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Selectivity filter instability dominates the low intrinsic activity of the TWIK-1 K2P K⁺ channel

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Abstract

Two-pore domain K⁺ (K2P) channels have many important physiological functions. However, the functional properties of the TWIK-1 (K2P1.1/KCNK1) K2P channel remain poorly characterized because heterologous expression of this ion channel yields only very low levels of functional activity. Several underlying reasons have been proposed, including TWIK-1 retention in intracellular organelles, inhibition by posttranslational sumoylation, a hydrophobic barrier within the pore, and a low open probability of the selectivity filter (SF) gate. By evaluating these potential mechanisms, we found that the latter dominates the low intrinsic functional activity of TWIK-1. Investigating this further, we observed that the low activity of the SF gate appears to arise from the inefficiency of K⁺ in stabilizing an active (i.e. conductive) SF conformation. In contrast, other permeant ion species, such as Rb⁺, NH₄⁺, and Cs⁺, strongly promoted a pH-dependent activated conformation. Furthermore, many K2P channels are activated by membrane depolarization via an SF-mediated gating mechanism, but we found here that only very strong nonphysiological depolarization produces voltage-dependent activation of heterologously expressed TWIK-1. Remarkably, we also observed that TWIK-1 Rb⁺ currents are potently inhibited by intracellular K⁺ (IC₅₀ = 2.8 mM). We conclude that TWIK-1 displays unique SF gating properties among the family of K2P channels. In particular, the apparent instability of the conductive conformation of the TWIK-1 SF in the presence of K⁺ appears to dominate the low levels of intrinsic functional activity observed when the channel is expressed at the cell surface.

Keywords

Author Keywords: ion channel; potassium channel; gating; membrane biophysics; membrane protein**KeyWords Plus:** LEAK; MECHANISM; PORE; PERMEATION; GATE

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