Biophysical *Journal*
New and Notable

Biophysical Society

Modeling the Hidden Pathways of *IKs* Channel Activation

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Potassium channels are widely distributed in the body, and investigating their function over the past 50 years has led to great advances in our understanding of their roles not only in normal physiology but also in the physiology of acquired and particularly inherited diseases.

KCNQ channels have historically been one of the less studied α-subunit subfamilies of the voltage-gated potassium channel superfamily, but now, the five members of the Kv7 family are fully established as playing vital roles in diseases as diverse as long QT interval syndrome, in which defects in KCNQ1 underlie the commonest form of the disease, and epilepsy, in which heteromultimers of KCNQ2 and KCNQ3 are targets for new antiepileptic therapies. KCNQ1 channels are known to associate with KCNE channel subunits in the heart to form *IKs* channels, although the full nature and diversity of their heteromultimeric interactions have still not been clearly elucidated (1).

When we attempt to understand the nanosecond-scale function of these potassium channels, investigators have classically used electrophysiological data to produce Markovian models of KCNQ1 (2), either with or without KCNE1, and these have been refined from the mid 2000s to the present day; they now describe sequential versus cooperative gating of the KCNQ1 channel and its coupling with KCNE1 (3–5) as well as new models of KCNQ1 inactivation (6,7). As crystal structures have become available, models have been built using homology modeling (8), describing docking of KCNE1 to KCNQ1 (9) and the effect of LQT mutations within these model schema (10). Molecular dynamics simulations have also been used on potassium channel homology models of KCNQ1 (11–13), and most of these studies have focused on the interactions of the accessory subunit KCNE1 with KCNQ1 to try to understand the effects that the accessory subunits have on the activation gating and conductance of the channel complex. Fewer studies have examined the permeation of ions through the KCNQ1 channel itself and the changes in energy profile of the pore conduction pathway and the energy barriers to potassium ion conduction that exist within it at different activating potentials. This may well be because most of the prior modeling studies precede the experimental description of the single-channel conductance and subconductance properties of KCNQ1 + KCNE1 itself (14), and so they lacked important experimental data sets required to constrain and validate such models.

The simulations of Ramasubramanian and Rudy (2018) differ from the modeling work to date, not only from their use of subconductance data to describe *IKs* function as a current carrier and their kinetic description of pore energy barriers at different times and different modeled structures during channel activation but also from the modeling methodology itself. Here, the structural space of a homology model based on the Kv1.2 crystal structure was extensively sampled and constrained by existing experimental and physiological knowledge, after which specific features that most prominently altered the computed energy, like the voltage sensor domain, were perturbed, and the resultant data were used to optimize the energy landscape for the transmembrane *IKs* structure via a machine learning algorithm. This process to obtain protein dynamics was sufficient to reproduce experimental data in the domains of single-channel currents and conductance, gating currents, and biphasic fluorescence transients, which was something that would be impossible to simulate if the energy of all possible *IKs* conformations were computed. Ramasubramanian and Rudy show particularly the temporal relationships between z displacement and pore dynamics and the modeled protein structures underlying these kinetic relationships. The modeling faithfully and impressively reproduced experimental data obtained using a range of

Submitted May 11, 2018, and accepted for publication May 16, 2018.

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Editor: Eric Sobie.
https://doi.org/10.1016/j.bpj.2018.05.020

different methodologies and highlights the importance of the environment of S4-charged residues and their proximity to KCNE1 residues in determining the time course and extent of S4 translation. It is notable, though, in their modeling that the stoichiometric ratio of KCNQ1:KCNE1 within the *IKs* channel complex is set to 4:2. Although there is still dispute about the ratio of the channel complex in myocytes, there seems to be little doubt that the stoichiometric ratio of KCNQ1 to KCNE1 can vary from 4:1 to 4:4 (15); indeed, it probably varied similarly in the single-channel studies by Werry et al. (14), on which the pore subconductance simulations in the Ramasubramanian and Rudy article were based. In the future, it will be of great interest to see what insights this modeling method can give to the possible effects of a variable stoichiometric ratio on channel gating and pore dynamics, particularly with respect to occupancy kinetics and levels of pore subconductance.

The modeling also suggests a sequential gating process for the channel complex rather than a concerted pore opening after activation of all four voltage sensors, in which small pore openings to small or intermediate subconductance levels are possible at lower S4 z translations. This highlights a current controversy in the present view of *IKs* channel gating in which different viewpoints exist regarding whether *IKs* channels may open before all the voltage sensors are activated (4) or not (16). Clearly, further experiments and modeling, perhaps utilizing the recent cryo-electron microscopy structures (17), are required to resolve this issue.

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