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Poster presentation

Homology modeling of a voltage-gated potassium channel (human $K_v7.1$)

Alexandr Goncearenco*[1], Yasmin Karimi-Nejad[2] and Konrad Koehler[2]

Address: [1]CUBIC, University of Cologne, Cologne, Germany, 50674 and [2]CADD, Solvay Research Laboratories, Hannover, Germany, 30173

Email: Alexandr Goncearenco* - neksa@neksa.net

* Corresponding author

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Background

Long QT Syndrome (LQTS) is a heart disease in which the QT interval of the electrocardiogram, required for repolarization of the ventricles in the heart, is abnormally long. It is associated with syncope, arrhythmias, *torsade de pointes* and sudden cardiac death due to ventricular fibrillation. LQT1, the most common type of LQTS, is caused by mutations in the KCNQ1 gene. The product of this gene is the $K_v7.1$ (K^+ channel voltage-dependent variant 7.1) protein. The $K_v7.1$ channel mediates the slowly activating delayed rectifier potassium current (I_{Ks}) which in turn is one of the two currents responsible for ventricular depolarization in the heart. The $K_v7.1$ α subunit co-assembles with the minK potassium channel β subunit (coded by the KCNE1 gene) with a α_4/β_4 stoichiometry to form the fully functional ion channel.

Materials and methods

This study focuses on the elucidation of the 3D structure of the human $K_v7.1$ channel using a homology modeling approach based on the mammalian $K_v1.2$ [1] and bacterial K_vAP (potassium channel-voltage gated – *Aeropyrum Pernix*) [2] crystallographic structure templates, which represent different gating states of the channel, i.e. intermediate vs. fully open. The Schrödinger molecular modeling software suite was used to build and refine the models. High emphasis was placed on sequence alignment, topology, restrained energy minimization and maintenance of symmetry.

Results and discussion

Validation of the two resulting homology models was carried out by comparison with experimental mutagenesis data. In particular, mutations in residues in the $K_v7.1$ channel that altered the potency of block by L-735821 (L-7), a high affinity benzodiazepine blocker of wild-type $K_v7.1$ channels [3], were observed to be in close proximity to L-7 docked into the inner channel vestibule in the $K_v7.1$ homology model, in good agreement with the experimentally determined results. 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 co-localized residues [4]. The model based on the K_vAP template is in closer agreement with the experimental observations. Accessibility of the gating site, as observed in the $K_v1.2$-based model, suggests putative KCNQ1-KCNE1 inter-subunit contacts and allosteric modulation of the I_{Ks} channel, which is also in agreement with the available experimental data [5].

To estimate the ability of the models to predict blocker potency, virtual screening was performed and correlations between experimental pIC_{50}s and docking scores were calculated. A literature search was carried out to collect a sufficient number of blockers with known inhibitory effects on the I_{Ks} channel, particularly IC_{50} values from patch-clamp experiments. None of the two models performed particularly well in these virtual screening runs. Although it is at present unclear which factors – apart from the known weaknesses of present-day scoring functions –

may have caused these disappointing results, we hypothesize that the conformational state of the channel model will have a significant effect on the docking results. The reason is that channel gating produces a substantial change in the volume of the inner vestibule, which is believed to be the principle binding site for small molecule channel blockers. In order to define conformations of templates and models with respect to gating, the swink (swivel and kink) algorithm [6], which analyzes hinges in the gating helices, was implemented as a PyMol plug-in. This study suggests that in the absence of mammalian channel structures in the fully open state, homology building of potassium channel models may profit from introducing conformational changes into structures of most closely related templates first, in order to improve blockade predictions. On the other hand, physicochemical properties of ligands, such as molecular weight and log D 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 the *in silico* screening of new compounds as a part of cardiotoxicity tests.

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