Homology Modeling of a Voltage-gated Potassium Channel (Human Kv7.1).

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Voltage-gated potassium channels play a crucial role in repolarization of the cardiac action potential to the resting state. They have long been recognized as important therapeutic targets for the treatment of cardiac arrhythmia. Prolongation of the QT interval of the electrocardiogram is a typical effect of Class III antiarrhythmic drugs, achieved through blockade of potassium channels. Several other classes of non-cardiovascular drugs have been known to have unwanted side effects on QT interval by blocking potassium channels.

Long QT Syndrome (LQTS) is a heart disease in which there is an abnormally long delay between depolarization and repolarization of the ventricles in the heart. It is associated with syncope, arrhythmias, *torsades de pointes* and sudden cardiac death due to ventricular fibrillation. LQT1, the most common type LQTS, is related to KCNQ1 gene. The IKs ion channel is responsible for delayed rectifier potassium current of the cardiac action potential. It assembles into a tetramer consisting of Kv7.1 (KCNQ1) alpha-subunits and minK (KCNE1) beta-subunits.

This study focuses on the elucidation of 3D structure of the human Kv7.1 channel using a homology modeling approach based on mammalian Kv1.2 and bacterial KvAP templates [1, 2]. Schrödinger Suite [3] was used to build and refine the models. High emphasis is placed on sequence alignment, topology, restrained energy minimization and maintenance of symmetry.

Experimentally determined specific residues in KCNQ1 that altered benzodiazepine derivative L-7 block [4] were observed to be determinants of in silico L-7 interactions in both models. Also, the observed contacts between the pore helix and transmembrane segments S5 and S6 were shown to be in agreement with experimental mutagenesis studies of colocalized residues [5]. The model, based on KvAP template is considered to be in closer agreement with the experimental observations. Accessibility of the gating active site, observed in Kv1.2-based model, suggests putative KCNE1 channel contacts and allosteric modulation of the IKs channel, which is also in agreement with the experimental data [6].

To estimate the predictive power of the models, virtual screening was performed and correlations between experimental pIC50s and docking scores were calculated. A literature search was carried out to collect a sufficient number of ligands with known inhibitory effect on IKs channel, particularly IC50 constants from patch-clamping experiments. It is surmised that the conformation of the channel has great effect on correlation. Swink (swivel and kink) algorithm [7, 8] for studying channel conformations by analysing hinges in the gating helices was implemented as PyMOL plugin. This study suggests that in shortage of close homologous templates in various conformations, particularly in the open state, conformational changes could be induced to improve blockade predictions. On the other hand, chemical properties of ligands, such as molecular weight and logD, also have to be considered as factors affecting the blockade and the voltage clamping results.

This effort facilitates the development of predictive pharmacophore models for in silico screening of new compounds as a part of cardiotoxicity tests.

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Figure 1. KvAP-based homology model of S5-pore-S6 KCNQ1 fragment. One subunit of the tetramer is not displayed for clarity. Extracellular side is on the top. A benzodiazepine derivative blocker (stick model) is docked in the pore cavity. Two potassium ions (violet) are in the selectivity filter.