Conformational dynamics and role of the acidic pocket in ASIC pH-dependent gating

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Acid-sensing ion channels (ASICs) are proton-activated Na(+) channels expressed in the nervous system, where they are involved in learning, fear behaviors, neurodegeneration, and pain sensation. In this work, we study the role in pH sensing of two regions of the ectodomain enriched in acidic residues: the acidic pocket, which faces the outside of the protein and is the binding site of several animal toxins, and the palm, a central channel domain. Using voltage clamp fluorometry, we find that the acidic pocket undergoes conformational changes during both activation and desensitization. Concurrently, we find that, although proton sensing in the acidic pocket is not required for channel function, it does contribute to both activation and desensitization. Furthermore, protonation-mimicking mutations of acidic residues in the palm induce a dramatic acceleration of desensitization followed by the appearance of a sustained current. In summary, this work describes the roles of potential pH sensors in two extracellular domains, and it proposes a model of acidification-induced conformational changes occurring in the acidic pocket of ASIC1a.
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