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Understanding the Microscopic Mechanisms for LQT1 Needs a Global View of the I_{Ks} Channel

Gea-Ny Tseng, PhD and Yu Xu, PhD

Department of Physiology & Biophysics, Virginia Commonwealth University, Richmond, VA 23298

The slow delayed rectifier (I_{Ks}) channel is composed of two main components: a pore-forming KCNQ1 channel and regulatory KCNE1 subunits. Due to its slow rate of activation, I_{Ks} makes little contribution to ventricular action potential repolarization under the ‘basal’ conditions¹. However, when the β -adrenergic tone is high or when other repolarizing currents are compromised (e.g. acquired LQT syndrome), I_{Ks} becomes larger and activates faster, assuming a more important role in repolarizing action potentials¹. There are at least two mechanisms for the increase in I_{Ks} under stressful conditions. First, high β -adrenergic tone accelerates the heart rate. The shortened diastolic intervals allow I_{Ks} channels to accumulate in the activated state, producing an increase in I_{Ks} amplitude during the early plateau phase of action potentials². Second, β -adrenergic stimulation leads to cAMP production and PKA activation. PKA phosphorylation of KCNQ1 and the associated AKAP9 leads to an increase in I_{Ks} amplitude and a left shift in its voltage-dependence of activation.

People carrying loss-of-function mutations in KCNQ1 (LQT1) have a higher risk for ventricular arrhythmia during exercise or under emotional stress. LQT1-related mutations in KCNQ1 can impair the I_{Ks} channel function by a number of mechanisms: (a) trafficking defects, (b) lower PIP₂ binding affinity, (c) reduced responsiveness to β -adrenergic stimulation, and (d) gating kinetic defects. Some of the LQT1 mutations occur in the pore-loop region, which presumably can reduce the I_{Ks} channel conductance. The design of ‘personalized medicine’ to treat LQT1 patients needs to consider the molecular mechanisms of I_{Ks} defects. For example, an I_{Ks} activator that works by enhancing the I_{Ks} single channel conductance will not be effective if there are very few or no I_{Ks} channels on the cell surface to respond to the drug.

In this issue of *Heart Rhythm*, David Fedida’s group reports the ‘microscopic mechanisms’ for LQT1 revealed by single channel analysis of I_{Ks} ³. They studied four LQT1-related mutations (D202H, I204F, V205M, and S209F) that occur in the S3 segment of the KCNQ1 channel. S3 is the third transmembrane helix in KCNQ1’s voltage-sensing domain. It helps stabilizing the main voltage-sensor, the S4 segment, in the lipid bilayer environment. S3 also participates in the formation of a ‘gating pore’ through which the arginine residues on S4

Correspondence: Gea-Ny Tseng, PhD, AHAF, Department of Physiology & Biophysics, Virginia Commonwealth University, Richmond, VA 23298, Phone: 804-827-0811, Fax: 804-828-7382, gtseng@vcu.edu.

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move in response to changes in the membrane voltage, triggering the opening or closing of the activation gate. A previous report from the same group used the whole cell (macroscopic) current recording to characterize these S3 mutations². They found that except S209F, the other S3 mutations shifted the voltage-dependence of I_{Ks} activation in the depolarizing direction, making it harder for the I_{Ks} channels to activate in the physiological plateau voltage range. The D202H mutation also accelerated I_{Ks} deactivation, thus reducing the degree of I_{Ks} accumulation in the activated state during tachycardia. S209F had the opposite phenotype: it stabilized the I_{Ks} channel in the activated state. S209F caused a loss of I_{Ks} function by reducing the channel's ability to traffic to the cell surface.

With the I_{Ks} channel defects associated with these S3 mutations well characterized at the macroscopic current level, what more information can one gain by studying these mutant channels at the single channel level? Macroscopic currents are the ensembles of stochastic opening and closing of single channels. Direct observations of channel behaviors at the single molecule level can reveal details about how the channel behaves. A good example is the gating behavior of Na channels. During membrane depolarization, macroscopic Na channel currents exhibit a fast rising phase followed by a slower decaying phase. This time course can be equally well explained by two opposite scenarios at the single channel level: fast activation followed by slow inactivation (as in the Hodgkin-Huxley formalism), or slow activation followed by fast inactivation. Single Na channel recordings supported the latter scenario⁴.

Given the value of single channel recordings in revealing the fundamental properties of channel gating behavior, what questions about the I_{Ks} channel can be better addressed by single channel than whole cell current recordings? One of the most intriguing and important question is: *how does KCNE1 slow the KCNQ1 gating transitions so dramatically?* The Fedida group has taken a meticulous approach to record I_{Ks} at the single channel level, and their data have provided new insights into how the I_{Ks} channels behave⁵. They showed that single I_{Ks} channel first opens to sub-conductance levels and then gradually reaches the fully open level. They argued that the sub-conductance states represent partial S6 gate opening before all four S4 voltage-sensors have reached the fully activated state. This argument was supported by their kinetic modeling⁵. The I_{Ks} gating scheme appears to be in conflict with the I_{Ks} gating scheme proposed by another group: the S6 gate of the I_{Ks} channel can open only after all four S4 voltage-sensors have reached the activated state⁶. However, this difference in opinion may be explained by the different modes of I_{Ks} recording, single channel⁵ vs whole cell current⁶.

In the current study, the Fedida group showed that at the single channel level, the S3 mutations displayed diverse kinetic defects in I_{Ks} gating³. D202H shortened the single channel open time and prolonged the closed times, without affecting the latency to first opening. I204F shortened the single channel open time and prolonged the latency to first opening, without affecting the closed time distribution. V205M was similar to I204F in the effects on gating kinetics. Furthermore, V205M accentuated the sub-conductance levels, preventing the I_{Ks} channel from reaching the fully open state. S209F prolonged the open time and shortened the latency to first opening, producing a marked increase in single channel open probability.

Do these sophisticated single channel recordings help us understand why the S3 mutations induce such diverse gating defects? Single channel recordings alone, despite the ability to reveal fundamental channel behavior, cannot tell us how the mutations affect the channel function or how the channel works. To gain this information, a more comprehensive, ‘global’, approach is necessary, that should include structural predictions. There is no KCNQ1 or KCNE1/KCNE1 crystal structure. Even if such crystal structures are available, their static nature will not tell us how live channels change their conformations in response to the membrane voltage, or how they open their pores to allow K^+ ions through. Given the current knowledge and technologies, we suggest that the best strategy to move forward is to combine structural modeling (based on existing Kv channel crystal structures⁷ and KCNE1 NMR structure⁸) with careful experimental validation, different methods of molecular dynamics simulations, and detailed computational analysis⁹. We are mindful of the many (potential) caveats in this process, e.g. the available Kv channel crystal structures may not be good templates for KCNQ1 homology modeling, and the currently achievable time scale of molecular dynamics simulations (hundreds of microseconds)¹⁰ is at least 10^4 fold shorter than the time scale of I_{Ks} gating. This process will be work-in-progress in the foreseeable future, during which the models need to be updated periodically as major new experimental data become available. After we have sufficient understanding of the structure and function of this important yet mysterious channel, can we begin to explain, or even predict, how KCNQ1 mutations lead to LQT1.

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