Development of a Biophysically Detailed Model of the Rapid-Delayed Rectifier Potassium Channel

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Abstract

The human ether-à-go-go-related-gene (hERG) encodes potassium channels responsible for the rapid-delayed rectifier current I_{Kr}, which plays a critical role in the repolarisation of cardiac action potentials. hERG/I_{Kr} channel mutations result in defective repolarisation, which may lead to life-threatening conditions such as the long and short QT syndromes.

To study the functional consequences of impaired hERG/I_{Kr} channel on arrhythmogenesis, we developed a Markov chain model of hERG current (I_{hERG}) that accurately reproduces the characteristics of normal and aberrant hERG/I_{Kr} during cardiac action potential waveforms.

The model was validated by comparing simulated results from different voltage clamp protocols against experimental data. The model accommodates alterations that reproduce changes to I_{hERG}.

1. Introduction

KCNH2, also known as the hERG (Human Ether-à-go-go-Related-Gene) encodes the K^+ channel responsible for the rapidly activating outward delayed rectifier potassium current (I_{Kr}) [1-3]. hERG/I_{Kr} is characterised by profound and rapid inactivation compared to activation at positive voltages, which gives rise to a region of negative slope in the current-voltage (I-V) relation ([1,3,4,5] and see Figure 1). I_{Kr} plays a significant role in ventricular repolarisation [6,7]: its rapid voltage-dependent inactivation limits the current's magnitude early during the ventricular action potential (AP), with its size increasing throughout the plateau phase before declining during terminal repolarisation (see Figure 2).

Defects in the hERG/I_{Kr} channel can result in life-threatening repolarisation abnormalities [8]. Impaired hERG function results in reduced I_{Kr} and gives rise to delayed ventricular repolarisation and increased arrhythmia risk in congenital and acquired forms of the Long QT Syndromes (LQTS) [8]. Gain of function mutations in hERG are responsible for variant 1 of the Short QT Syndrome (SQTS), which is associated with an increased risk of arrhythmia and sudden death [8-10].

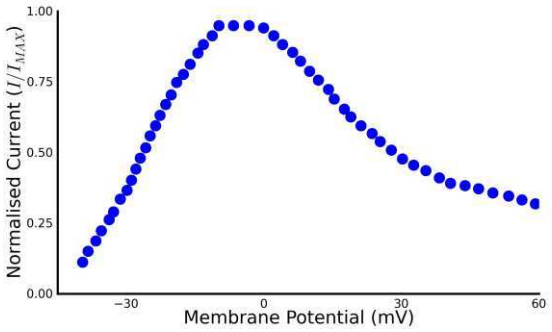

Figure 1. Simulated current-voltage relation for wild-type (WT) hERG

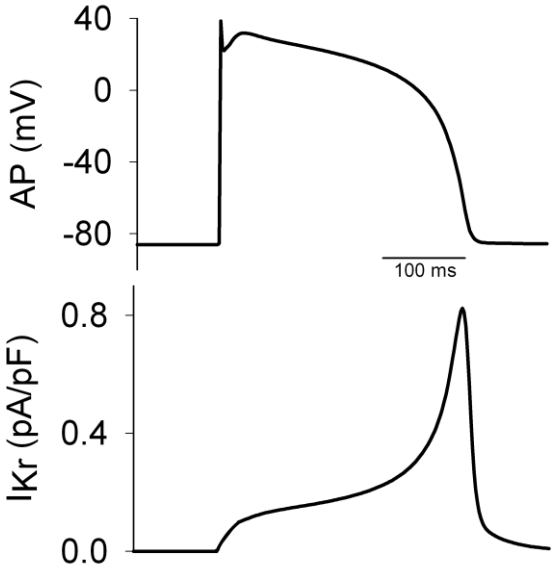

Figure 2. Ventricular AP and current profile for hERG/I_{Kr}.

2. Markov models

Hodgkin-Huxley-type models assume independent channel gating processes. Independent gating means that the transition from an open state to a closed state for a gate G is considered to be independent of the activities of an inactivation gate H. There are potential disadvantages to this approach because the occupancy of one state may

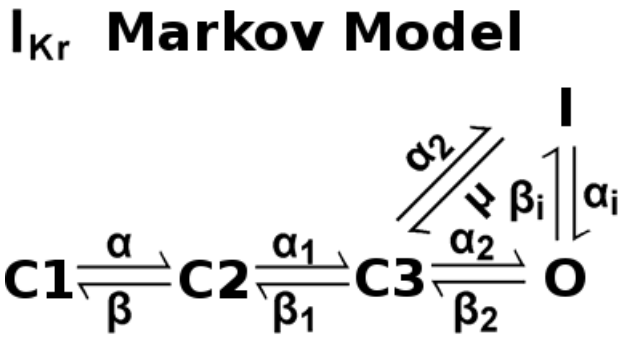

Figure 3. I_{Kr} Markov Model gating scheme

depend on the occupancy of another. For example, Armstrong and Bezanilla [11] and Bezanilla and Armstrong [12] showed that the inactivation of the sodium channel will occur with a greater probability when the channel occupies an open state (i.e. the probability of inactivation is not entirely independent of prior activation).

Markov chain type models, however, work on the basis that the present configuration of channel state occupation will influence its transition between states. This eliminates the stated shortcomings of the Hodgkin-Huxley-type models [13].

3. Methods

The initial base Markov model (Figure 3) was based on the hERG/I_{Kr} Markov model formulation of Kiehn et al. [14], Clancy and Rudy [15] and Lu et al. [16]. It consists of three closed states (C1, C2 and C3), an open state (O) and an inactivated state (I). Inactivation can occur either from the open or the closed state but does so preferentially from the open state [13].

Experimental current-voltage (I-V) relationships for hERG/I_{Kr} [17] were simulated using the voltage clamp protocol in [17]. In order to simulate the experimental I-V relationship, the original I_{Kr} transition rate equations were modified. First, a simulated voltage clamp as described above was set up. The currents at the end of the 2000 ms depolarising steps were normalised and compared to the experimental data.

To obtain a good agreement with the experimental data, variables that modified each transition rate were introduced. The values of these variables were calculated by minimising the least squared difference between the experimental data and the simulation result. The BFGS (Broyden-Fletcher-Goldfarb-Shano) method [18] and a cubic spline interpolation algorithm [19] were used for the minimisation. The variables that produced the best fit and behaviour of macroscopic currents relative to the experimental data were selected.

In order to facilitate the study of the effects of altered hERG gating on the contribution of I_{Kr} to cardiac cell

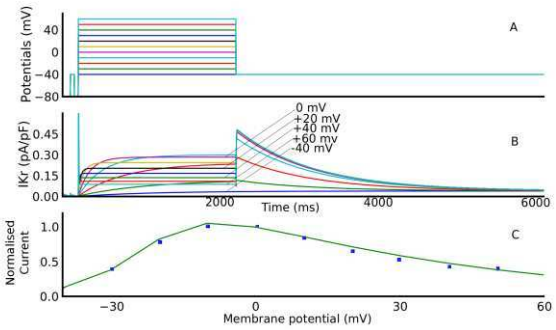

Figure 4. Simulated voltage clamp of I_{Kr} using the Markov gating scheme shown in Figure 3. (A) Voltage Clamp Protocol used. (B) Current Profiles elicited by the protocol in A. (C) End pulse current–voltage (I-V) relation [Markov model (green), experimental data (blue squares)].

electrophysiology, the hERG/I_{Kr} Markov model was incorporated into the ten Tusscher et al. human ventricular cell model [20]. This cell model reproduces human ventricular cell and membrane channel properties and it reproduces the transmural heterogeneity in the epicardial (epi), mid-myocardial (M cell) and endocardial (endo) APs. It is also suitable for tissue modeling and it is computationally efficient [20]. In 2006, Xia et al. [21] updated and modified the ten Tusscher et al. model based on newly available experimental data. We employed their modified model here.

4. Results and conclusion

The Markov hERG/I_{Kr} formulation was incorporated into the ten Tusscher model and then a series of validations against experimental data were performed to test the viability of the formulation. Experimental current-voltage (I-V) relationships for hERG/I_{Kr} acquired under physiologically-relevant recording conditions [17] were simulated using the following voltage-protocol: the membrane potential was held at -80 mV and then depolarised briefly to -40 mV (to evaluate instantaneous current), followed by 2s depolarisations to a range of potentials from -40 mV to +60 mV (in 10 mV increments); finally, 'tail' currents were elicited by repolarisation to -40 mV for 4000 ms.

Figure 4 shows a simulated square voltage clamp command experiment using the Markov hERG/I_{Kr} formulation and the protocol (Figure 4A) described above. Currents elicited by this protocol are shown in Figure 4B, reproducing the marked, characteristic rectification of I_{Kr} at positive voltages and resurgent 'tail' currents on repolarisation to -40mV.

The end-pulse I-V relationship shown in Figure 4C exhibits the anticipated region of negative slope, positive to ~0 mV. Collectively, the data in Figure 4 indicate that

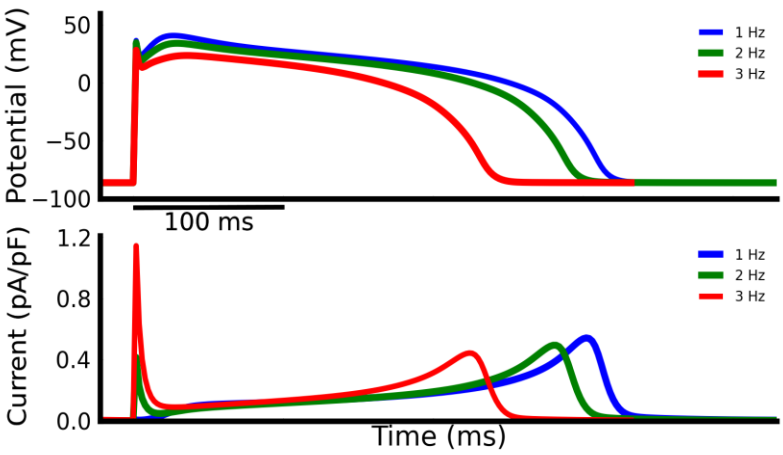

Figure 5. Ventricular APs at different stimulation rates. Top panel: APs elicited at 1, 2 and 3Hz. Bottom panel: hERG/I_{Kr} current profile at 1, 2 and 3Hz.

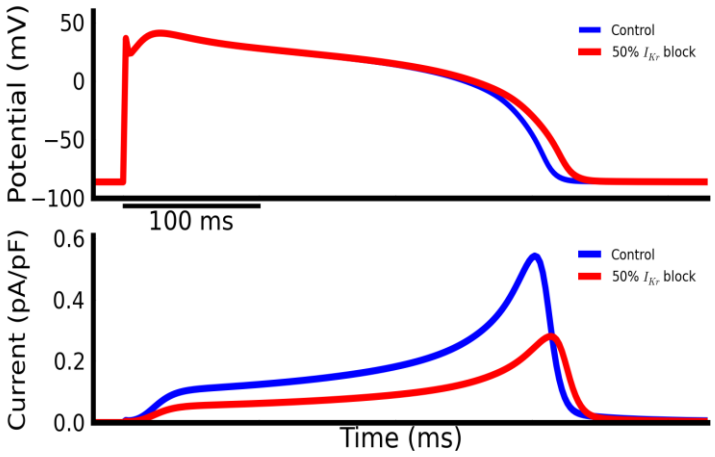

Figure 6. Ventricular AP at 1 Hz (equivalent to a heart rate of 60 beats per minute) with I_{Kr} decreased by 50 %. Top panel: Action Potential with I_{Kr} at 100% (blue) and decreased by 50% (red). Bottom panel: The corresponding hERG/I_{Kr} current profile.

our model accurately reproduces voltage-dependent profiles of I_{Kr}.

Figure 5 shows ventricular APs and the associated hERG/I_{Kr} profile at three stimulation rates; 1Hz, 2Hz and 3Hz (corresponding to heart rates of 60, 120 and 180 beats per minute). In addition to a marked I_{Kr} during the AP plateau phase, a pronounced transient current was evident at the start of the AP at 2Hz and 3Hz but not at 1Hz. This rapid transient current is associated with incomplete I_{Kr} deactivation and is believed to help protect the heart from premature stimuli [16].

Figure 6 shows a similar simulation as Figure 5 (at 1Hz) but with I_{Kr} decreased by 50%. This pseudo loss-of-function shows the expected decrease in I_{Kr} current and the consequent lengthening of the APD, which increased by 4-5%. This degree of APD lengthening was similar to that observed using the original Hodgkin-Huxley style I_{Kr} formulation in the ten Tusscher model (not shown).

In conclusion, this work has generated a Markov chain model of hERG/I_{Kr} that reproduces known channel behaviour and that can be incorporated into cell and tissue in order to investigate the functional consequences of altered hERG/I_{Kr}, either through channel mutations or, in principle, simulated pharmacological modulation.

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