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Mysteries of pH sensing in the HV1 proton channel

Because pH is a fundamental property of solutions, response to pH changes must be an ancient control feature for proteins. Despite this, in only a few examples are the mechanisms of pH control of protein behavior well characterized. One of the defining properties of the H_V1 proton channel is its response to ΔpH , the difference between external and internal pH ($\Delta\text{pH} = \text{pH}_o - \text{pH}_i$). WT H_V1 channels from species as diverse as humans and dinoflagellates follow 'The Rule of Forty', in which the threshold voltage for opening changes 40 millivolts for every 1 unit of ΔpH . Mutations to dozens of sites have not affected H_V1's Rule of Forty behavior. While exploring other properties of the channel, we serendipitously discovered two mutants that affect ΔpH response of H_V1. Surprisingly, each mutant senses pH_i senses differently from pH_o , implying the presence of two different pH sensors. Despite this advance in understanding, the identity and properties of H_V1's pH sensors remain mysterious. The results will be discussed in the context of structural models of the channel.

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