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Title: hERG channel pharmacology – relation to proarrhythmia and novel molecular determinant

Abstract in English:

The human ether-ago-go related gene (hERG) channel is essential for the repolarisation phase of cardiac action potentials. hERG (Kv11.1) encodes the pore forming α-subunit of potassium channel, IKr. Reduction of hERG current, either by inherited mutations or by drugs that inhibit the channel may lead to prolonged action potential duration (APD) and fatal arrhythmias. A multitude of drugs from different therapeutic classes block hERG current, leading to acquired long QT syndrome and in some cases to sudden cardiac death.

Screening for adverse cardiac effects normally involves tests for inhibition of hERG current. hERG inhibition by drugs prolongs the human adult ventricular action potential and event linked to the generation of arrhythmias particularly Torsade de Pointes (TdP). In this thesis, using a series of dofetilide analogs I established correlation between hERG inhibition and action potential duration (APD) in hiPSC-cardiomyocytes using the CellOPTIQ platform. Functional studies were performed either with two-microelectrode voltage clamp on xenopus oocytes expressing hERG or alternatively making use of automated patch clamp and mammalian cell lines stably transfected with hERG. My data indicate that some derivatives with relatively high affinity for hERG have complex effects on cardiac APD due to multiple ion channel block.

Structurally diverse drugs block the inner pore cavity oft he hERG channel thereby inhibiting the outward potassium current. The well-known key binding residues are T623, S624 and V625, from the pore helix and residues G648, Y652 and F656 located on the S6 segment. Several studies previously suggested that helix S5, which is in close contact with S6 segments, is likely to also influence blockers. The result of this thesis reveals the role of segment S5 in drug channel block. A novel molecular determinant F557 on segment S5 was identified.

Drug trapping in the inner cavity of hERG has been an important phenomenon that explains slow recovery from block by some compounds. This thesis investigated the influence of trapped blockers on the gating dynamics oft he channel. Using a trapped small molecule tetrabutylammoniuim (TBA) and large molecule FB213 (propafenone analog) highlights the conformational changes of the key binding residue F656 during gate closure. Further this study reveals the extent of gate opening required for drug dissociation from the channel.

Together, this results in this thesis present new insights on the link between hERG inhibition and cardiac action potential prolongation. A new potential binding determinant on segment S5 was identified and interactions of hERG blockers with gate structures were described.