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

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Abstract

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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^+, NH_4^+, 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^+ (IC_{50} = 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. © 2020 Nematian-Ardestani et al. Published under exclusive license by The American Society for Biochemistry and Molecular Biology, Inc.

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