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KCNE1 Slows the Voltage Sensors of KCNQ1

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KCNQ1 α-subunits assemble with KCNE1 forming the slow cardiac potassium channel I_{Ks}. KCNE1 alters currents of α-subunits by slowing activation and deactivation kinetics, suppressing inactivation, and increasing single-channel conductance. Attempts to elucidate the mechanism of KCNE1-induced slowing of kinetics have come to discrepant conclusions. Two studies using chemical modifiers and cys-substitution in the KCNQ1 S4 supported one model where KCNE1 acts on voltage-sensors alone and another where only the activation-gate is affected. A fluorimetric study argued for effects on sensors and the gate (Osteen et al, PNAS 2010). To address the controversy, we used cut-open oocyte vaseline-gap clamp to record gating currents, ionic currents and perform site-directed, voltage-clamp fluorimetry (VCF).

Gating currents show that voltage-sensor movement precedes pore opening in channels with only KCNQ1 α-subunits. VCF confirms this result. While ionic currents have a lag before activation, gating and fluorescence changes do not; this indicates a final concerted step after voltage sensors move before pore opening. In contrast, channels with KCNE1 show voltage-sensor movements with no lag that are ~20-fold slower and mirror slowing of ionic current activation. These findings are unlike those made by Osteen et al. We used a smaller dye inserted closer to S4 and measured ionic current and fluorescence simultaneously in the same cells. We observe a matching and expected shift in the I_{Ks} fluorescence-voltage and ionic current-voltage relationships of +50 mV with KCNE1 and do not see voltage-sensor movements at hyperpolarized voltages as they report.

Both KCNQ1 and I_{Ks} channels have voltage-sensor kinetics almost as slow as ionic activation. Our simultaneous kinetic recordings of fluorescence and ionic currents support a model in which I_{Ks} channels are slowed purely by an effect of KCNE1 on the KCNQ1 voltage sensors. Support: HL105949 and GM030376.