P-2.34

Regulatory Domains of Kcne4 in Kv1.3 Channel Modulation

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Voltage-gated ion channels respond to changes in membrane potential regulating the depolarization in cells. Their biophysical properties are modulated by interactions with ancillary subunits. KCNE family members are single-transmembrane proteins that associate promiscuously with Kv channels producing a wide range of effects. KCNE4 is a negative regulator of the Kv1.3 channel that plays a key role in mediating the immune response. When both proteins oligomerize, KCNE4 interferes with Kv1.3 forward trafficking enhancing the pool of channels located at the endoplasmic reticulum. Moreover, KCNE4 also enhances the characteristic slow C-type inactivation of Kv1.3. In this work, we analyzed how each KCNE4 domain —N-terminal, transmembrane and C-terminal— interacts and regulates Kv1.3 activity. Our findings show that the C-terminus of KCNE4 is the main determinant of Kv1.3 association. Additionally, we identify the transmembrane domain as a contributor to C-type inactivation modulation. By mapping key residues using a previously established Kv1.3/KCNE4 docking model, we provide new insights into the molecular mechanisms governing potassium channel regulation. Our results suggest that KCNE4 induces conformational rearrangements in Kv1.3, altering its inactivation kinetics.

Supported by MICINN/AEI, Spain (PID2020-112647RB-I00, PID2023-148085OB-I00 and 10.13039/501100011033) and FEDER.