{2+}\), which is also voltage dependent. ANO1 is expressed in epithelia of salivary glands, pancreas, kidney, pulmonary airways, the retina, and sensory neurons where endogenous CaCC currents were found. ANO1 has 8 transmembrane domains and putative pore region between TM5 and TM6. ANO1 has 9 additional homologs.

Consistent with the expression of ANO1 in DRG neurons, ANO1 is activated by heat over 44oC. ANO1 is highly co-expressed with TRPV1, a marker for nociceptors, suggesting the involvement in nociception. To determine its physiological implication in nociception, Ano1-deficient mice specifically in DRG neurons were generated. As expected these Ano1-deficient mice showed reduced responses to painful heat. In addition, Ano1 appears to mediate chronic pain because Ano1-deficient mice elicited reduced inflammatory hyperalgesia and neuropathic allodynia. Thus, Ano1 plays an important role in mediating nociception in sensory neurons.

Another issue around CaCC is its role in fluid secretion in GI tracts. Cl\(^{-}\) secretion is important for protection of intestinal epithelia. Whether CaCC plays a role for the Cl\(^{-}\) secretion in GI tracts is in controversy. Using Ano1-floxed mice, we generated two different mutant mice that lack Ano1 specifically in t ganglion (DRG) neurons, small intestine, and large intestine. When Ano1 is deleted in small and large intestines. When Ano1 is abolished in small and large intestines, carbachol-induced Cl\(^{-}\) conductance was significantly reduced in duodenum, jejunum and proximal colon. In addition, the colon of Ano1 deficient mice was edematous indicating a mild colitis. Furthermore, when colitis was induced by dextran sodium sulfate (DSS), Ano1-deficient mice developed severe colitis in colon. These results clearly suggest that ANO1 plays an active role in secreting Cl\(^{-}\) in intestines, which is important for protection of intestine epithelium and that intestines are susceptible to inflammation or some types of cancer when Ano1 is ablated.

In addition, the structural aspect of activation mechanism of ANO1 by Ca2+ will be discussed in this talk.

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