Contribution of the Slow Delayed Rectifier K^+ current to Pacemaker Activity of the Human Sinoatrial Node

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The slow delayed rectifier K^+ current (I_{Ks}) is present in sinoatrial node (SAN) cells of various species, but both *in vitro* and *in silico* data on the contribution of I_{Ks} to SAN pacemaker activity are not consistent. To assess the contribution of I_{Ks} to human SAN pacemaker activity, we experimentally determined the biophysical properties of I_{Ks}, both under control conditions and upon β-adrenergic stimulation, and used the thus obtained data in computer simulations of human SAN pacemaker activity.

KCNQ1/KCNE1 channels were expressed in HEK-293 cells through transfection with both *KCNQ1* and *KCNE1* cDNA, encoding the α and β subunits of the I_{Ks} channel, respectively. KCNQ1/KCNE1 current was recorded at 37°C in absence and presence of forskolin (10 μM) to increase the cAMP level, thus mimicking β-adrenergic stimulation. Human SAN pacemaker activity was simulated using the Fabbri–Severi model of a single human SAN cell, with the biophysical properties of I_{Ks} based on our experimental observations.

Block of I_{Ks} under control conditions resulted in a 15.4% increase in pacing rate of the model cell, demonstrating that the inhibiting effect of I_{Ks} on diastolic depolarization dominated over its shortening effect on action potential duration. Running the model with its '1 μM isoprenaline' settings, thus simulating β-adrenergic stimulation, revealed higher effects of I_{Ks} block, the increase in pacing rate now amounting to 29.4%. These higher effects were not only due to the 25% increase in I_{Ks} conductance, the −14.6 mV shift in its steady-state activation curve, and the ≈40% increase in its activation rate upon β-adrenergic stimulation, but also to the shorter diastolic interval between subsequent action potentials available for I_{Ks} deactivation during the higher pacing rate induced by the β-adrenergic stimulation.

We conclude that I_{Ks} exerts an important slowing effect on human SAN pacemaker activity, in particular during β-adrenergic stimulation.