Computational modeling of bursting pacemaker neurons in the pre-Bötzinger complex

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Abstract

Bursting pacemaker neurons in the pre-Bötzinger complex (pBC) were modeled in the Hodgkin-Huxley style. The single neuron model included the fast sodium, persistent sodium, and delayed rectifier potassium channels. The kinetics of the fast and persistent sodium channels were modeled using experimental data obtained from pBC neurons *in vitro*. Our analysis focused on the investigation of possible mechanisms and conditions providing transition in firing behavior of single pBC neurons and neural population from tonic to bursting firing behavior. The results of modeling are discussed in the context of possible role of the pBC in generation of the respiratory rhythm and in reconfiguration of the respiratory network under different conditions.

Summary

Two concepts were put forward to explain the generation of the respiratory rhythm in the brainstem. A *network* theory (based on *in vivo* studies) suggests that the rhythm is generated due to the network (mostly inhibitory) interactions between functionally different populations of respiratory neurons (i.e. without contribution of endogenous bursting properties in the involved neurons) (Cohen, 1979; Richter and Ballantyne, 1983; Richter et al., 1991). In contrast, a *pacemaker-based* or a *hybrid* theory (based mostly on *in vitro* data) suggests that a subpopulation of conditional pacemaker neurons within the pre-Bötzinger complex comprises a rhythm-generating "kernel" providing a necessary bursting drive to a wider pattern-forming network (Rekling and Feldman, 1998; Smith, 1997; Smith et al., 2000). The network theories and models have been successful in providing explanations to various systems-level phenomena, such as separate regulation of respiratory phase durations, respiratory reflexes (e.g. the Hering-Breuer reflex) and various phase resetting phenomena. However, the network theory strongly requires the reciprocal inhibitory interactions between respiratory neurons and therefore has been unable to explain the pacemaker-driven rhythm recorded *in vitro*, which was proven to persist after blockade of synaptic inhibition (Shao and Feldman, 1997). Alternatively, the pacemaker-based theories and models face principal difficulties in providing explanations for various systems-level phenomena, such as respiratory reflexes, independent regulation of respiratory phases, various resetting phenomena. In order to "build a bridge" between the two theories we have offered a *switching* concept which suggests that the complex ponto-medullary respiratory network *can generate rhythmic output by either a pure network or a hybrid pacemaker-network mechanisms depending on conditions* (Rybak et al., 2001; 2002). This concept raises a series of fundamental questions, specifically: (1) *What are the conditions that define each of the mechanisms of rhythmogenesis?* (2) *How is the respiratory network re-organized to switch from one mechanism of rhythmogenesis to another?*

In order to address these questions we developed a model of pBC and focused on the computational investigation of possible mechanisms and conditions providing transition in firing behavior of single pBC neurons and neural population from tonic to bursting firing behavior.

Jeff Smith and his colleagues developed the first realistic models of single pacemaker neurons and populations in the pre-Bötzinger (pBC) that closely reproduced the generation of pacemaker-driven rhythm *in vitro* (Butera et al. 1999). The intrinsic bursting behavior in these models was based on the activation of the persistent sodium current. By the time these models were developed, sodium channels, including the persistent sodium, in pBC had not been experimentally characterized, and the authors could only use a generic description for kinetics of these channels. However, despite the generic descriptions of ionic channels, these models closely captured the endogenous bursting activity recorded in pBC *in vitro*. Recently Ptak et al. (2001) experimentally characterized the kinetics of both fast and persistent sodium channels in pBC *in vitro*. We used this data to develop more realistic computational models of pBC neurons. Similar to models by Butera et al. (1999) and Del Negro et al. (2000) our pBC neuron models were able to generate endogenous busting activity under certain conditions.

Computational analysis of our single neuron and population models demonstrated that the following factors can transfer the tonic firing behavior to endogenous bursting activity: (1) a decrease in the excitatory drive; (2) an increase in external potassium concentration; (3) suppression of potassium currents; (4) additional activation of the persistent sodium current.

Our modeling studies demonstrated that suppression or release of endogenous bursting activity at the cellular level might be explicitly dependent upon the excitatory drive to pBC and on the balance between the potassium currents and persistent sodium current.

The obtained results allow the suggestion that generation of endogenous pacemaker-driven bursting rhythm *in vitro* may occur because of the reduced excitatory drive.

Many data implicitly support the suggestion that hypoxia induces gasping through direct modulation of channel conductances and via alteration of ionic homeostasis in the extracellular environment. Specifically, it was shown that hypoxia suppresses several types of potassium channels (Conforti and Millhorn, 1997; Gebhardt and Heinemann, 1999; Jiang and Haddad, 1994; Liu et al., 1999; Lopez-Barneo et al., 2001; Thompson, and Nurse,1998) and activates the persistent sodium channels (Hammarström and Gage, 1998; Horn and Waldrop, 2000; Kawai et al., 2000) in different areas of the brain. In addition, hypoxia induces the augmentation of the extracellular concentration of potassium (Melton et al., 1996), which also reduces the potassium currents. According to the present modeling results, all these factors can shift the pBC firing behavior to pacemaker-driven oscillations. This allows the suggestion that these factors may indeed initiate the release of pacemaker-driven oscillations during hypoxic gasping *in vivo*.