

Beta-Adrenergic Modulation of Heart Rate: Contribution of the Slow Delayed Rectifier K⁺ Current (I_{Ks})

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Under control conditions, the slow delayed rectifier potassium current (I_{Ks}) has little effect, if any, on the pacemaker activity of sinoatrial (SA) node cells. However, this outward current is enhanced by β -adrenergic stimulation, in which case it may affect pacing rate, either through its shortening effect on the action potential or through its inhibiting effect on diastolic depolarization. To assess the role of I_{Ks} in the β -adrenergic modulation of heart rate, we experimentally determined the effect of β -adrenergic stimulation on I_{Ks} and used the thus obtained data in computer simulations of SA nodal pacemaker activity, using the mathematical model of a primary rabbit SA node pacemaker cell by Kurata and coworkers.

Experimental data were obtained from HEK-293 cells that were transiently transfected with 1 μ g wild-type KCNQ1 cDNA and 1 μ g KCNE1 cDNA, encoding the α and β subunits of the I_{Ks} channel, respectively. KCNQ1/KCNE1 currents were studied at 37°C using the perforated patch-clamp technique in absence and presence of forskolin (10 μ mol/L) to increase the cAMP level, thus mimicking β -adrenergic stimulation. Forskolin significantly increased the KCNQ1/KCNE1 current density by \approx 25%, shifted the steady-state activation curve to more negative membrane potentials by \approx 15 mV, and increased the activation rate by \approx 50%.

Incorporation of our experimental findings into the SA nodal cell model resulted in a 6-ms decrease in cycle length, the shortening effect on action potential duration dominating over the inhibiting effect on diastolic depolarization. The decrease in cycle length is similar to the 10-ms decrease observed upon incorporation of a +8-mV change in the voltage dependence of the HCN4-encoded hyperpolarization-activated 'pacemaker current' (I_f), reflecting our earlier experimental data on the effect of forskolin on HCN4 current expressed in undifferentiated human cardiac myocyte progenitor cells.

We conclude that I_{Ks} is an important contributor to the β -adrenergic modulation of heart rate. This may explain the impaired heart rate response to exercise observed in long-QT syndrome type 1 and type 5 patients, who carry a loss-of-function mutation in the KCNQ1 or KCNE1 gene, respectively.