Modifiers of hERG K^+ channel gating

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hERG α-subunits coassemble to form channels that conduct I_{Kr}, the rapid delayed rectifier K^+ current that contributes to normal repolarization of cardiac action potentials. Loss-of-function mutations in hERG cause inherited long QT syndrome (LQTS), a disorder characterized by delayed repolarization of ventricular action potentials. Inherited and acquired LQTS are associated with an increased risk of *torsades de pointes*, an arrhythmia that can degenerate into ventricular fibrillation and cause sudden death. The acquired form of LQTS is more common and is most often caused by unintended block of hERG channels by a plethora of common medications. We have characterized the mechanisms of action and the molecular determinants for binding of hERG channel blockers and activators. Blockers preferentially bind to aromatic residues located in the S6 domain and to a Thr and/or Ser residue(s) located at the base of the pore helix. Activators (*e.g.*, RPR) induce a concentration-dependent slowing in the rate of deactivation and enhanced current magnitude by shifting the voltage dependence of inactivation to more positive potentials. This mechanism was confirmed by demonstrating that RPR slowed the rate of deactivation, but did not increase current magnitude of inactivation-deficient mutant channels. Point mutations of specific residues located in the S4-S5 linker or cytoplasmic ends of the S5 and S6 domains greatly attenuated or ablated the effects of RPR on deactivation, inactivation or both gating mechanisms. These findings confirm the importance of an interaction between the S4-S5 linker and the S6 domain in electromechanical coupling of voltage-gated K^+ channels.