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The effect of hyperpolarizing inputs on the dynamics of a bursting pacemaker neuron model in the pre-Bötzinger complex

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ABSTRACT

The pre-Bötzinger complex (pre-BötC), a subregion of the ventrolateral medulla involved in respiratory rhythm generation, contains intrinsically bursting pacemaker neurons. A previous study proposed Hodgkin–Huxley type minimal models for pacemaker neurons and predicted the effect of a hyperpolarizing input on the dynamics of a model under certain conditions. In this model, bursting is explained by the dynamics of a persistent sodium current. In the present study, the effect of a hyperpolarizing input on the dynamics of a model was investigated under variable conditions. It was observed that immediately after an input of sufficient intensity and duration, an increase in the maximal value of the gating variable h of a persistent sodium current was brought about by a decrease in the timing of the hyperpolarizing input. This corresponds to an observation that immediately after the input, a monotonic increase in the number of spikes in the neuron model was brought about by a decrease in the timing of the hyperpolarizing input. In addition, the dependency of burst duration immediately after the input on the timing of the hyperpolarizing input varied depending on the condition of input. The present study is the first to elucidate that the influence of hyperpolarizing inputs on the number of spikes within a burst in a pacemaker neuron model in the pre-BötC is dependent on the timing of the hyperpolarizing input and to clarify the possible mechanism of this influence, thereby facilitating a detailed understanding of the dynamics of a pacemaker neuron model in the pre-BötC.

The pre-Bötzinger complex (pre-BötC), a subregion of the ventrolateral medulla [15], is a site necessary for normal breathing in mammals [5] and a major source of endogenous inspiratory rhythmicity in vitro [12,14,15]. Intrinsically bursting pacemaker neurons are present in the pre-BötC [2,3,6–10,15,16,17]. Minimal models for the pacemaker neuron with a persistent sodium current (I_{NaP}) have been proposed [1]. Computational analysis indicates that pacemaker neurons play a role in increasing the robustness of the rhythm-generating network [11].

Pacemaker neurons recorded from in vitro transverse medullary slice preparations from neonatal rats after blocking synaptic transmission by low Ca^{2+} conditions exhibit voltage-dependent properties as follows [1]. When the neuron is depolarized to a certain level, it undergoes a transition from the resting state to an oscillatory bursting state. In the oscillatory bursting mode, burst frequency increases and burst duration decreases with increasing depolarization. Further depolarization above the action potential threshold causes a transition from a bursting to a beating state. These experimentally observed features are reproduced in model 1 for the pacemaker neuron by Butera et al. [1]. The dynamics of model 1 are based on one-compartment Hodgkin–Huxley formalism, where three voltage-dependent ionic currents – I_{NaP}, fast sodium current (I_{Na}), and delayed rectifier potassium current (I_K) – are included. I_{NaP} is involved in burst initiation and termination, while I_{Na} and I_K are involved in the generation of action potentials. Although other voltage-dependent ionic currents, such as low- and high-voltage-activated calcium channels, are known to exist in pacemaker neurons [4], these are not included in the model. The model is based on a neuron under low Ca^{2+} conditions.

From this model, Butera et al. [1] derived the resetting response as a testable prediction. That is, a hyperpolarizing input applied to a neuron model during an active burst phase terminates the current burst as well as makes the subsequent burst appear earlier. In addition, the earlier an input is applied to a burst, the earlier the subsequent burst appears. However, burst duration after the input is not affected. Since these predictions are based on simulation only under a specific condition (by simulating a neuron model at $E_L = -59$ mV (E_L indicates the reversal potential of the leakage current of a neuron model, and the level of depolarization of a neuron model is controlled by varying E_L) to which a 50 ms and 10 pA hyperpolarizing input is applied), it is not known whether these predictions may also apply to the different conditions. In particular, it remains to be seen whether burst duration after the input is also unaffected under different conditions. Taking these into account,

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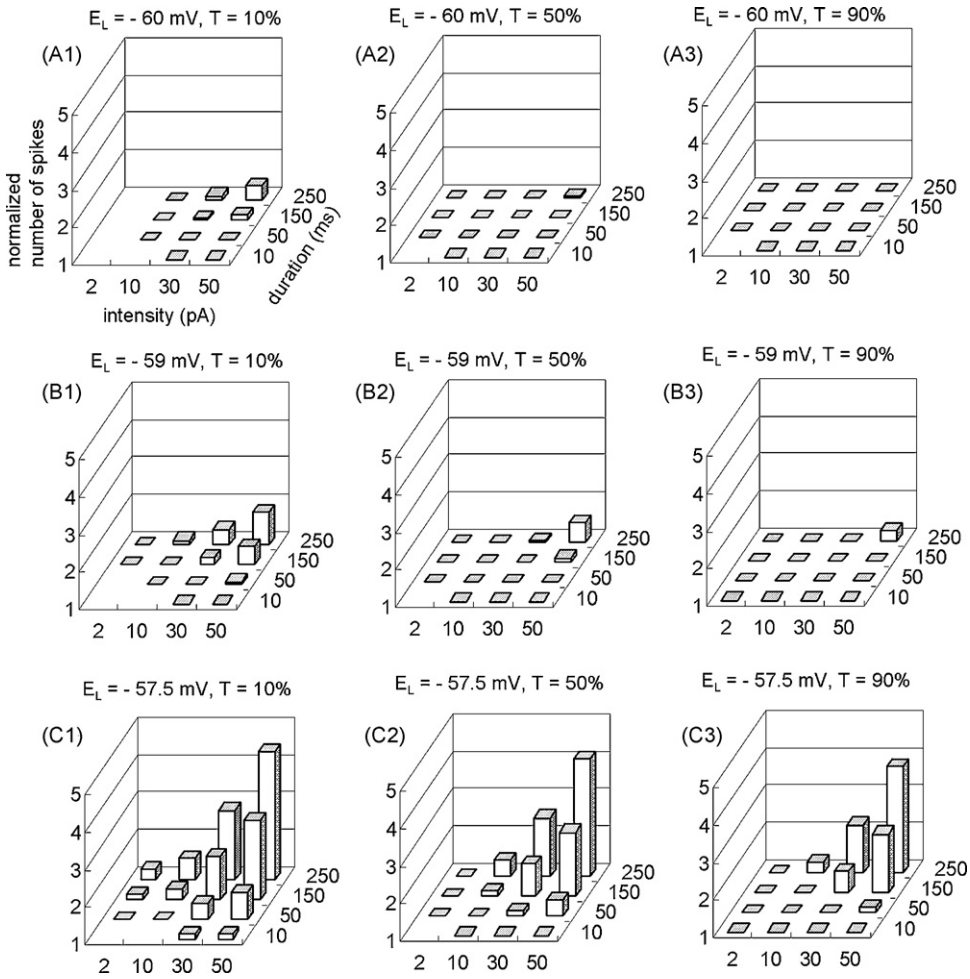

Fig. 1. The effect of a hyperpolarizing input on the number of spikes. (A1–3) The hyperpolarizing current is injected into the neuron model at $E_L = -60$ mV at very early ($T = 10\%$) (A1), intermediate ($T = 50\%$) (A2), and very late ($T = 90\%$) (A3) stages of an active phase of one burst cycle. The normalized number of spikes is plotted against intensity and duration of the hyperpolarizing input. (For example, in case of a 10 pA and 50 ms hyperpolarizing input, the normalized number of spikes is 1.) (B1–3) $E_L = -59$ mV and (C1–3) $E_L = -57.5$ mV. In (A1–3), (B1), (B2), (C1), and (C2), no resetting response was observed where no value is plotted.

the resetting response might not have been characterized precisely in previous studies. This might have prevented a future experimental test of the resetting response for demonstrating the validity of the model from being performed precisely. Thus, it is important to extend the analysis to the different conditions and to clarify the model's behavior in more detail. In the present study, the dynamics of the model proposed by Butera et al. [1], in particular excitability and burst duration after a hyperpolarizing input, were investigated under different conditions.

In this study, the original model 1 [1] was used. Although some parameters of the original model 1 were adjusted to match recent experimental data more closely, simulation with the adjusted model showed a behavior very similar to that of the original model 1 [11]. The dynamics of the original model 1 have been described in detail in a previous report [1] and will be briefly summarized here. The dynamics of membrane potential V (mV) of a pacemaker neuron model in the pre-BötC obeyed the following differential equation: $C^*(dV/dt) = I_{ext} - \Sigma I_i$ based on one-compartment Hodgkin–Huxley formalism, where C is the membrane capacitance (21 pF), t is the time (ms), I_{ext} is an externally applied current (pA), and I_i is the ionic current (pA). The ionic currents included in the differential equation are I_{NaP}, I_{Na}, I_K, and leakage current (I_L). The currents are as follows: $I_{NaP} = g_{NaP}{}^* m_{NaP\infty}(V)^* h^*(V - E_{Na})$, $I_{Na} = g_{Na}{}^* \{m_{Na\infty}(V)\}^3{}^*(1-n)^*(V - E_{Na})$, $I_K = g_K{}^* n^4{}^*(V - E_K)$, and $I_L = g_L{}^*(V - E_L)$. g_{NaP}, g_{Na}, and g_K are maximum conductances for I_{NaP}, I_{Na}, and I_K, respectively ($g_{NaP} = 2.8$ nS, $g_{Na} = 28$ nS, $g_K = 11.2$ nS). g_L is the leak conductance (2.8 nS). E_{Na}, E_K, and E_L are the reversal potentials ($E_{Na} = 50$ mV, $E_K = -85$ mV, $E_L = -60$ mV, -59 mV, or -57.5 mV). E_L changes when the extracellular potassium concentration changes. h and n are the gating variables, which obey the following differential equations, respectively: $dh/dt = [\{1 + \exp((V+48)/6)\}^{-1} - h]/[10^4/\cos h((V+48)/12)]$ and $dn/dt = [\{1 + \exp((V+29)/(-4))\}^{-1} - n]/[10/\cos h((V+29)/(-8))]$. $m_{NaP\infty}(V)$ and $m_{Na\infty}(V)$ are steady-state voltage-dependent activation functions of the gating variables m_{NaP} and m_{Na}, respectively, which are as follows: $m_{NaP\infty}(V) = \{1 + \exp((V+40)/(-6))\}^{-1}$ and $m_{Na\infty}(V) = \{1 + \exp((V+34)/(-5))\}^{-1}$. The free software Scilab (http://www.scilab.org/) was used to solve differential equations numerically.

One burst cycle consists of an active phase (action potentials fire repetitively) and a silent phase (membrane potential varies slowly at a hyperpolarized value). Burst duration was measured as the active phase duration of one burst cycle. The number of spikes per burst cycle and burst duration immediately after a hyperpolarizing input to the neuron model at $E_L = -y$ mV were calculated and normalized in such a way that the number of spikes per burst cycle and burst duration without a hyperpolarizing input at $E_L = -y$ mV were both equal to 1. Without a hyperpolarizing input, burst duration was 0.64 s at $E_L = -60$ mV, 0.60 s at $E_L = -59$ mV, and 0.44 s at $E_L = -57.5$ mV, and the number of spikes per burst cycle was 26 at $E_L = -60$ mV, 17 at $E_L = -59$ mV, and 7 at $E_L = -57.5$ mV. A variable T was introduced to designate the time of input, and was expressed as