



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

Ehsan Nematian-Ardestani¹, M. Firdaus Abd-Wahab¹, Franck C. Chatelain², Han Sun³, Marcus Schewe⁴, Thomas Baukrowitz⁵ and Stephen J. Tucker^{6*}

+ Author Affiliations

* Corresponding author; email: stephen.tucker@physics.ox.ac.uk

Author contributions: E.N.-A. data curation; E.N.-A., H.S., M.S., and S.J.T. formal analysis; E.N.-A., M.F.A.-W., F.C.C., H.S., and M.S. investigation; E.N.-A., M.F.A.-W., F.C.C., and T.B. methodology; E.N.-A. and S.J.T. writing-original draft; E.N.-A., M.F.A.-W., F.C.C., H.S., M.S., T.B., and S.J.T. writing-review and editing; H.S. and S.J.T. visualization; T.B. and S.J.T. conceptualization; T.B. and S.J.T. resources; T.B. and S.J.T. supervision; T.B. and S.J.T. funding acquisition; T.B. and S.J.T. project administration; S.J.T. validation.

Abstract

Two-pore domain (K2P) K⁺ 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 post-translational sumoylation, a hydrophobic barrier within the pore, and a low open probability of the selectivity filter (SF) gate. By evaluating these various potential mechanisms, we found that the latter dominates the low intrinsic functional activity of TWIK-1. Investigating the underlying mechanism, 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 a SF-mediated gating mechanism, but we found here that only very strong, non-physiological 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.

[membrane biophysics](#) [gating](#) [membrane protein](#) [potassium channel](#) [ion channel](#)

Received August 14, 2019.
Accepted December 5, 2019.

Published under [license](#) by The American Society for Biochemistry and Molecular Biology, Inc.

Recommended for you

Acid-sensitive TWIK and TASK Two-pore Domain Potassium Channels Change Ion Selectivity and Become Permeable to Sodium in Extracellular Acidification

Liqun Ma et al., *Journal of Biological Chemistry*, 2012

Formation of Functional Heterodimers by TREK-1 and TREK-2 Two-pore Domain Potassium Channel Subunits

Miklós Lengyel et al., *Journal of Biological Chemistry*, 2016

Physiologic Alterations in Ataxia Channeling Changes Into Novel Therapies

Vikram G. Shakkottai et al., *JAMA Neurology*, 2009

Understanding Atomic Interactions to Achieve Well-being

Juan M. Pascual et al., *JAMA Neurology*, 2016

The Function of Potassium Channel in KCNQ2 G271V Mutants of Benign Familial Neonatal Convulsions

PDF

Help

TWIK-2, an Inactivating 2P Domain K⁺ Channel

Amanda J. Patel et al., Journal of Biological Chemistry, 2000

Modulation of the Two-pore Domain Acid-sensitive K⁺ Channel TASK-2 (KCNK5) by Changes in Cell Volume

Francisco V. Sepúlveda et al., Journal of Biological Chemistry, 2001

An Extracellular Ion Pathway Plays a Central Role in the Cooperative Gating of a K2P K⁺ Channel by Extracellular pH

Wendy González et al., Journal of Biological Chemistry, 2013

HUI Zhi-yan et al., Journal of Sichuan University (Medical Science Edition), 2018

PWE-071 Etrolizumab induction in moderate/severe anti-TNF intolerant/refractory (IR) UC: the hickory open-label induction (OLI) trial

Helen Tyrrell et al., Gut, 2018

Cryo-EM reveals ligand induced allostery underlying InsP 3 R channel gating

Guizhen Fan et al., Cell Research, 2018

Powered by **TREND MD**

Advertisement

PDF

Help