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Modeling the ponto-medullary respiratory network

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Abstract

The generation and shaping of the respiratory motor pattern are performed in the lower brainstem and involve neuronal interactions within the medulla and between the medulla and pons. A computational model of the ponto-medullary respiratory network has been developed by incorporating existing experimental data on the medullary neural circuits and possible interactions between the medulla and pons. The model reproduces a number of experimental findings concerning alterations of the respiratory pattern following various perturbations/stimulations applied to the pons and pulmonary afferents. The results of modeling support the concept that eupneic respiratory rhythm generation requires contribution of the pons whereas a gasping-like rhythm (and the rhythm observed in vitro) may be generated within the medulla and involve pacemaker-driven mechanisms localized within the medullary pre-Bötzinger Complex. The model and experimental data described support the concept that during eupnea the respiration-related pontine structures control the medullary network mechanisms for respiratory phase transitions, suppress the intrinsic pacemaker-driven oscillations in the pre-BötC and provide inspiration-inhibitory and expiration-facilitatory reflexes which are independent of the pulmonary Hering–Breuer reflex but operate through the same medullary phase switching circuits.

Keywords: Brainstem, ponto-medullary respiratory network; Model, computational; Pattern of breathing, rhythm generation, eupnea, apneusis, gasping; Reflexes, respiratory

1. Introduction

The normal respiratory pattern ("eupnea") in mammals is generated in the lower brainstem and may involve several medullary and pontine regions (e.g., Lumsden, 1923; Cohen, 1979). Early studies of

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Lumsden (1923) and a series of later investigations have demonstrated that a removal of the rostral pons or perturbations applied to some areas within this region convert eupnea to apneusis, an abnormal pattern characterized by sustained or significantly prolonged inspiration, whereas the complete removal of the pons results in a gasping-like pattern (Cohen, 1979; Wang et al., 1993; Jodkowski et al., 1994; Morrison et al., 1994; St.-John, 1998). Although some medullary regions, e.g., the pre-Bötzinger Complex can generate a respiration-related rhythm in vitro (e.g., Smith et al., 1991; Rekling and Feldman, 1998; Koshiya and Smith, 1999; Lieske et al., 2000), many researches maintain that the in vitro rhythm essentially differs from eupnea and that the reduced medullary preparations without the pons cannot generate the eupneic pattern (e.g., see Duffin, 2003; St.-John and Paton, 2003a). The reduced medullary preparations cannot also reproduce apneusis, which is consistent with the suggestion that the rhythmogenesis in these preparations differs from the rhythmogenesis of eupnea. These observations support the concept that respiration-related pontine regions are necessary parts of the brainstem respiratory network responsible for the generation of eupnea (Wang et al., 1993; Dick et al., 1994; St.-John, 1998; Rybak et al., 2001, 2002; St.-John et al., 2002; St.-John and Paton, 2003a, 2003b). However the specific ponto-medullary interactions involved in the generation, shaping and control of the respiratory pattern have not been well characterized. Here we present and analyze a computational model of the ponto-medullary respiratory network and compare its performance under different conditions with both the existing experimental data and the results of our experiments performed for evaluation of some modeling predictions. The model is considered a basis for future interactive modeling-experimental studies of the role of the pons in respiratory rhythm and pattern generation.

2. Model description

The model (Fig. 1) contains interacting populations of respiratory neurons that have been characterized

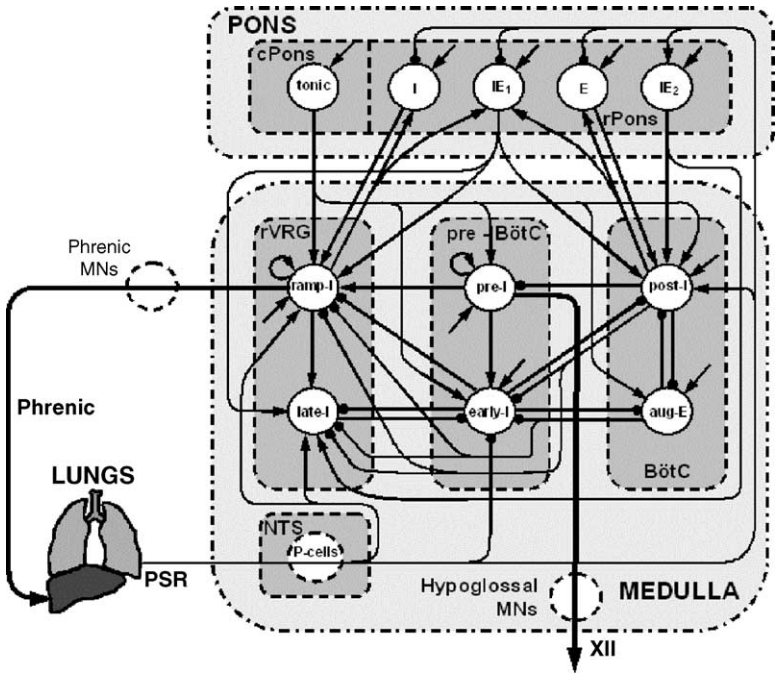

Fig. 1. Schematic of the model of the ponto-medullary respiratory network. The white circles represent populations of different respiratory neurons (the populations of phrenic and hypoglossal motoneurons and NTS pump (P) cells are not present in the current model). Arrows and small black circles show excitatory and inhibitory synaptic connections respectively.

in the rostroventolateral medulla (RVLM) and pons in vivo. The medullary component of the model includes three major regions: rostral ventral respiratory group (rVRG), pre-Bötzinger Complex (pre-BötC), and Bötzinger Complex (BötC). The pontine component is conditionally subdivided into a rostral (rPons) and caudal (cPons) parts. The neural populations of the rPons in the model are considered to perform the functions of the nucleus parabrachialis medialis (NPBM), Kölliker–Fuse (KF) nucleus, and other respiratory areas located in the dorsolateral (dl) and ventrolateral (vl) pons. The cPons is assumed to contain a part of the pontine reticular formation that partly provides excitatory tonic drive to the medulla. The following neural populations have been included in the model: ramp-I, and late-I (both in rVRG); early-I and pre-I (in pre-BötC); post-I and aug-E (in BötC); I-modulated, E-modulated and two distinct IE-modulated, IE_1 and IE_2 (in rPons,), and tonic (in cPons).

All neurons were modeled in the Hodgkin–Huxley style and incorporated biophysical properties and channel kinetics characterized in respiratory neurons in vitro. Specifically, the fast sodium current and the persistent sodium current (included only in pre-I neurons) were described using recent experimental data obtained from the studies of neurons of the rostoventrolateral medulla of rat (Rybak et al., 2003a); the high-threshold and low-threshold calcium currents were described using data of Elsen and Ramirez (1998); intracellular calcium dynamics was based on data of Frermann et al. (1999); other cellular parameters were accepted from the previous models (Rybak et al., 1997a, 1997b, 1997c, 2003b, 2004). Each population consisted of 50 neurons. Neuronal parameters were randomized over each population with some variance.

Some connectivities among the medullary neural populations were assigned based on published direct and indirect data. Other connections included in the model have not been studied and are open for testing; these were assigned to support the inspiratory off-switch (IOS) and expiratory off-switch (EOS) mechanisms incorporated. The network interactions among rVRG and pre-BötC populations (ramp-I, early-I, and late-I) and between these populations and BötC populations define the basic circuitry for IOS mechanism. The late-I population plays the key role in the initiation of inspiratory off-switching (Cohen, 1979; Richter et al., 1986; Cohen et al., 1993; Richter, 1996; Rybak set al., 1997b; Haji et al., 2002; Okazaki et al., 2002) by providing inhibition of the early-I population. The latter disinhibits the post-I population which completes switching to expiration making it irreversible. Interactions among BötC populations (post-I and aug-E) and between post-I population and pre-I population of pre-BötC define the basic circuitry for the EOS mechanism with the pre-I population explicitly performing the inspiratory on-switching (and hence the EOS) function (Richter, 1996). During expiration, the pre-I population is inhibited by the post-I population. When the pre-I population fires, after a release from inhibition, it provides the initial activation to the early-I and ramp-I populations, which complete switching to inspiration.

Reciprocal excitatory connections were assigned between the medullary ramp-I and the pontine I and IE_1 populations, and between the medullary post-I and the pontine IE_1 and E populations. These connections provided I, IE or E modulation of activity of the corresponding pontine populations. We, therefore, suggest the existence of topically organized bidirectional mapping between the BötC-VRG areas in the medulla and the corresponding respiration-related areas in the rostral pons (Núñez-Abades et al., 1993; Gaytán et al., 1997). We also suggest that a sub-population of excitatory post-I neurons is present in BötC-VRG and projects post-inspiratory excitation to the pons (see also Saito et al., 2002). At the same time, some pontine populations, e.g., IE_2 in our model, may receive excitation from pulmonary stretch receptor afferents (via the pump cells in the Nucleus Tractus Solitarius (NTS)) and contribute to the Hering–Breuer (HB) reflex. In addition, we assume that reticular neurons from the caudal pons (the tonic population) may provide an additional excitatory tonic drive to the medullary respiratory neurons.

Integrated activities of medullary ramp-I and pre-I populations in the model represent phrenic (Int. PNA) and hypoglossal (Int. XII) outputs respectively. Simplified models of the lungs and slowly adapting pulmonary stretch receptors (PSR) were included in the model to provide pulmonary feedback to the respiratory network. The pulmonary feedback controls the activity of the key neural populations involved in the IOS and EOS mechanisms (activates the late-I, post-I and ramp-I populations and inhibits the early-I population) and hence provides regulation of the duration of the respiratory phases through the HB reflex. In addition,

this feedback suppresses activity of the pontine neural populations that receive excitation from the medullary populations (I, IE_1, E). Importantly, the IOS and EOS mechanisms operate under control of both pontine input and pulmonary feedback which are both excitatory to the late-I, ramp-I and post-I populations (Haji et al., 2002; Okazaki et al., 2002).

3. Model performance: comparison with experimental data

The model generates a stable "eupneic" respiratory rhythm and exhibits realistic firing patterns and membrane potential trajectories of individual respiratory neurons (see Fig. 2A). Specifically, the firing bursts of individual ramp-I neurons as well as the bursts of phrenic discharges exhibit "augmenting" patterns (Fig. 2A).

In the model, the pulmonary feedback provides the HB reflex via an increase of excitability of late-I neurons by the direct excitatory input, an indirect excitation through the ramp-I population, and reducing inhibition from the early-I population (see Fig. 1). Disconnection of this feedback ("vagotomy") produces an increase in the amplitude and duration of phrenic discharges (Fig. 2B), which reflects the loss of the HB reflex. Also in agreement with HB reflex control of IOS is that mild continuous vagal stimulation shortens inspiration and prolongs expiration (Fig. 3A) (e.g., see Cohen, 1979; von Euler, 1986; Feldman, 1986; Hayashi et al., 1996) whereas strong continuous stimulation arrests the rhythm in the post-inspiratory phase ("post-inspiratory apnea" see Fig. 3B) (Lawson, 1981; Remmers et al., 1986; Hayashi et al., 1996). Short stimuli applied to the vagal afferents during inspiration can terminate the current inspiratory phase, and the threshold for inspiratory termination decreases during inspiration (Fig. 3C). The above simulation results are consistent with much experimental data (e.g., see Clark and von Euler, 1972; Cohen, 1979; von Euler, 1986; Feldman, 1986). Further, stimuli delivered during post-inspiration prolong expiration, whereas vagal stimulation during the late part of expiration has no effect on

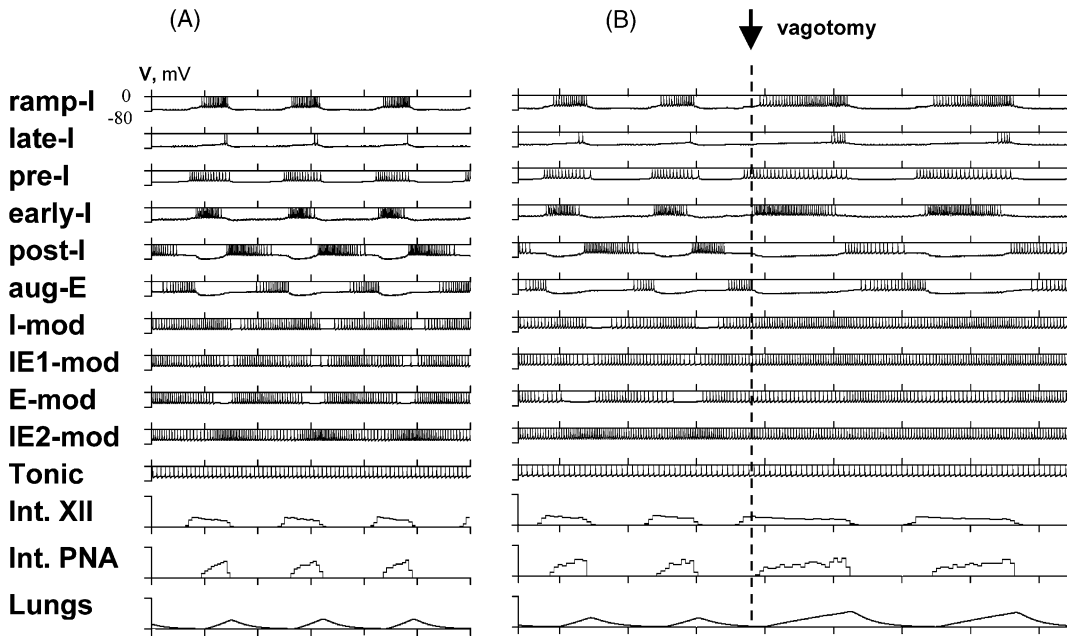

Fig. 2. Model performance under normal conditions and after vagotomy. In this and following figures, the activity of each neural population is represented by the trace of the membrane potential of one representative neuron from the population. In this and following figures except Figs. 5 and 6, tick marks on the time axes correspond to seconds. (A) The eupneic respiratory pattern generated by the model under normal conditions. (B) Disconnection of vagal feedback ("vagotomy") produces an increase in amplitude and duration of phrenic discharges.

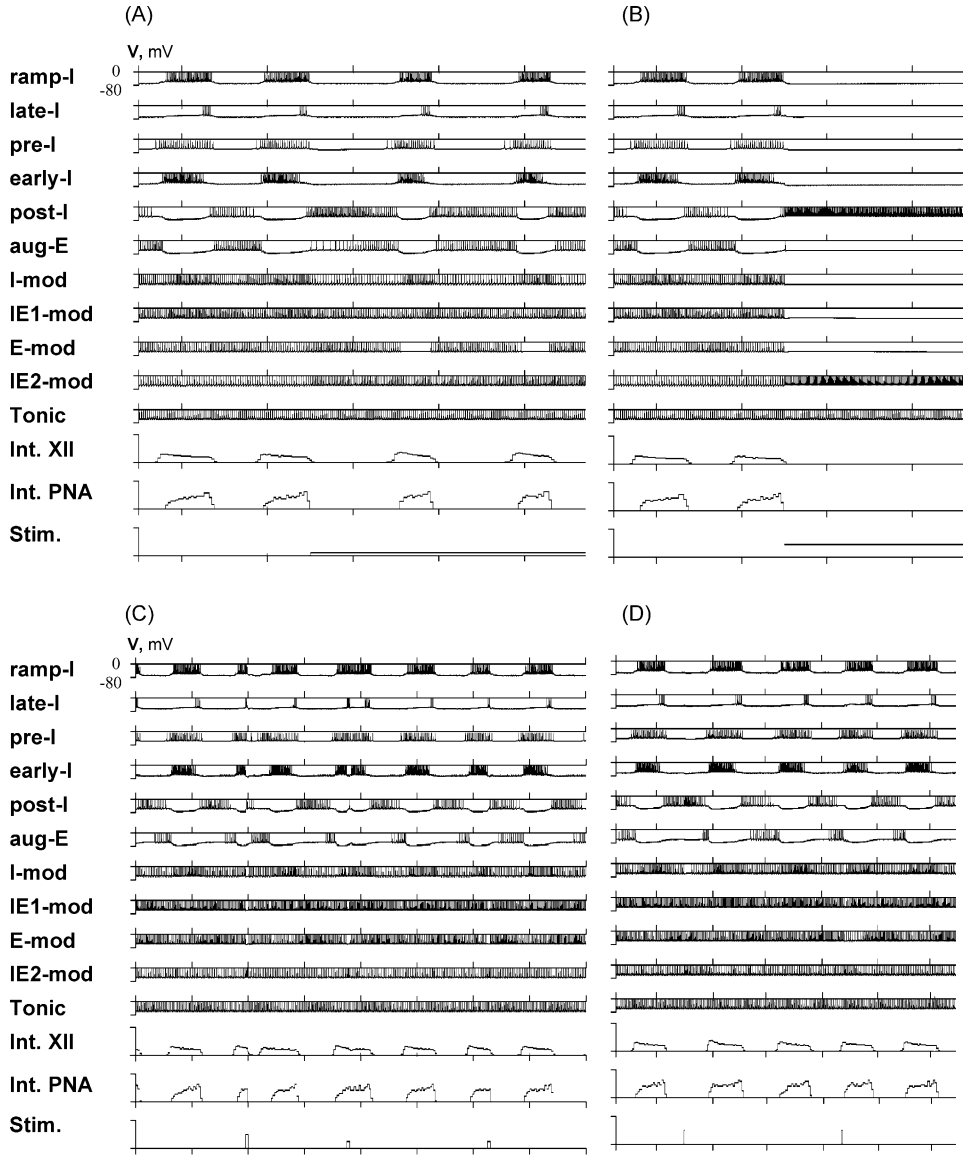

Fig. 3. Effects of vagus nerve stimulation. (A) Continuous vagal stimulation shortens inspiration and prolongs expiration reflecting the HB reflex. (B) Stronger stimulation arrests the respiratory rhythm in the post-inspiratory phase ("post-inspiratory apnea"). (C) Simulation of the effects of brief vagal stimulation applied during inspiration. The results of simulation demonstrate a decrease of the threshold for inspiratory termination during the inspiratory phase. The first high-amplitude stimulus being applied at the beginning of inspiration terminates this inspiration. The second stimulus has lower amplitude. Although applied at the same phase, it cannot terminate inspiration. The third stimulus has the same amplitude as the second one, but is delivered at a later time during inspiration. This effectively terminates inspiration. (D) Brief vagal stimulation delivered in the middle of expiration (first stimulus) prolongs expiration. The same stimulus delivered at the end of expiration has no effect on the duration of expiration (demonstrates an "insensitive period" at the end of expiration).

expiratory duration (Fig. 3D) (e.g., see Knox, 1973; Feldman, 1986; Remmers et al., 1986).

Disconnection of vagal feedback eliminates the suppressing influence of vagal afferents upon the pontine I-mod, IE_1-mod and E-mod populations (see Fig. 1) and hence increases the role of these populations in control of respiratory phase switching. This control is provided via the same medullary IOS and EOS circuits that are controlled by pulmonary vagal feedback when the latter is intact (Okazaki et al., 2002). Short stimulation of the pontine IE_1-mod population terminates inspiration (Fig. 4A1). Experimentally, a similar effect of inspiratory termination by stimulation of the rostral pons (e.g., NPBM/KF region that contains many I- and IE-modulated pontine neurons) was previously demonstrated in both cats and rats (e.g., Lumsden, 1923; Bertrand and Hugelin, 1971; Cohen, 1979; Feldman, 1986; Wang et al., 1993; Jodkowski et al., 1994; Haji et al., 2002; Okazaki et al., 2002). Fig. 4B (from Wang et al., 1993) shows an example of such inspiratory off-switching produced by stimulation of the rostral pons in rat. Also in our model, continuous stimulation of the pontine IE_1-mod population shortens inspiration and prolongs expiration (Fig. 4A2) whereas the same stimulation applied to the E-mod population prolongs expiration without altering inspiration (Fig. 4A3). The latter was experimentally demonstrated by stimulation of vl pons, which is known to contain mainly expiratory modulated neurons (see Fig. 4C from Jodkowski et al., 1997).

Starting from Lumsden's classic work (1923), many studies have demonstrated that removal of the rostral pons or chemical blockade of some respiration-related areas within this region converts eupnea to apneusis especially in vagotomized animals (Cohen, 1979; Wang et al., 1993; Jodkowski et al., 1994; Morrison

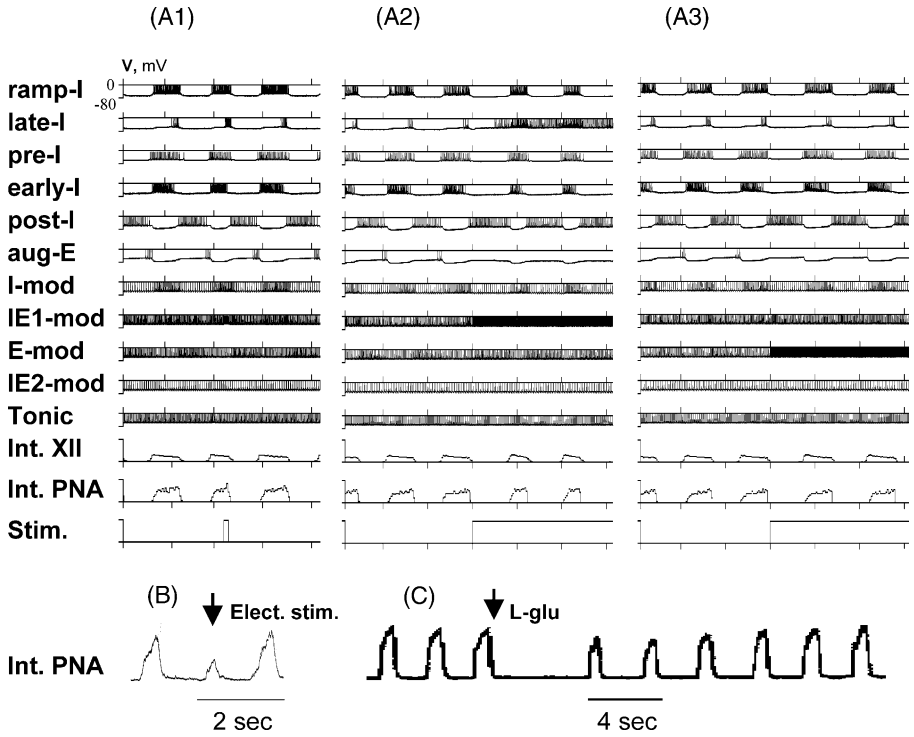

Fig. 4. Effects of pontine stimulations after vagotomy. (A1) Short stimulation of the pontine IE_1 population terminates inspiration. (A2) Continuous stimulation of the pontine IE_1 population shortens inspiration and prolongs expiration. (A3) Continuous stimulation of the pontine E population prolongs expiration. (B) Off-switching of phrenic activity by electrical stimulation of rostral pons in adult rat (adapted from Wang et al., 1993, Fig. 1 with permission). (C) Expiratory phase prolongation elicited by chemical stimulation (L-glutamate) in vl pons in adult rat (adapted from Jodkowski et al., 1997, Fig. 4 with permission).

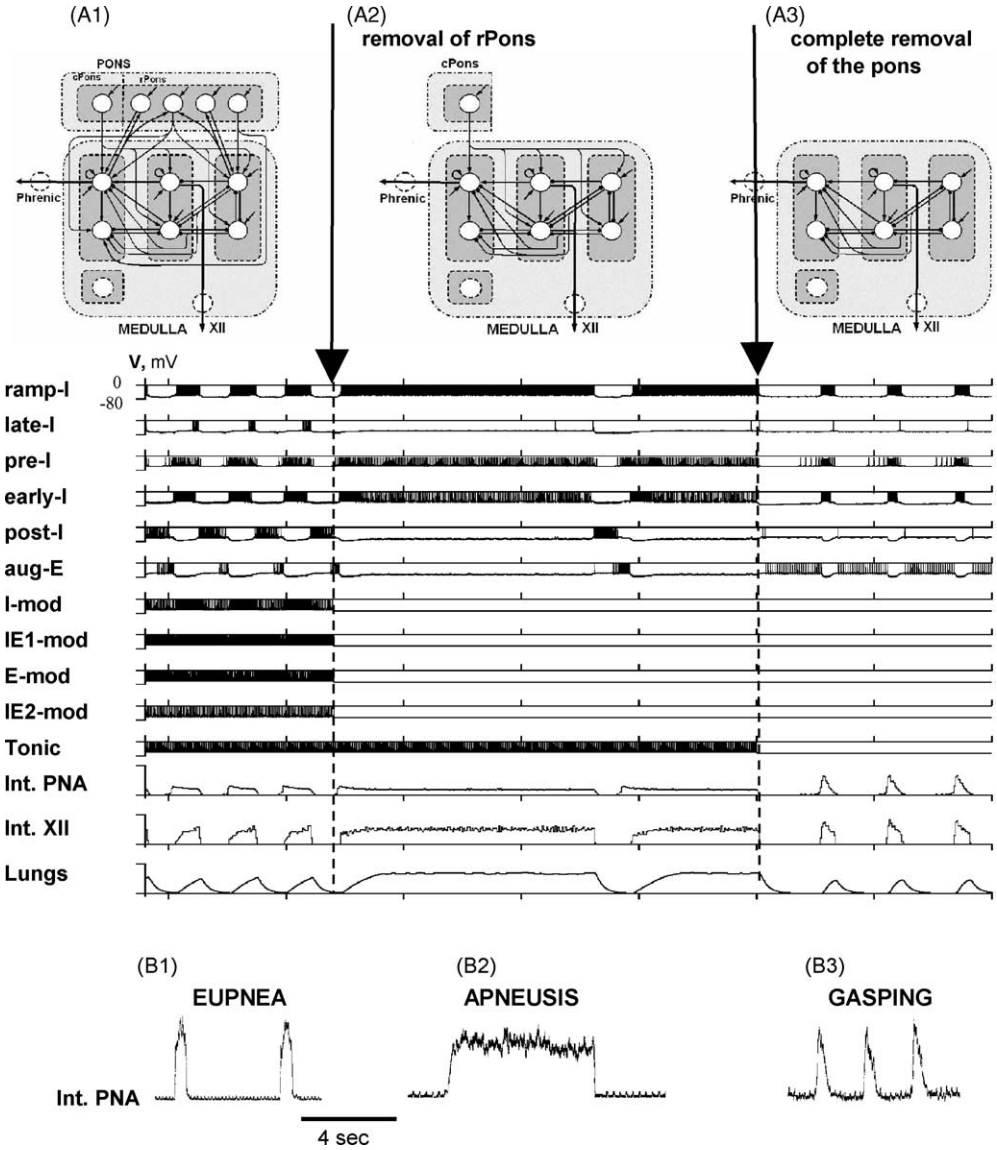

Fig. 5. Simulation of pontine lesions. (A1) The eupneic respiratory pattern (the pons is intact). (A2) Removal of rPons converts the eupneic pattern to apneusis. (A3) The following removal of the cPons releases an intrinsic pacemaker-driven rhythm generated in the pre-I population of the pre-BötC and converts apneusis to a gasping-like (in vitro-like) "decrementing" discharges. Tick marks on the time axes correspond to 2.5 s. (B1–B3) Alterations in pattern of phrenic activity following brainstem transections between the pons and medulla in WHBP preparation of juvenile rat (adapted from St.-John et al., 2002, Fig. 4 with permission). Eupnea (B1) was recorded in a preparation having an intact mesencephalon, pons and medulla. Apneusis (B2) was observed after a transection through the dorsal half of brainstem at the ponto-medullary junction. Gasping (B3) followed completion of the brainstem transaction.

et al., 1994; St.-John, 1998). A complete removal of the pons produces a gasping-like pattern (Lumsden, 1923; St.-John, 1998), which therefore may be generated by some mechanisms inherent to the medulla. Similarly, the removal of rPons in our model converts the eupneic pattern to apneusis (Fig. 5A1 and A2), and the complete elimination of the pons (additional removal of cPons) replaces apneusis with a gasping-like pattern (Fig. 5A3). Fig. 5B1–B3 demonstrates similar changes in the phrenic motor pattern obtained in the perfused working heart-brainstem preparation (WHBP) of rat under the control conditions with pons intact (Fig. 5B1), after removal of the rostral pons (Fig. 5B2) and after the complete removal of the pons (Fig. 5B3) (from St.-John et al., 2002).

The long apneustic inspiratory bursts observed after the removal of the rPons (see Fig. 6A1) may be terminated by brief stimulation of vagal afferents (Fig. 6A2) (e.g., see Lumsden, 1923; Cohen, 1979; Haji et al., 2002) whereas continuous vagal stimulation shortens the apneustic inspiratory discharges (Fig. 6A3), which is consistent with the data of Jodkowski et al. (1994) (see Fig. 6B1 and B2).

Fig. 7A1 and A2 compares the eupneic pattern generated in the model with the pons intact (A1) and the gasping-like pattern produced after complete removal of the pons (A2). In our model, the loss of the rPons reduces excitatory input to the post-I neurons and hence reduces the phasic inhibitory influence of these neurons on the pre-I population of the pre-BötC (see Fig. 1). In

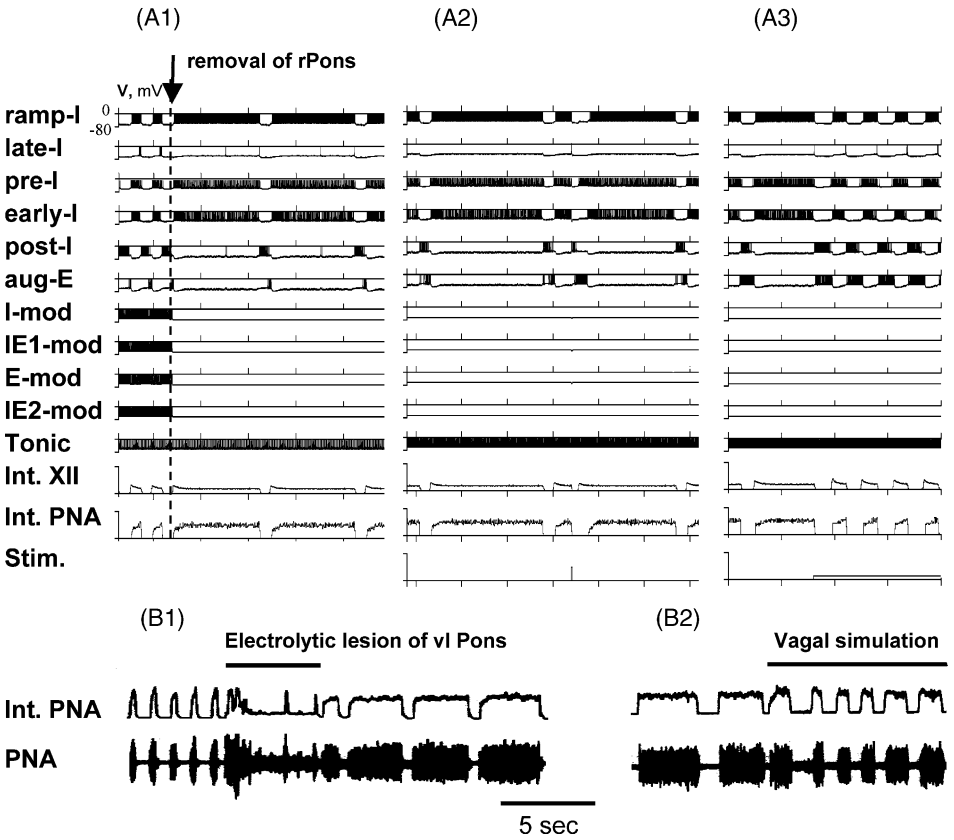

Fig. 6. Effects of stimulation of vagal afferents during apneusis. (A1) Removal of rPons converts the eupneic pattern to apneusis. (A2) Short vagal stimulation terminates apneustic inspiration. (A3) Continuous vagal stimulation shortens the apneustic inspiratory discharges. Tick marks on the time axes correspond to 2.5 s. (B1) Unilateral electrolytic lesion in the vl pons in an anesthetized vagotomized adult rat produces apneusis. (B2) Continuous electrical vagal stimulation shortens apneustic discharges (B1 and B2 adapted from Jodkowski et al., 1994, Fig. 1 with permission).

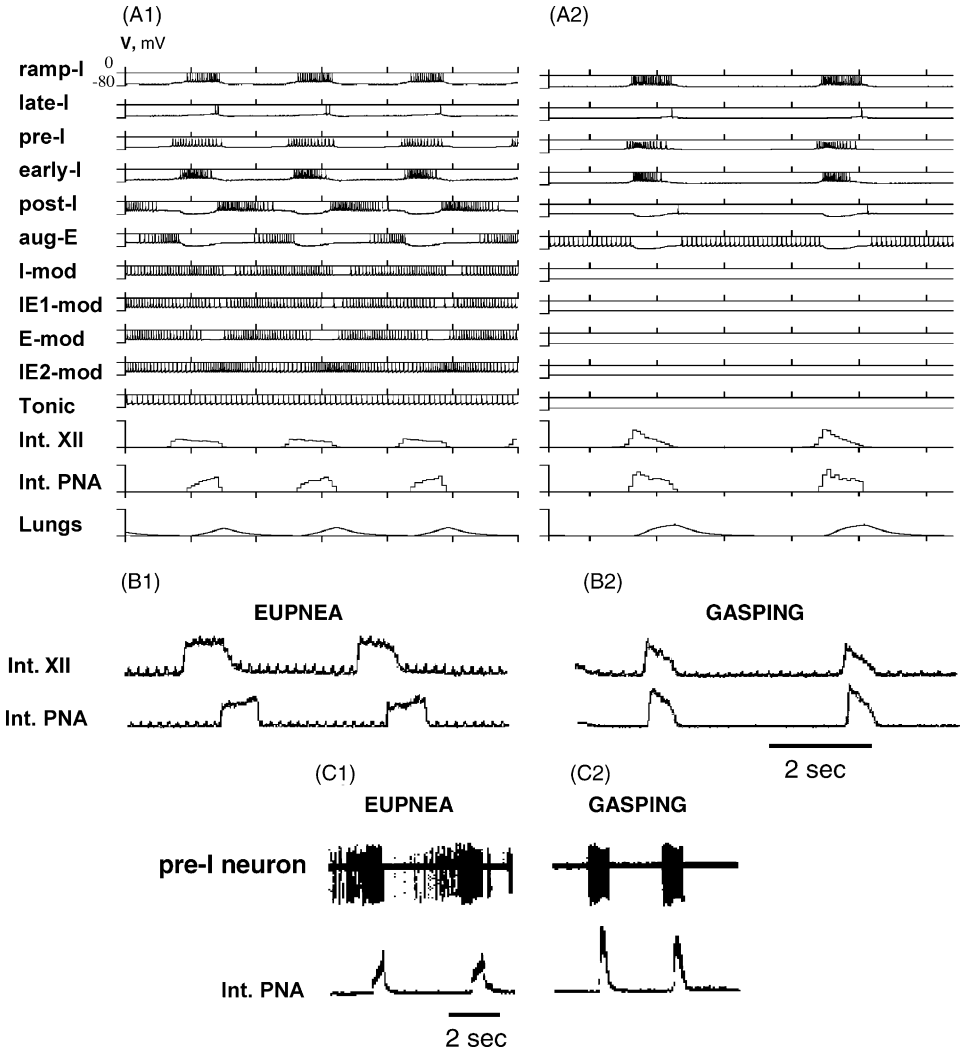

Fig. 7. Comparison of the eupneic pattern generated in the model with pons intact (A1) and the gasping-like pattern produced after complete removal of the pons (A2). Note (1) the characteristic difference in the shape of phrenic discharges: "incrementing" during eupnea vs. "decrementing" after removal of the pons, (2) significant reduction of the post-inspiratory activity after removal of the pons, (3) shortening of the delay in the onset of firing between pre-I and ramp-I neurons and between the hypoglossal and phrenic discharges. (B1 and B2) Examples of the delay between the hypoglossal and phrenic discharges in gasping (B2) vs. eupnea (B1) in the WHBP preparation of juvenile rat (adapted from St.-John et al., 2002, Fig. 3 with permission). (C1 and C2) Examples of pre-inspiratory neuronal discharges in gasping (C2) vs. eupnea (C1). Note (1) the switch in integrated activity of the phrenic nerve from incrementing in eupnea to decrementing in gasping and (2) a reduction of the delay between the onset of pre-I neuronal activity and phrenic discharge (adapted from St.-John and Paton, 2003b, Fig. 2 with permission).

turn, the removal of the cPons reduces excitatory tonic drive to the medulla, specifically to the pre-I population (see Fig. 1). Both the above release the pacemaker properties of the pre-I population of in pre-BötC (Rybak et al., 2003b, 2004). The intrinsic oscillations of this population may now drive the entire medullary network and produce phrenic discharges with a decrementing gasping-like shape (Figs. 5A3 and 7A2) (Rybak et al., 2001, 2002, 2003b, 2004; St.-John et al., 2002) that is similar to that recorded in vitro. Besides this characteristic change in phrenic pattern (from "incrementing" to "decrementing"), two other important differences

between gasping and eupnea may be noticed in our simulations. First, gasping is characterized by a significant reduction in the post-inspiratory activity (see Fig. 7A2 versus A1). Second, the transition from eupnea to gasping is accompanied by a significant shortening in the delay between the onset of firing of pre-I and ramp-I neurons and between the hypoglossal and phrenic discharges (see Fig. 7A2 versus A1). This observation was reported recently (see Peever et al., 2001; St.-John et al., 2002). Examples of the delay between the hypoglossal and phrenic discharges in gasping versus eupnea are shown in Fig. 7B1 and B2 (from St.-John et al., 2002). Fig. 7C1 and C2 demonstrates a reduction in the delay of onset of firing between pre-I neuronal activity and phrenic discharge (from St.-John and Paton, 2003b).

4. Experimental studies

The model described above suggests that the medullary post-inspiratory neurons significantly contribute to both the irreversible IOS by inhibition of inspiratory neurons (early-I, ramp-I, late-I) and the regulation of expiratory duration through inhibition of pre-I and aug-E neurons (see Fig. 1). Moreover, the post-I neurons are considered key elements of both phase switching mechanism (IOS and EOS) and operate under control of both vagal feedback and inputs from the rostral pons. According to our model, these neurons are excited by vagal afferents as well as by E- and IE-modulated pontine neurons (see Fig. 1). The excitatory influence of vagal stimulation (including lung inflation) upon post-inspiratory neurons has been reported in many previous studies (von Euler, 1986; Remmers et al., 1986; Richter et al., 1987; Hayashi et al., 1996; Haji et al., 2002, etc.). In experimental studies described below, we focused on the role of the post-I neurons in the pontine control of the respiratory pattern.

All experiments were performed using the working heart-brainstem preparation (WHBP) described in detail previously (Paton, 1996; Dutschmann et al., 2000; Dick et al., 2001; St.-John et al., 2002; St.-John and Paton, 2003b). In two separate series of experiments, we investigated the role of the vl ($n = 9$) and dl ($n = 6$) pons in the respiratory pattern formation. The phrenic nerve activity (PNA) in all experiments and the activity of the recurrent laryngeal nerve (RLNA) in the second series of experiments were recorded via suction electrodes. In the first series of experiments, a glass microelectrode filled with NaCl (4 mM) was used for extracellular recordings of single-unit activity in the ventrolateral medulla. In the second series, the RLNA was considered as index of post-inspiratory activity. In both series, L-glutamate (10 mM, 10–50 nl) was bilaterally injected in the vl pons or dl pons (area of KF nucleus) through a glass micropipette. The effective sites were identified by an increase in the duration of expiration and marked with pontamine Sky Blue for histological verification. Also, in the second series of experiments, AP5 (DL-2-amino-5-phosphonopentanoic acid), a potent and selective NMDA-receptor antagonist, was bilaterally injected to block glutamatergic neurotransmission. AP5 was injected into the loci in the dl pons that were previously characterised by the effective glutamate injections. In some experiments ($n = 4$), the vagus nerve was electrically stimulated with short stimulus trains (20 Hz, 50 μs pulse-range, 200–300 ms duration, 2–10 mA intensity) via a programmable stimulus-generator.

Injections of L-glutamate into either the vl pons (Fig. 8A) or dl pons (Fig. 8B) evoked prolongation of expiration revealed form PNA recordings. The latter was accompanied by an increase in the duration and discharge frequency of medullary post-inspiratory neurons (8 of 9; Fig. 8A) or an increase in the post-inspiratory discharge in RLNA (in all cases; Fig. 8B). The histological analysis revealed that all effective injection sites were in the vl pons in the first experimental series and in the area of the Kölliker-Fuse nucleus in the second series.

Bilateral injection of AP5 (10 mM, 50–80 nl) in the dl pons (area of KF) produced apneusis indicated by a prolongation in the duration of PNA discharges (from 0.85 ± 0.13 to 2.30 ± 0.33 s, $P < 0.01$, Fig. 8C). The apneustic bursts evoked by NMDA receptor blockade in the KF could be terminated by vagal stimulation in all cases investigated ($n = 4$, see Fig. 8D).

In a separate set of experiments we analyzed the effect of vagal stimulation on the PNA and discharge patterns of medullary post-inspiratory neurons. In all cases ($n = 5$), the vagal stimulation produced an early termination of inspiration accompanied by a strong activation of post-I neurons (Fig. 8E).

These results support our suggestions that the rostral pons controls the durations of inspiration and

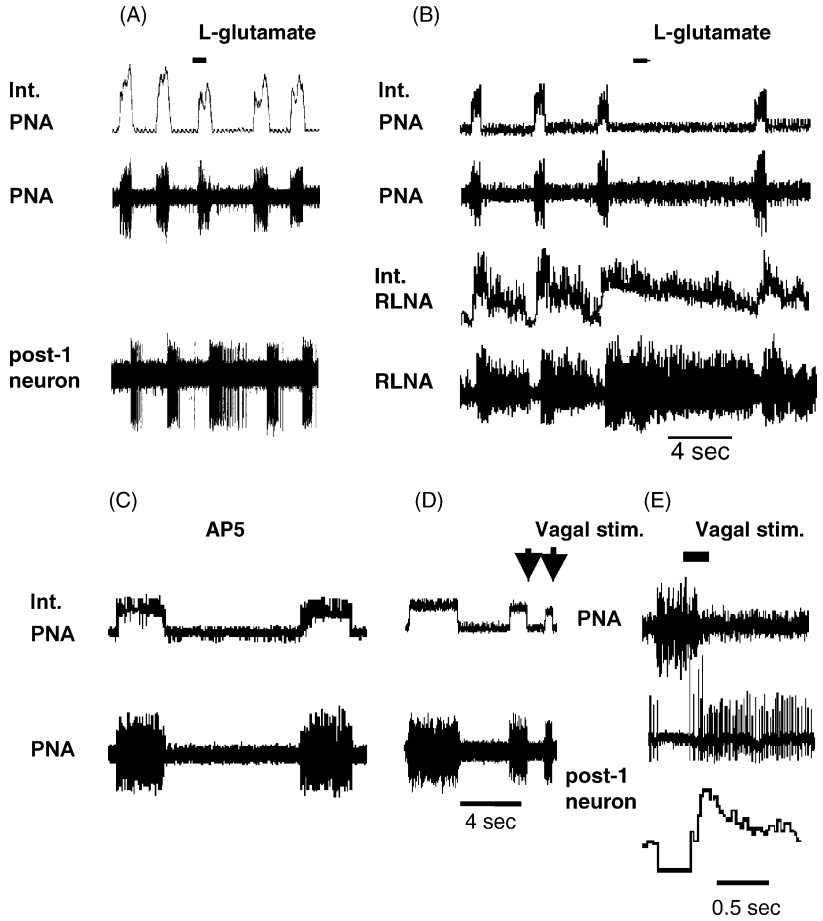

Fig. 8. (A) Activation of vl pons by injection of L-glutamate prolonged expiration and increased activity of a medullary post-inspiratory neuron (bottom trace). (B) Injection of L-glutamate into the intermediate KF (dl pons) prolonged expiration and dramatically augmented the post-inspiratory related activity recorded from the RLNA. (C) Bilateral injection of AP5 in the dl pons produced apneusis. (D) Electrical stimulation of the vagus nerve, applied after AP5 injection, terminated the apneustic inspiratory bursts. (E) Electrical stimulation of the vagus nerve produced an early termination of inspiration accompanied by a strong activation of post-I neuron activity.

expiration in a similar manner but independent of vagal afferents and that this control involves activation of medullary post-inspiratory neurons.

5. Discussion and conclusion

The model presented here was based on a series of assumptions and simplifications concerning both the medullary mechanisms (including these for respiratory phase transitions) and ponto-medullary connectivities. Specifically, many connections in the model, especially these from pulmonary afferents to the ponto-medullary circuitry and between the pons and medulla, have been considered monosynaptic, despite they are most likely polysynaptic; interactions among the pontine populations have not been incorporated; possible connections between rostral pons and pre-BötC (e.g., Herbert et al., 1990) have not been considered; the suppression of respiratory modulated activity in the pons by vagal input should most likely be presynaptic rather than postsynaptic (e.g., see Feldman et al., 1976), etc. The current paucity of experimental data, especially this on ponto-medullary interactions, does not allow us to state that the present model represents the only possible solution. Other modeling solutions are possible. At

the same time, this work represents the first attempt of computational modeling of the ponto-medullary respiratory network, and the resultant model could simultaneously reproduce many complex experimental phenomena. This explicitly supports our assumptions used for model construction. Moreover, the model allowed us to formulate some predictions which then were confirmed in our experimental studies (see the previous section).

The model described here is consistent with the concept that, under normal conditions in vivo, the eupneic respiratory rhythm is generated by a ponto-medullary network. Hence, although the pre-BötC is a necessary part of this network (and various perturbations applied to this area may indeed disturb the respiratory rhythm generation), the intrinsic oscillations in this region are suppressed during eupnea by ponto-medullary interactions. Specifically, our model suggests that pontine inputs activate medullary post-I neurons which, in turn, provide phasic inhibition to the pre-I population in the pre-BötC. In addition, tonic drive from the caudal pons holds the excitability of this population out of the voltage range necessary for pacemaking behavior. However, endogenous oscillations in the pre-BötC may be released under some conditions, e.g., in vitro, because of the lack of the pons, or during hypoxia in vivo (Rybak et al., 2001, 2002, 2003b; St.-John et al., 2002).

Our modeling studies support the concept that the rostral pons provides inspiration-inhibitory and expiration-facilitatory ponto-medullary reflexes that are independent of the Hering–Breuer reflex and are partly suppressed by pulmonary feedback. Moreover, our studies support the suggestion of Okazaki et al. (2002) that both the Hering–Breuer and ponto-medullary reflexes operate through activation or modulation of the same phase switching circuits present in the medulla that receive vagal pulmonary feedback and inputs from the pons and major afferent nerves.

In summary, the present model reproduces much experimental data and observations concerning alterations of the respiratory motor pattern following various perturbations/stimulations applied to the pons and pulmonary feedback. We believe that through continual interactions between our modeling and experimental studies we will advance our understanding of pontine influences on respiratory rhythmogenesis, an area that remains poorly understood.

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