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

Ismail Adeniran*, Jules Hancox and Henggui Zhang

Biological Physics Group, School of Physics and Astronomy, University of Manchester, Manchester, United Kingdom

The human ether-a-go-go-related-gene (hERG) encodes potassium channels responsible for the rapid-delayed rectifier current (IKr). IKr plays a critical role in the repolarisation of cardiac action potentials (AP). hERG/IKr 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/IKr channel on arrhythmogenesis, models of human ventricular cells incorporating IKr channel current are often used. However, the IKr current formulation in many models simplify the inactivation process and are unable to replicate dynamic gating changes in the channel. Accurate simulation of dynamic behaviour such as the response to premature depolarising stimuli requires more complex formulations (e.g. Lu et al).

The aim of this study was to develop a model that accurately reproduces the characteristics of normal and aberrant hERG/IKr during cardiac action potential waveforms. A Markov chain model of hERG current (IhERG) was developed based on experimental (AP voltage clamp) data on its kinetic properties, particularly (1) its fast and profound inactivation upon activation by depolarisation; (2) its rectification at positive potentials; (3) the generation of transient, outward currents 'in response' to premature, depolarising stimuli.

To derive the parameters of the model, the Levenberg-Marquardt algorithm and the Broyden-Fletcher-Goldfarb-Shanno method were used to minimise the residual between the experimental data and the simulated result, and obtain parameters that reproduced the experimental AP voltage clamp IhERG profile. The resulting formulation was further validated by comparing simulated results from different voltage clamp protocols activation, inactivation and deactivation against experimentally-observed results. Moreover, the model could accommodate alterations that reproduced changes to IhERG associated with short QT syndrome.

In conclusion, this work provides a new Markov chain model of hERG/IKr that can be used to investigate the functional consequences of hERG/IKr channel mutations on cardiac electrical activity.