PD increases hERG1 current by multiple effects, including a shift of inactivation to a more positive voltage, slowing of deactivation and an increase in single channel current probability. The efficacy of PD was increased in proportion to the WT:Leu646 allele ratio. The Hill coefficient was 1.40 - 1.55 for all the heteromeric concatamers, suggesting a weak positive cooperativity for PD binding. At a fully effective concentration of PD (10μM), each WT binding site contributes ~20% towards the maximum response of 80% enhancement of current.

ICA increases hERG1 current by a profound attenuation of inactivation. An increase in the WT:F557L subunit ratio enhanced the agonist activity of ICA (10μM and 30μM) in a synergistic fashion. For 2WT/2F557L concatenated channels, synergy required adjacent (as opposed to diagonal) WT subunits. In summary, four intact binding sites per channel are required to fully activate hERG1 by PD or ICA.

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Drug Trapping in hERG Channels does not Require Closure of the Activation Gate
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Human ether-a-go-go related gene (hERG) channel inhibitors can be trapped in the channels at rest. The structural peculiarities of hERG blockers that enable trapping or alternatively resting state dissociation are currently unknown. Propafenone (small molecule, MW 341 g/mol) is efficiently trapped in the closed hERG channel pore (1). To investigate whether the size of the blocking molecule plays a role in trapping we synthesized bulky propafenone derivatives containing benzoyl and trimethylphenyl side chains, attached by piperazine linkers, with molecular weights of 500 (Fba212) and 650 g/mol (Fba213) respectively. hERG channels were expressed in Xenopus laevis oocyte and potassium current inhibition was studied using the two - microelectrode voltage clamp technique.

It was found: first, both compounds are potent hERG blockers with IC50 3.7 μM (Fba212) and 52M (Fba213). Secondly, channel block by Fba212 and 213 was prevented by mutations Y652A and F656A as previously shown for propafenone (small molecule, MW 341 g/mol) is efficiently trapped in the closed hERG channel pore (1). To investigate whether the size of the blocking molecule plays a role in trapping we synthesized bulky propafenone derivatives containing benzoyl and trimethylphenyl side chains, attached by piperazine linkers, with molecular weights of 500 (Fba212) and 650 g/mol (Fba213) respectively. hERG channels were expressed in Xenopus laevis oocyte and potassium current inhibition was studied using the two - microelectrode voltage clamp technique.

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