

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

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Abstract

To assess the role of the slow delayed rectifier potassium current (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, employing the mathematical model of a primary rabbit SA node pacemaker cell by Kurata and coworkers.

Incorporation of our experimental findings into the SA nodal cell model resulted in a 12 ms decrease in cycle length. This decrease in cycle length is similar to the 13 ms decrease observed upon incorporation of our experimental data on the effect of β -adrenergic stimulation on the hyperpolarization-activated 'funny current' (I_f), also known as 'pacemaker current'.

We conclude that I_{Ks} is an important contributor to the β -adrenergic modulation of heart rate.

1. Introduction

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 [1]. 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, employing the mathematical model of a primary rabbit SA node pacemaker cell by Kurata et al. [2].

2. Methods

2.1. Patch-clamp experiments

HEK-293 cells 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. Undifferentiated cardiac myocyte progenitor cells were transduced with a lentiviral hHCN4-ires-GFP vector.

KCNQ1/KCNE1 and HCN4 currents were studied at 37°C using the amphotericin-B perforated patch-clamp technique in absence and presence of forskolin (10 μ M) to increase the cAMP level, thus mimicking β -adrenergic stimulation.

2.2. Computer simulations

SA nodal pacemaker activity was simulated using the Kurata et al. model of a primary rabbit SA node pacemaker cell [2]. The I_{Ks} current density of the model was increased by a factor of 3, based on experimental I_{Ks} in SA nodal pacemaker cells from Lei et al. [3]. Furthermore, the I_{Ks} reversal potential was set equal to the potassium equilibrium potential (E_K) of -87 mV, in accordance with our experimental data on the KCNQ1/KCNE1 current, instead of the model value of -49 mV, which results from a presumed non-zero permeability of the I_{Ks} channel to sodium ions.

3. Results

3.1. Patch-clamp experiments

In paired experiments (n=7) on HEK-293 cells transfected with KCNQ1 and KCNE1 cDNA, forskolin increased the KCNQ1/KCNE1 current density by \approx 25%, shifted its steady-state activation curve to more negative membrane potentials by \approx 15 mV, and increased its activation rate by \approx 50% [4]. The reversal potential of the KCNQ1/KCNE1 current was not affected by forskolin.

In paired experiments (n=6) on human cardiac myocyte progenitor cells transduced with a lentiviral hHCN4-ires-GFP vector, forskolin increased the HCN4 current density by \approx 15% and shifted the voltage dependence of the steady-state activation curve as well as the time constant of activation and deactivation to less negative membrane potentials by \approx 8 mV [5]. The reversal potential of the HCN4 current was not affected by forskolin.

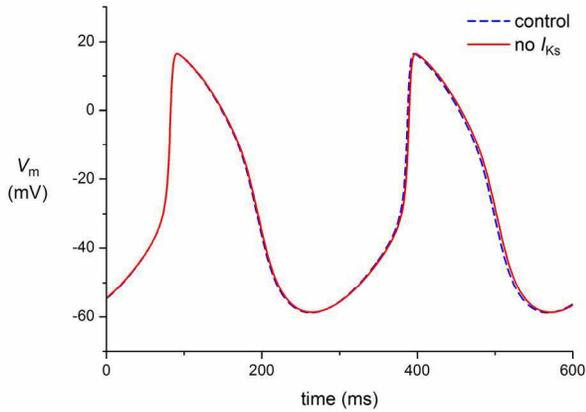


Figure 1. Action potential of the SA nodal cell model (Kurata et al. model [2] with modified I_{Ks}) under control conditions (blue dashed line) and upon blockade of I_{Ks} (red solid line). V_m denotes membrane potential.

3.2. Computer simulations

First, we tested the effect of I_{Ks} on pacemaker activity under control conditions, i.e. in the absence of β -adrenergic stimulation. As illustrated in Fig. 1, full block of I_{Ks} results in a <2 ms increase in cycle length, which changes from 305.2 to 306.9 ms. This minor effect of I_{Ks} under control conditions is in accordance with the

experimental observations by Lei et al. [1], who found a 1.2 ms increase in the cycle length of spontaneously active SA nodal cells upon block of I_{Ks} by the selective blocker chromanol 293b.

Next, we tested the effects of β -adrenergic stimulation of I_{Ks} as well as I_f . Our experimental findings on the KCNQ1/KCNE1 current were incorporated into the rabbit SA nodal cell model as changes in I_{Ks} , viz. a 25% increase in its current density, a -15 mV shift in its steady-state activation, and a 50% increase in its rate constant of activation. Our experimental data on the HCN4 current were incorporated as changes in the ‘funny current’ I_f , viz. a 15% increase in its current density and a $+8$ mV change in its voltage dependence.

Figure 2A shows the effects of β -adrenergic stimulation on I_{Ks} per se. The increase in I_{Ks} (Fig. 2A, middle) results in a 12 ms decrease in cycle length, the shortening effect on action potential duration dominating over the inhibiting effect on diastolic depolarization (Fig. 2A, top). The effects of β -adrenergic stimulation on I_f per se are shown in Fig. 2B. The increase in I_f (Fig. 2B, bottom) results in a 13 ms decrease in cycle length, mainly through its increasing effect on the rate of diastolic depolarization (Fig. 2B, top). As shown in Fig. 2C, the combined effect of the β -adrenergic stimulation of I_{Ks} and I_f is a 25 ms decrease in cycle length through a decrease in action potential duration and an increase in diastolic depolarization rate.

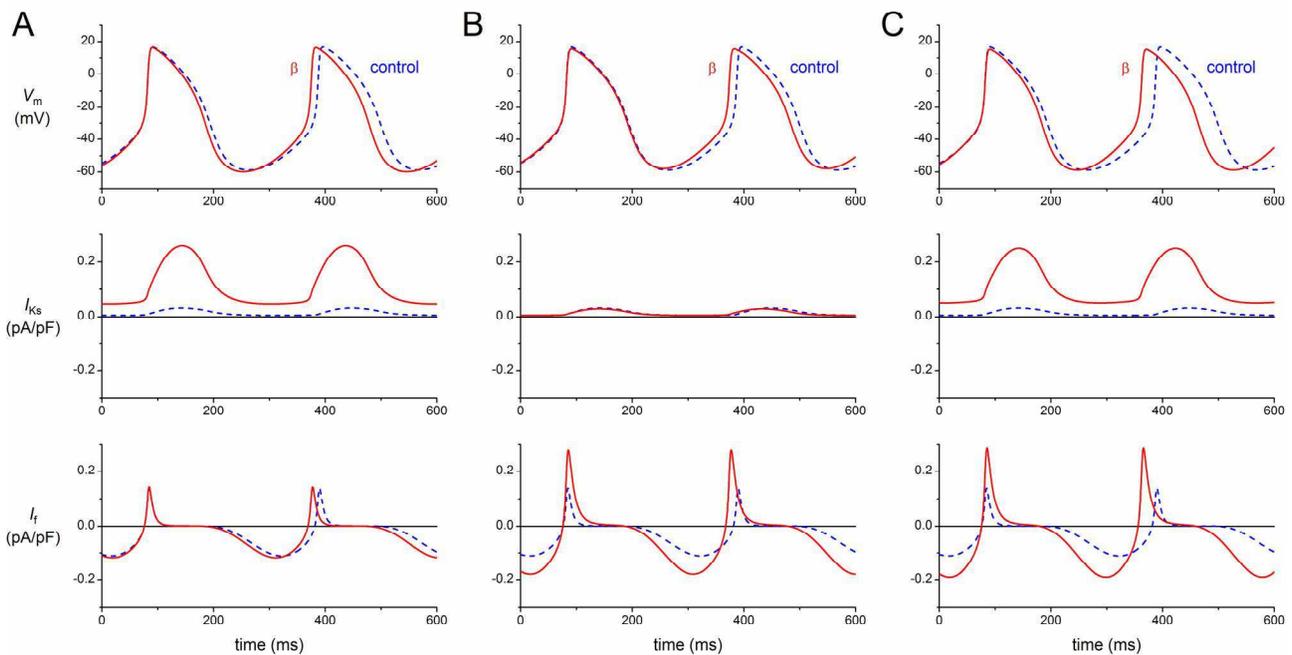


Figure 2. Simulated effects of β -adrenergic stimulation of (A) I_{Ks} per se, (B) I_f per se, and (C) both I_{Ks} and I_f on the pacemaker activity of a rabbit SA nodal cell (Kurata et al. model [2] with modified I_{Ks}). Blue dashed lines show the membrane potential (V_m , top), I_{Ks} (middle) and I_f (bottom) under control conditions, whereas red solid lines show V_m , I_{Ks} and I_f upon β -adrenergic stimulation of only I_{Ks} (left), only I_f (middle), and I_{Ks} as well as I_f (right).

4. Conclusion

We conclude that I_{Ks} is an important contributor to the β -adrenergic modulation of heart rate (as important as I_f). This may explain the impaired heart rate response to exercise observed in patients with the long-QT syndrome types 1 and 5 (LQT1 and LQT5), who carry a loss-of-function mutation in the I_{Ks} channel genes KCNQ1 or KCNE1, respectively.

References

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