Hyperpolarization-Activated 'Pacemaker Current' — A Funny Current in Models of SA Nodal Pacemaker Cells

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Abstract

A typical feature of sinoatrial (SA) nodal pacemaker cells is the presence of an ionic current that activates upon hyperpolarization. The contribution of this hyperpolarization-activated current, I_f, which is also known as the 'funny current' or 'pacemaker current', to the spontaneous pacemaker activity of SA nodal cells remains a matter of intense debate.

We used experimentally recorded action potentials of a single isolated rabbit SA nodal pacemaker cell to reconstruct the time course of I_f according to the mathematical models of Maltsev and Lakatta (2009) and Severi et al. (2012). The thus reconstructed I_f was compared to that obtained with a simple and straightforward first-order Hodgkin and Huxley-type model of I_f based on experimental data acquired in our laboratory.

In terms of steady-state activation and fully-activated current amplitude, the model of Maltsev and Lakatta (2009) better fits our experimental data than that of Severi et al. (2012). However, with both models, the reconstructed time course of I_f shows several discrepancies with the time course based on our experimental data, which is largely due to the almost instantaneous deactivation of I_f at depolarized potentials in either model.

1. Introduction

The sinoatrial node (SA node) is the normal pacemaker of the mammalian heart and generates the electrical impulse for the regular, rhythmic contraction of the heart. The intrinsic pacemaker activity, or spontaneous electrical activity, of an SA nodal pacemaker cell is based on the spontaneous diastolic depolarization that depolarizes the cell towards the action potential threshold. During this diastolic depolarization there is a tiny net inward current across the cell membrane of no more than a few picoamps in amplitude. Animal studies, almost exclusively carried out on cells isolated from rabbit heart, have learned that this net inward is the result of a complex interaction of multiple inward and outward ion currents, including a hyperpolarization-activated current of mixed ionic nature, known as 'funny current', I_f, or 'pacemaker current'. Despite the numerous experimental studies, the contribution of I_f to SA nodal pacemaker activity has been and still is a matter of, often intense, debate, particularly in relation to the 'calcium clock' (e.g., [1,2]). Computer simulations have not only been used to support a limited role for I_f (Maltsev and Lakatta [3]), but also to underscore that I_f is "the major inward diastolic ionic current" (Severi et al. [4]).

2. Mathematical models of I_f

2.1. Model of Maltsev and Lakatta

In their 2009 model, Maltsev and Lakatta [3] adopted the I_f equations of Kurata et al. [5], who in turn based their equations on the model that van Ginneken and Giles presented with their experimental work carried out in the 1980s [6]. Accordingly, I_f is given by

$$I_f = y^2 \times g_f \times (V_m - E_f), \quad (1)$$

in which y is a Hodgkin and Huxley-type activation gate, g_f is the fully-activated conductance of I_f, V_m is the membrane potential, and E_f is the reversal potential of I_f. The associated steady-state activation, i.e., y_∞^2, and fully-activated current, with $E_f = -26.6$ mV, are shown in red in Figure 1, A and B, respectively. Of note, Maltsev and Lakatta [3] reduced the fully-activated I_f conductance of Kurata et al. [5] by 60%, from 0.375 to 0.15 nS/pF.

2.2. Model of Severi et al

In the recent "updated computational model of rabbit sinoatrial action potential to investigate the mechanisms of heart rate modulation" by Severi et al. [4], the kinetic and conductive properties of I_f are largely based on the work of DiFrancesco and Noble from the 1980s. The kinetics are adopted from the early SA nodal cell model by Noble et al. [7], who used a Hodgkin and Huxley-type model with two identical y gates, as in Equation 1. However, Severi et al. [4] shifted the voltage dependence of the associated rate constants to more depolarized

potentials by ≈11 mV. Furthermore, they assumed identical conductance values for the sodium and potassium components of I_f, thus arriving at an I_f reversal potential of −4.4 mV. The steady-state activation and fully-activated current are shown in green in Figure 1, A and B, respectively.

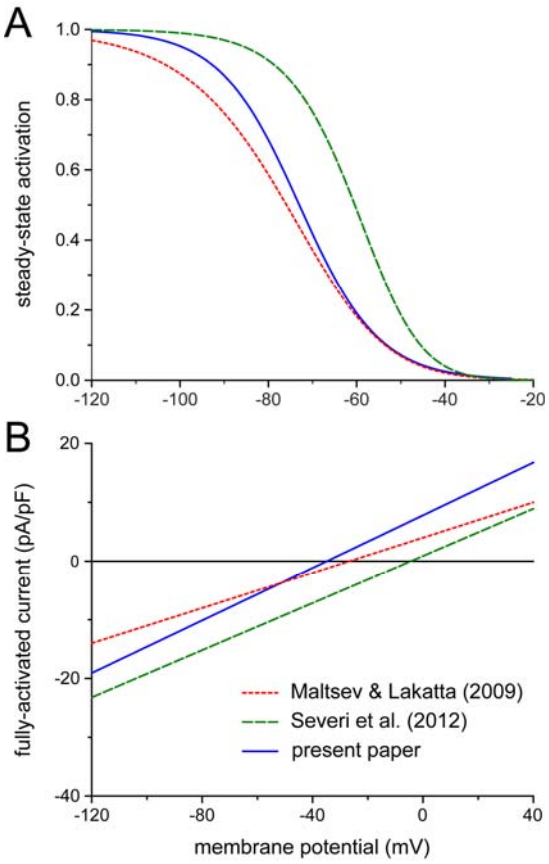

Figure 1. (A) Normalized steady-state activation and (B) fully-activated current in three mathematical models of the hyperpolarization-activated current I_f in rabbit SA nodal pacemaker cells.

2.3. Novel model

Figure 1 also shows curves in blue that are labelled 'present paper'. These curves represent a novel model for I_f based on the experimental data that we acquired in our laboratory with the perforated patch clamp technique under close-to-physiological conditions (Figure 2) [8]. In this model, I_f is described by

$$I_f = y \times 0.224 \times (V_m + 34.8), \quad (2)$$

with the steady-state value y_∞ and time constant τ of the single Hodgkin and Huxley-type activation gate y given by

$$y_\infty = 1 / \{ 1 + \exp[(V_m + 73) / 9] \}, \quad (3)$$

$$\tau = 0.05 + 1 / [75.8 \times \exp(0.083 \times V_m) + 0.0233 \times \exp(-0.043 \times V_m)], \quad (4)$$

where I_f is in pA/pF, V_m is in mV and τ in s.

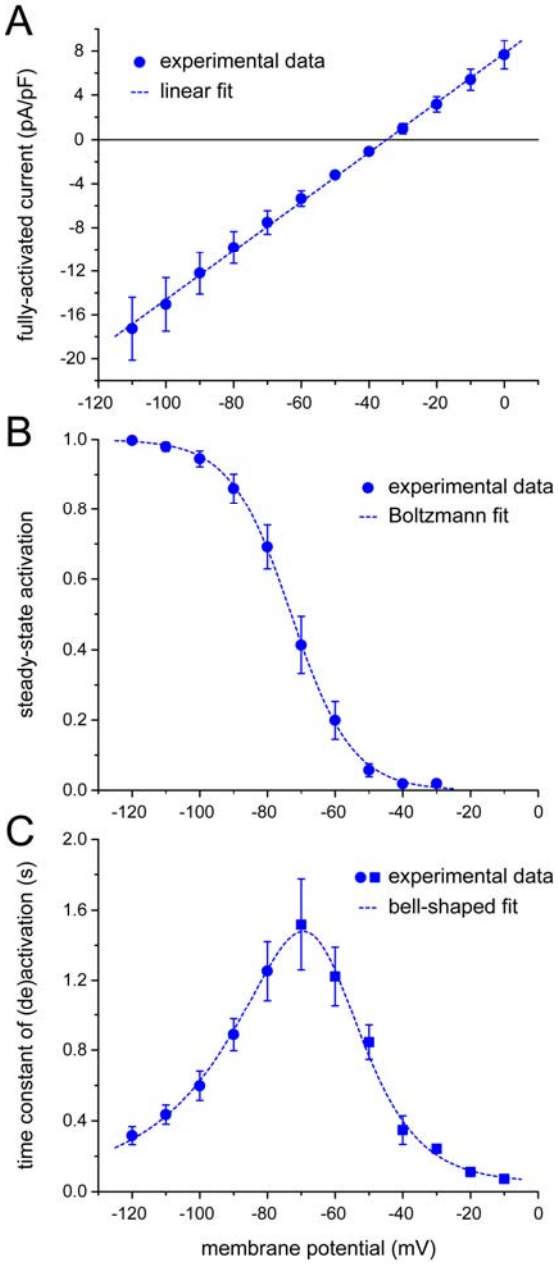

Figure 2. Characteristics of the hyperpolarization-activated current I_f as determined from voltage clamp experiments on single pacemaker cells isolated from the rabbit SA node. (A) Fully-activated current, normalized to membrane capacitance. (B) Normalized steady-state activation. (C) Time constant of I_f activation (filled circles) and deactivation (filled squares). All membrane potential values are corrected for the estimated liquid junction potential.

As can be appreciated from Figure 1A, the steady-state activation curve of our model closely matches that of Maltsev and Lakatta [3] in the physiological membrane potential range, but less so that of Severi et al. [4]. Our I_f conductance of 0.224 nS/pF, on the other hand, closely matches the value of 0.201 nS/pF of Severi et al. [4], as can be appreciated from the similar slopes of the lines in Figure 1B. However, Figure 1B also illustrates that the I_f reversal potential of the Severi et al. model [4] differs from that of our model by as much as 30 mV, which creates an almost two-fold difference in I_f driving force near the maximum diastolic potential of an SA nodal action potential.

The (dis)similarities between the models are further illustrated in Figure 3, which compares the steady-state characteristics of I_f at −60 mV in each of the three models. In combination, the steady-state activation of Figure 3A and the fully-activated current amplitude of Figure 3B determine the amplitude of I_f that can be activated at −60 mV. Accordingly, we multiplied the fully-activated current amplitude of Figure 3B by the steady-state activation of Figure 3A to arrive at the steady-state current amplitude of Figure 3C. With a value of 5.4 pA/pF, the model by Severi et al. [4] shows a remarkably large amplitude (Figure 3C).

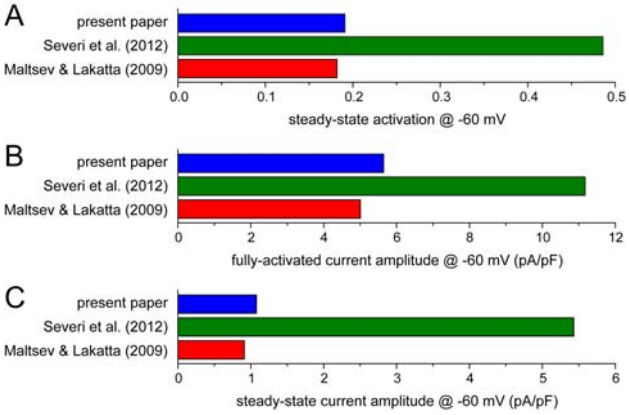

Figure 3. (A) Steady-state I_f activation, (B) fully-activated current amplitude, and (C) steady-state current amplitude at −60 mV in three mathematical models of the hyper-polarization-activated current I_f in rabbit SA nodal pacemaker cells.

3. Reconstructed time course of I_f

Figure 3 shows that the amount of I_f that can be activated at −60 mV varies widely between the models, but this does not imply that this is also the case during the course of an SA nodal action potential. In the latter case, the rate at which I_f activates and deactivates plays an important role. Therefore, we subjected each of the models to an 'action potential clamp': we reconstructed I_f during the experimentally recorded action potentials of Figure 4A. These action potentials were applied as part of a sufficiently long train and I_f was computed according to the equations of each of the models. The resulting I_f traces are shown in Figure 4B, together with the net membrane current, I_{net}, which was computed from the time derivative (dV_m/dt) of the membrane potential trace of Figure 4A.

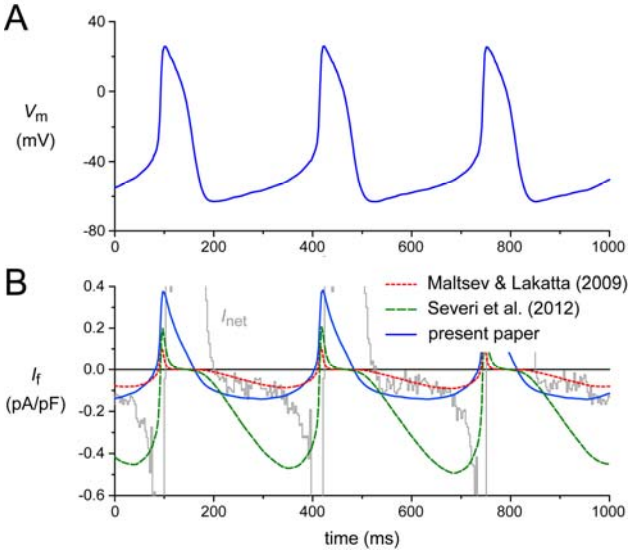

Figure 4. Numerical reconstruction of the time course of I_f during pacemaker activity of rabbit SA node pacemaker cells. (A) Experimentally recorded action potentials of a single rabbit SA nodal pacemaker cell. (B) Associated time course of I_f as reconstructed using the membrane potential values of the recorded action potentials and mathematical models of this current. Also shown is the net membrane current (I_{net}), as derived from $I_{net} = -C_m \times dV_m/dt$, where C_m and V_m denote membrane capacitance and membrane potential, respectively.

In the models by Maltsev and Lakatta and Severi et al., I_f deactivates almost instantaneously at depolarized potentials [3,4]. This results in an almost complete deactivation of I_f near the overshoot of the SA nodal action potential and a slowly developing I_f during the subsequent diastolic phase (Figure 4B). However, I_f deactivation is fast but certainly not instantaneous at depolarized potentials (see [8] and primary references cited therein). If this is taken into account, as in our novel model, I_f is available early in diastole and of relatively constant amplitude during diastolic depolarization.

Interestingly, Zaza et al. [9] already noted that the presence of a measurable inward 2 mM Cs^+ sensitive current almost immediately after repolarization in their action potential clamp experiments on rabbit SA nodal cells is apparently at odds with the slow kinetics of I_f activation at diastolic potentials, that this suggests that I_f

may not deactivate completely during repetitive activity, and that this would also increase the amount of I_f available during diastolic depolarization.

From the I_f traces of Figure 4B, we computed the diastolic I_f current amplitude at −60 mV (Figure 5A) as well as the maximum I_f current amplitude during diastole (Figure 5B). Also, we computed the charge carried by I_f during the 200-ms, 25-mV diastolic depolarization (Figure 5C). Both Figure 4B and Figure 5A demonstrate that only a fraction of the steady-state current of Figure 3C is actually activated during an action potential.

Figure 5C shows that, in the absence of other inward or outward membrane currents, the charge carried by I_f during the 200-ms diastolic depolarization would be sufficient or almost sufficient to depolarize the membrane by the observed 25 mV. For example, our model based on the experimental data of Figure 2 predicts a charge carried by I_f of 0.024 pC/pF, which is equivalent to a depolarization of 24 mV. Notably, the models of Maltsev and Lakatta [3] and Severi et al. [4] predict depolarizations of 12 and 67 mV, respectively (Figure 5C).

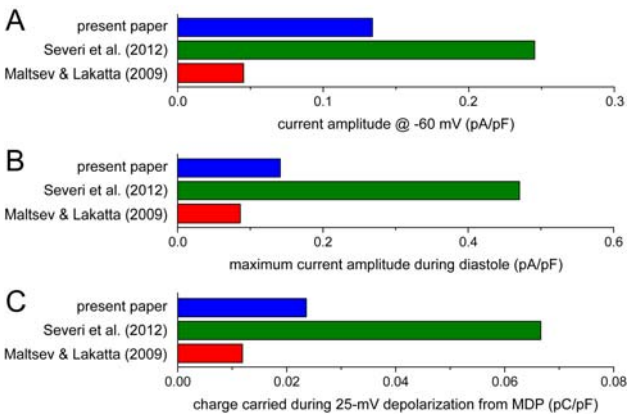

Figure 5. (A) Diastolic I_f current amplitude at −60 mV, (B) maximum I_f current amplitude during diastole, and (C) charge carried by I_f during the 25-mV, 200-ms diastolic depolarization from the maximum diastolic potential (MDP) of −63 mV to −38 mV for each of the reconstructed I_f current traces of Figure 4B.

4. Conclusion

The mathematical descriptions of I_f that have been used by Maltsev and Lakatta [3] and Severi et al. [4] show strikingly different characteristics when reconstructing the course of I_f during an SA nodal action potential. This explains—at least to some extent—that Severi et al. [4] could successfully use computer simulations to support their view that I_f plays a fundamental role in the generation of pacemaker activity and its rate control, while Maltsev and Lakatta [3] could provide computer simulation results in favour of their view that the role of I_f is limited to a modest contribution to rate control.

We have identified some important caveats regarding the mathematical description of I_f. An obvious one is the use of appropriate activation kinetics and an appropriate I_f conductance. A somewhat less obvious caveat is the selection of an I_f reversal potential near −30 mV. The final and most important caveat is that I_f deactivation is not almost instantaneous at depolarized potentials. Our novel model for the reconstruction of I_f in mathematical models of SA nodal pacemaker cells is simple and straightforward, but takes care of all of these caveats.

References

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