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

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Abstract

The slow delayed rectifier K^+ current (I_{Ks}) is present in sinoatrial node (SAN) cells of various species, but data on the contribution of I_{Ks} to SAN pacemaker activity are not consistent. Yet, sinus bradycardia is a common finding in case of gain-of-function mutations in the KCNQ1 gene, encoding the pore-forming α-subunit of the I_{Ks} channel.

We carried out computer simulations of human SAN pacemaker activity using the Fabbri–Severi model of a single human SAN cell. Biophysical properties of I_{Ks} were updated, based on our recent patch clamp data on I_{Ks} channels expressed in HEK-293 cells.

Under vagal tone, block of the original I_{Ks} of the Fabbri–Severi model had only a marginally small effect on action potential duration and diastolic depolarization, and thus cycle length. However, with the formulation of I_{Ks} based on our patch clamp data, block of I_{Ks} had a substantial effect on diastolic depolarization and cycle length, increasing pacing rate by 17%. A qualitatively similar, but less substantial effect was observed under control conditions and under β-adrenergic tone, with an increase in pacing rate of 5.2% in either case. Simulation of a gain-of-function mutation in KCNQ1 revealed a strong bradycardic effect during vagal tone.

We conclude that I_{Ks} contributes to human SAN pacemaker activity at all levels of autonomic tone.

1. Introduction

The cardiac ion channel carrying the slow delayed rectifier K^+ current (I_{Ks}) is formed by co-assembly of pore-forming Kv7.1 (also named KCNQ1) α-subunits and KCNE1 β-subunits, which are encoded by the *KCNQ1* and *KCNE1* genes, respectively [1,2]. Kv7.1 was initially named K_VLQT1, for its relation to long QT syndrome type 1-related loss-of-function mutations in *KCNQ1* [3], whereas KCNE1 was initially named minK or IsK [4]. In their characterization of the 'molecular architecture' of the human sinoatrial node (SAN), Chandler et al. [5] found a quite abundant expression of Kv7.1 at the mRNA level, suggesting a functional role for I_{Ks} in the human SAN. Such functional role is also suggested by the sinus bradycardia that has often been observed in case of (heterozygous) gain-of-function mutations in *KCNQ1*, like the short QT syndrome-related V141M mutation that was studied in silico by Whitaker et al. [6]. However, compared to the several hundreds of loss-of-function mutations in *KCNQ1*, such gain-of-function mutations in *KCNQ1* are scarce [7].

Recently, we carried out patch clamp experiments to characterize the electrophysiological properties of I_{Ks} channels that were expressed in HEK-293 cells. Because I_{Ks} channels are sensitive to β-adrenergic stimulation [8], these experiments were not only carried out under control conditions, but also at elevated cyclic AMP levels. We used these data to update the formulation of I_{Ks} in the comprehensive mathematical model of a single human SAN pacemaker cell by Fabbri et al. [9], which is known as the Fabbri–Severi model. The thus updated Fabbri–Severi model was used to study the effects of I_{Ks} on human SAN pacemaker activity. These computer simulations were carried out with the standard settings of the model and at different levels of autonomic tone through the simulated administration of acetylcholine (ACh; vagal tone) or isoprenaline (Iso; β-adrenergic tone).

2. Methods

2.1. Formulation of I_{Ks}

As in the Fabbri–Severi model, the time and membrane potential (V_m, in mV) dependence of I_{Ks} was described by

$$I_{Ks} = n^2 \cdot g_{Ks} \cdot (V_m - E_{Ks}),$$

with its second-order Hodgkin-and-Huxley-type gating variable n, its fully-activated conductance g_{Ks}, and its reversal potential E_{Ks}. Analysis of our recently obtained patch clamp data yielded the equations

$$n_\infty = 1 / (1 + \exp(-(V_m+15.733)/27.77))$$

$$\beta_n = 1.93 \cdot \exp(-V_m/83.2)$$

for the steady-state value of n (n_∞) and its rate constant β_n (in s^{-1}), respectively. From these two equations, the remaining rate constant α_n (in s^{-1}) was computed through

$$\alpha_n = (n_\infty / (1 - n_\infty)) \cdot \beta_n$$

β-Adrenergic stimulation resulted in a leftward shift of the n_∞ Boltzmann curve by 14.568 mV, thus arriving at

$$n_\infty = 1 / (1 + \exp(-(V_m+30.301)/27.77)),$$

whereas β_n did not change and g_{Ks} increased by 25%.

Furthermore, to match our patch clamp data, we changed the K^+ : Na^+ permeability ratio of 1 : 0.12 used in the Fabbri–Severi model to 1 : 0.0018. Thus, we changed E_{Ks} from −49.3 mV in the original model to −85.7 mV in the updated model. Finally, to maintain an I_{Ks} amplitude in the range of the original model, we decreased g_{Ks} by 80%, from 0.65 nS to 0.13 nS.

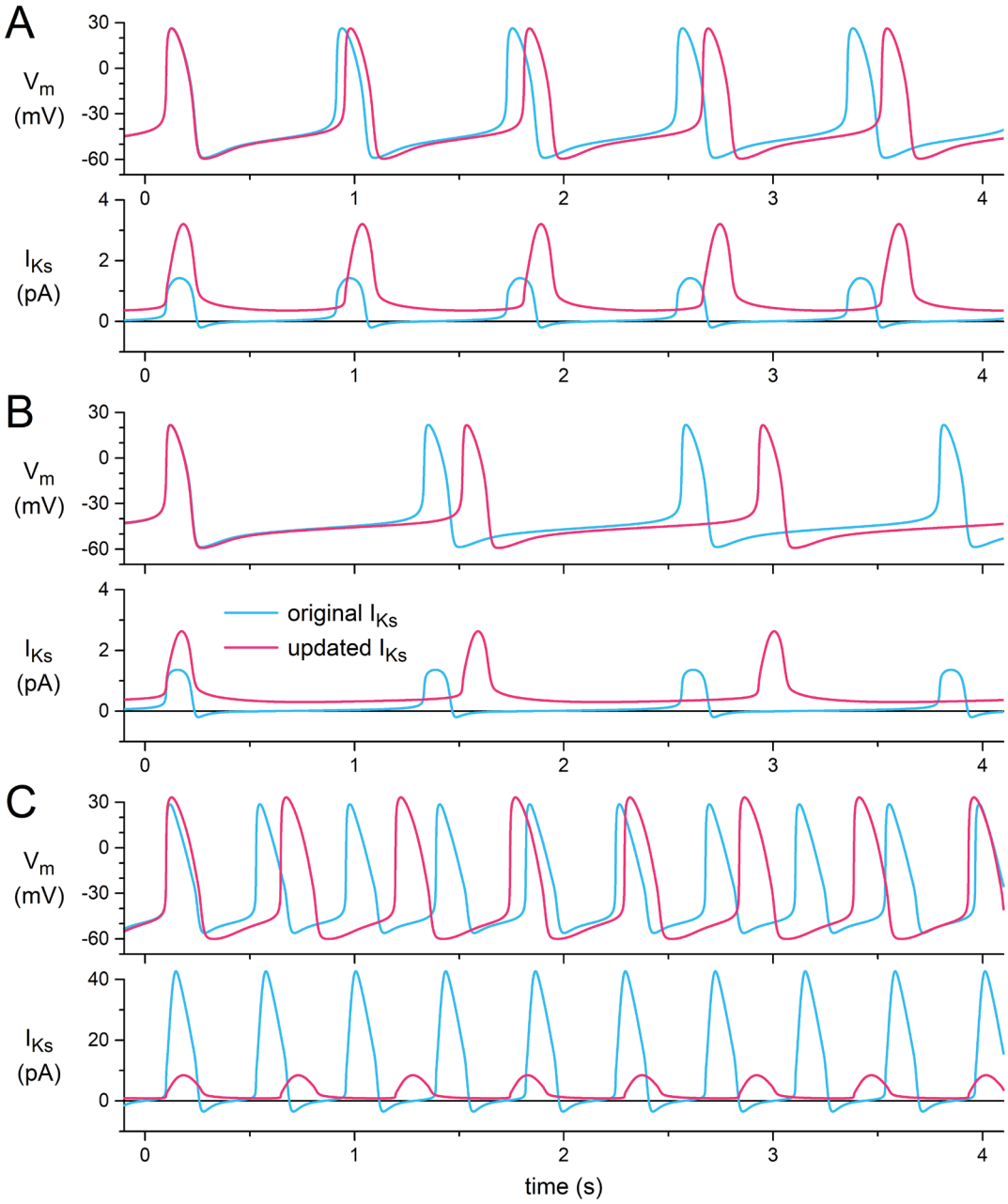

Figure 1. Membrane potential (V_m) and slow delayed rectifier K^+ current (I_{Ks}) in the Fabbri–Severi model of a single human sinus node pacemaker cell [9] with original and updated I_{Ks} (cyan and magenta traces, respectively) at different levels of autonomic tone. (A) Control conditions. (B) Vagal tone (20 nM). (C) β-Adrenergic tone ('high Iso').

2.2. Computer simulations

The updated I_{Ks} equations were implemented in the CellML code [10] of the Fabbri–Severi model [9]. The CellML code was edited and run in the Cellular Open Resource (COR) environment [11], version 0.9.31.1409. Vagal tone was simulated by setting the concentration of ACh to 20 nM, whereas β-adrenergic tone was simulated by adopting 'high Iso' settings between the '1 μM Iso' settings used by Fabbri et al. [9] in their original model and their settings used to obtain a pacing rate of 180 beats/min. All simulations were run for a sufficiently long time to reach steady-state behaviour.

3. Results

3.1. Updated I_{Ks} versus original I_{Ks}

First, we compared the action potential and I_{Ks} traces of the updated model with those of the original model at different levels of autonomic tone, as illustrated in Figure 1. Under control conditions, the cycle length of the updated model is slightly longer (+5.0%) than that of the original model (Fig. 1A, top), due to the slowing effect of the updated I_{Ks} on diastolic depolarization in the absence of a recognizable effect on action potential duration. In the original model, the driving force of I_{Ks} is almost zero during diastole because of its reversal potential near −50 mV, which results in an almost negligible amplitude of I_{Ks} during diastolic depolarization as compared to the updated model with its reversal potential negative to −80 mV (Fig. 1A, bottom). Under vagal tone, I_{Ks} is slightly smaller than under control conditions, unlike its effect on cycle length, which is substantially larger (Fig. 1B): the cycle length of the updated model is 184 ms longer than that of the original model (+15%).

Under β-adrenergic tone (Fig. 1C), cycle length is also larger in the updated model than in the original model. The main effect of the updated I_{Ks} is a slowing of diastolic depolarization, thus increasing cycle length, whereas the original I_{Ks} decreases cycle length through its shortening effect on action potential duration, as a large outward current during the action potential, as well as its accelerating effect on diastolic depolarization, as an inward current during more than half of the diastolic phase. As a result, the pacing rate goes as high as 140 beats/min in the original model, while only reaching 110 beats/min in the updated model.

3.2. Effect of block of I_{Ks}

Next, we studied the effects of block of I_{Ks} at different levels of autonomic tone, as illustrated in Figure 2. Under control conditions, block of I_{Ks} has a marginal effect in the

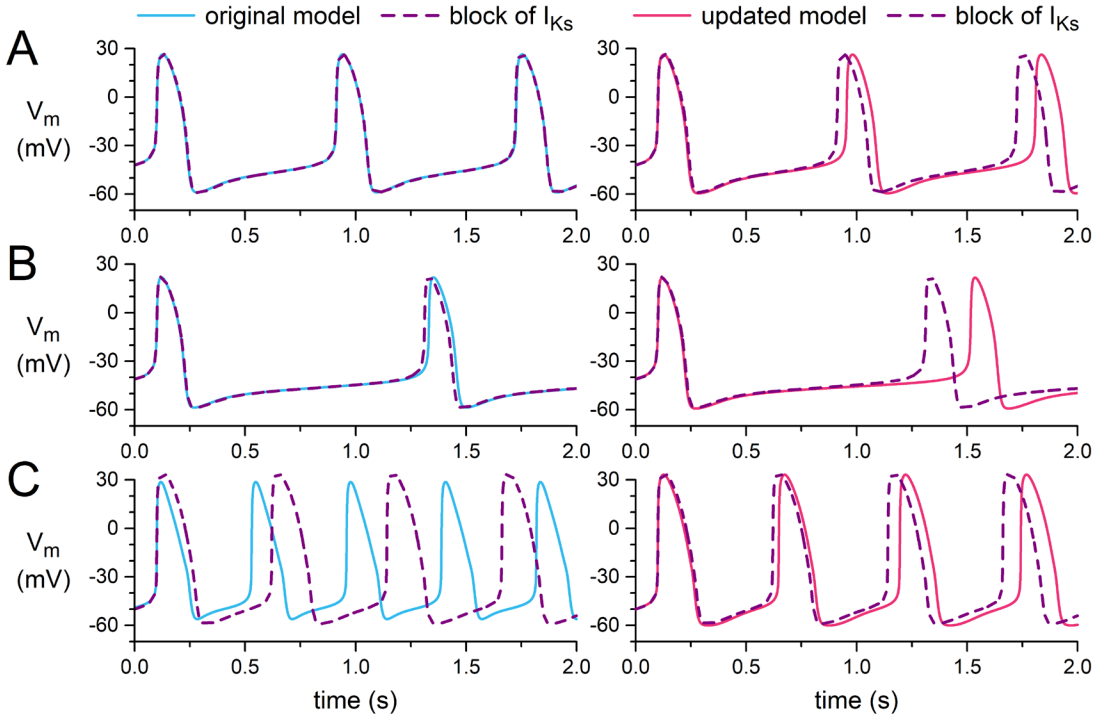

Figure 2. Action potentials of the Fabbri–Severi model of a single human sinus node pacemaker cell [9] with original (solid cyan traces, left panels) or updated I_{Ks} (solid magenta traces, right panels) and upon block of I_{Ks} (dashed purple traces) at different levels of autonomic tone. (A) Control conditions. (B) Vagal tone (20 nM). (C) β-Adrenergic tone ('high Iso').

original model (Fig. 2A, left). Cycle length is reduced by only 1.4 ms (−0.2%). In the updated model, however, cycle length is reduced by 42.4 ms (−5.0%) (Fig. 2A, right).

Under vagal tone (Fig. 2B), the effects of block of I_{Ks} are larger than under control conditions. In the original model (Fig. 2B, left), cycle length is reduced by 19.7 ms (−1.6%). In the updated model (Fig. 2B, right), however, this reduction is considerably larger and amounts to 204 ms (−14%), in line with the observations of Fig. 1B.

Under β-adrenergic tone (Fig. 2C), the effects of block of I_{Ks} are essentially different between the original and the updated model. In the updated model (Fig. 2C, right), block of I_{Ks} results in a decrease in cycle length. However, as might be anticipated from Fig. 1C, block of I_{Ks} results in an increase in cycle length in the original model rather than a decrease (Fig. 2C, left). The change in cycle length amounts to +91 ms (+21%) in the original model and −27 ms (−4.9%) in the updated model, respectively.

Overall, block of I_{Ks} in the updated model results in a 5.2% increase in pacing rate under control conditions as well as under β-adrenergic tone. Under vagal tone, however, the increase in pacing rate is as large as 17%, which suggest a potentially strong bradycardic effect of a gain-of-function mutation in *KCNQ1*, as observed for several of such mutations, as set out in Section 1.

3.3. Effect of a gain-of-function mutation

Under vagal tone, the cycle length of the original model is 1231 ms and that of the updated model 1415 ms (Fig. 1B), corresponding with pacing rates of 48.7 and 42.4 beats/min, respectively. Doubling the fully-activated conductance of I_{Ks}, i.e., g_{Ks}, as a simple test to get insight into the bradycardic effect of a gain-of-function mutation in *KCNQ1*, resulted in a pacing rate of 47.9 beats/min in the original model (−1.8%) and a pacing rate as low as 31.4 beats/min in the updated model (−26%).

4. Conclusions

We conclude that I_{Ks} contributes to human SAN pacemaker activity at all levels of autonomic tone, in particular under vagal tone. Its prominent contribution to pacemaking under vagal tone is in line with the strong bradycardic effect that has been observed in case of gain-of-function mutations in *KCNQ1*.

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