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PIP2 modulation of KCNQ1 channels

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Voltage-gated ion channels generate dynamic ionic currents that are vital to the physiological functions of many tissues. These proteins contain separate voltage-sensing domains, which detect changes in transmembrane voltage, and pore domains, which conduct ions. Coupling of voltage sensing and pore opening is critical to the channel function and has been modeled as a protein-protein interaction between the two domains. However, our data show that coupling in Kv7.1 channels requires the lipid phosphatidylinositol 4,5-bisphosphate (PIP2). We found that voltage-sensing domain activation failed to open the pore in the absence of PIP2. This result is due to loss of coupling because PIP2 was also required for pore opening to affect voltage-sensing domain activation. We identified a critical site for PIP2-dependent coupling at the interface between the voltage-sensing domain and the pore domain. This site is a conserved lipid-binding site among different K⁺ channels, suggesting that lipids play a significant role in coupling in many ion channels. To further investigate the mechanism of PIP2 mediated VSD-pore coupling, we identified a compound that mimics PIP2 structure and function as a molecular probe. This compound was identified using an in-silico screening approach based on molecular docking of a library of compounds to the PIP2 binding site in a homology model of the Kv7.1 channel. Our results show that this compound can substitute PIP2 in activating the Kv7.1 channel.

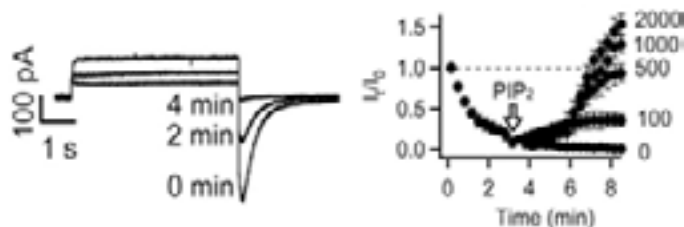


Figure 1. Kv7.1 activation depends on PIP2. Left: Kv7.1 currents in an inside-out patch decreases with time due to PIP2 diffusion out of the membrane patch. Right: Cytosolic PIP2 application (μM) activates Kv7.1.

Biography

Jianmin Cui is a Professor on the Spencer T. Olin Endowment at Washington University in St. Louis, in the Department of Biomedical Engineering. He received PhD in Physiology and Biophysics from State University of New York at Stony Brook and a Post-Doctoral training at Stanford University. He was an assistant professor of Biomedical Engineering at Case Western Reserve University before moving to St. Louis. His research interests include BK-type calcium-activated potassium channels and I_{K_s} channels.

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