Characterizing Conformational Changes of ASIC1a During Gating and Peptide Modulation

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Acid-sensing ion channels (ASICs) are ligand-gated cation channels that are involved in synaptic plasticity, and implicated in a wide variety of disease processes, including pain, stroke, and ischemia. The Acid-Sensing Ion Channel (ASIC) family comprises several members that are activated by extracellular protons, and their function is of interest in understanding the mechanism of activation and pharmacological modulation. Here, we use several approaches to introduce fluorescent reporter tags to monitor conformational changes and dynamics of ASIC1a during gating and desensitization.

**Poster: Characterizing Conformational Changes of ASIC1a During Gating and Peptide Modulation**


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Acid-sensing ion channels (ASICs) are trimeric cation-selective channels activated by decreases in extracellular pH. The intracellular N and C terminal domains of ASIC1a variably influence channel gating, ion selectivity, channel trafficking, and signaling in ischemic cell death. While there are numerous x-ray and cryo-EM structures of the extracellular and transmembrane segments of ASIC1a, these important intracellular tails remain unresolved. Here we set out to map the topology of these intracellular domains using the voltage-sensitive dipicrylamine as a dark acceptor for fluorescence resonance energy transfer (FRET) donors inserted in various positions of chicken ASIC1a tails. With this patch clamp FRET approach, we find that the N-term of the channel undergoes an axial motion between the resting and desensitized states of the channel, while no movement of the C-tail is apparent. Further, when labeling both tails with pH-insensitive FRET donor-acceptor pairs, we find that the C-tails of the channel do not appear to separate as the channel transitions between the resting and active/desensitized states. Together, these data allow us to build a topological model of the intracellular tails of ASIC1 that will be a foundation for working hypotheses in future experiments.