

# 105 Neural Regulation of Respiration: Rhythmogenesis and Afferent Control

D.W. RICHTER

## Contents

105.1	Introduction .....	2079
105.2	Respiratory Rhythm and Ventilatory Mechanics .....	2079
105.3	Medullary Respiratory Network .....	2080
105.4	Postsynaptic Activities in Respiratory Neurons .....	2082
105.5	Synaptic Interaction Within the Respiratory Network .....	2084
105.6	Neurotransmitters and Neuromodulators .....	2085
105.7	Drive of the Respiratory Network .....	2086
105.8	Ontogenetic Changes of Respiratory Neurons .....	2086
105.9	Primary Respiratory Oscillations in Mature Mammals .....	2086
105.10	Respiratory Rhythm and Pattern Generation in Mature Mammals .....	2087
105.11	A Common Cardiorespiratory Network .....	2088
105.12	Reflex Control of Central Respiratory Activity .....	2088
105.12.1	Central Processing of Slowly Adapting Pulmonary Afferents .....	2088
105.12.2	Central Processing of Other Afferent Fibers .....	2091
105.13	Disturbance of the Respiratory Rhythm .....	2091
	References .....	2091

## 105.1 Introduction

The primary function of respiration is to exchange gases between the external environment and the internal milieu of the organism. Gas exchange occurs through coordinated action of the respiratory and cardiovascular systems. In the mammal, the respiratory system controls ventilation of the lung, while the cardiovascular system transports O<sub>2</sub> and CO<sub>2</sub> between the pulmonary and systemic capillaries. These processes adjust to varying physiological circumstances to maintain homeostasis (cf. Chap. 108).

Ventilation of the lungs depends on periodic movements of respiratory muscles. These muscles are innervated by spinal motoneurons that are activated by a rhythm-generating network in the lower brain stem. The activity of this central respiratory network is adjusted continually by sensory feedback from the periphery and by inputs from higher nervous structures, e.g., the motor cortex and the hypothalamus. This regulation of neural respiratory activity requires a high degree of coordination of synaptic interaction and modulation of membrane properties of neurons.

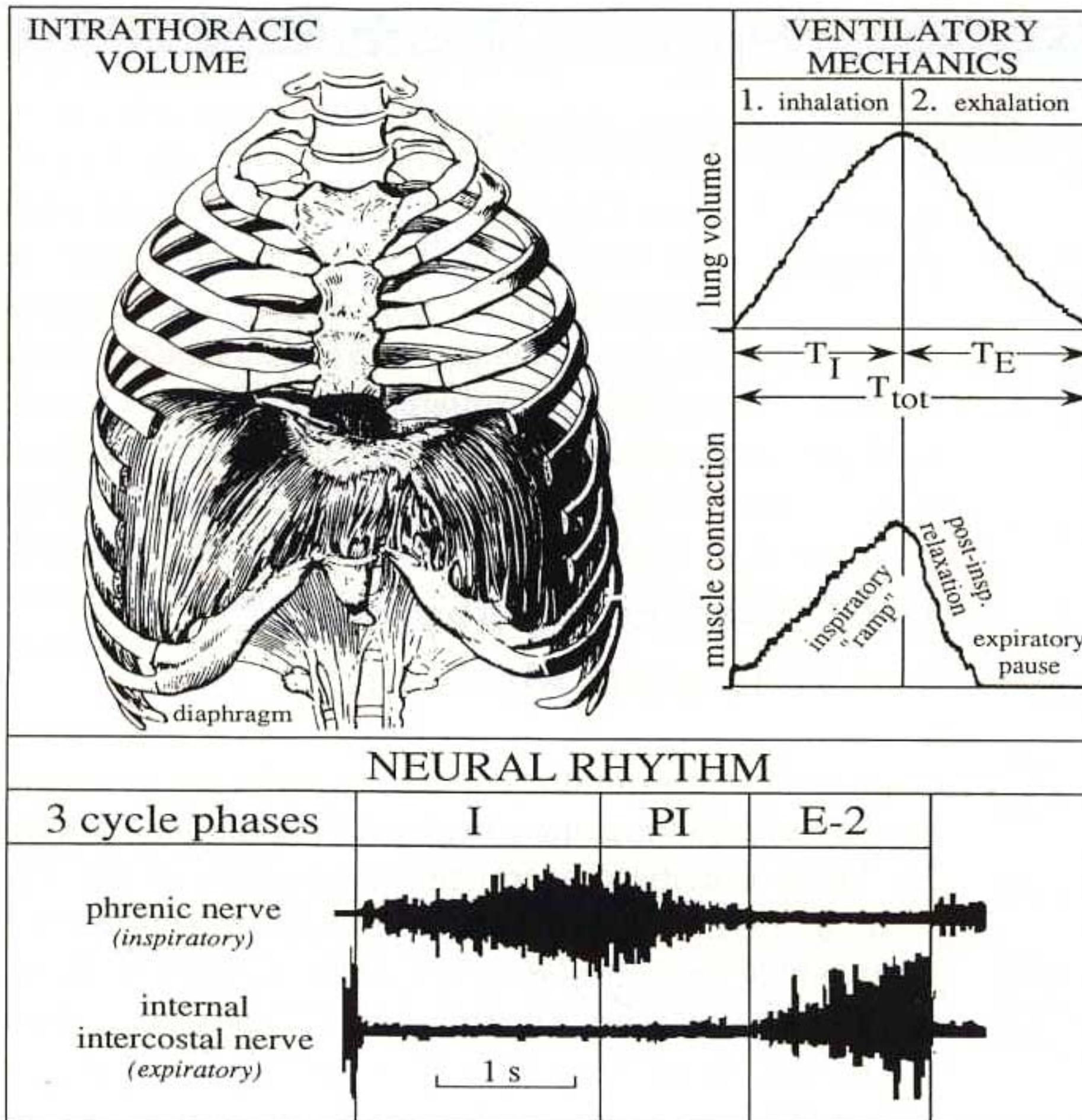
## 105.2 Respiratory Rhythm and Ventilatory Mechanics

Inspiratory and expiratory neural activities are necessary for normal breathing movements and ventilatory mechanics. These activities control the movements of the diaphragm, the thorax and the abdominal wall (Fig. 105.1). Variation of the intrathoracic volume ultimately determines the pulmonary pressure which causes air to flow in and out of the lungs, i.e., inhalation and exhalation of air. The dimensions of the upper airways – the pharynx, the larynx, the trachea, and the bronchial tree – determine the resistance to air flow and are adjusted through muscles innervated by cranial motoneurons or bronchomotor neurons in the brain stem which are synaptically coupled with the central respiratory network [15,26,61,182].

The two phases of ventilatory mechanics are controlled by three neural phases (Fig. 105.1) [145,148,154]. The neural respiratory phases are:

- Inspiration (I phase)
- Postinspiration (PI phase, passive expiration)
- Expiration (E2 phase, active expiration).

These three phases can be discerned easily in the motor outflow to the inspiratory muscles, such as the diaphragm or external intercostal muscles, and to expiratory muscles, such as internal intercostal or abdominal muscles [26,116]. They are also evident in the activity of laryngeal muscles [15,16]. During the I phase, an augmenting contraction of the diaphragm and inspiratory intercostal muscles expands the thoracic volume, which steadily decreases pulmonary pressure, thus drawing air into the lungs. The augmenting contraction of the diaphragm results from recruitment of phrenic motoneurons and from a ramp-like increase of their discharge, as seen in the phrenic neurogram (Fig. 105.1). Laryngeal abductor muscles are also activated during inspiration and dilate the larynx [15,16]. Their activity has a plateau-type pattern, i.e., the activity quickly reaches maximum levels and remains there throughout the I phase. The energy for exhalation accumulates during inspiration and is stored in the recoil forces of lung tissue. This energy is released during the PI phase when inspiratory movements end. Thus, without activation of expiratory muscles, exhalation occurs “passively”



**Fig. 105.1.** Control of ventilation. Contractions of respiratory muscles produce changes in intrathoracic volume and airway pressure, causing inhalation and exhalation of air. During quiet breathing, the respiratory cycle lasts for several seconds ( $T_{tot}$ ), the duration of inhalation ( $T_I$ ) normally being shorter than the duration of exhalation ( $T_E$ ). The muscles are innervated by respiratory motoneurons, which are controlled by the reticulospinal output of the medullary respiratory network. The central respiratory rhythm passes cyclically through three phases: inspiration (*I*),

postinspiration (*PI*) and expiration (*E-2*). These three phases are evident in phrenic and internal intercostal nerve activities. The activity of phrenic nerves and the contraction of the diaphragm increases more or less linearly during the *I*-phase (inspiratory ramp) and declines slowly during the *PI* phase (after-discharge) controlling the postinspiratory relaxation of the muscle. During the *E-2* phase, expiratory muscles are activated by an augmenting pattern of nervous activity in internal intercostal nerves while inspiratory nerves are silent (expiratory pause)

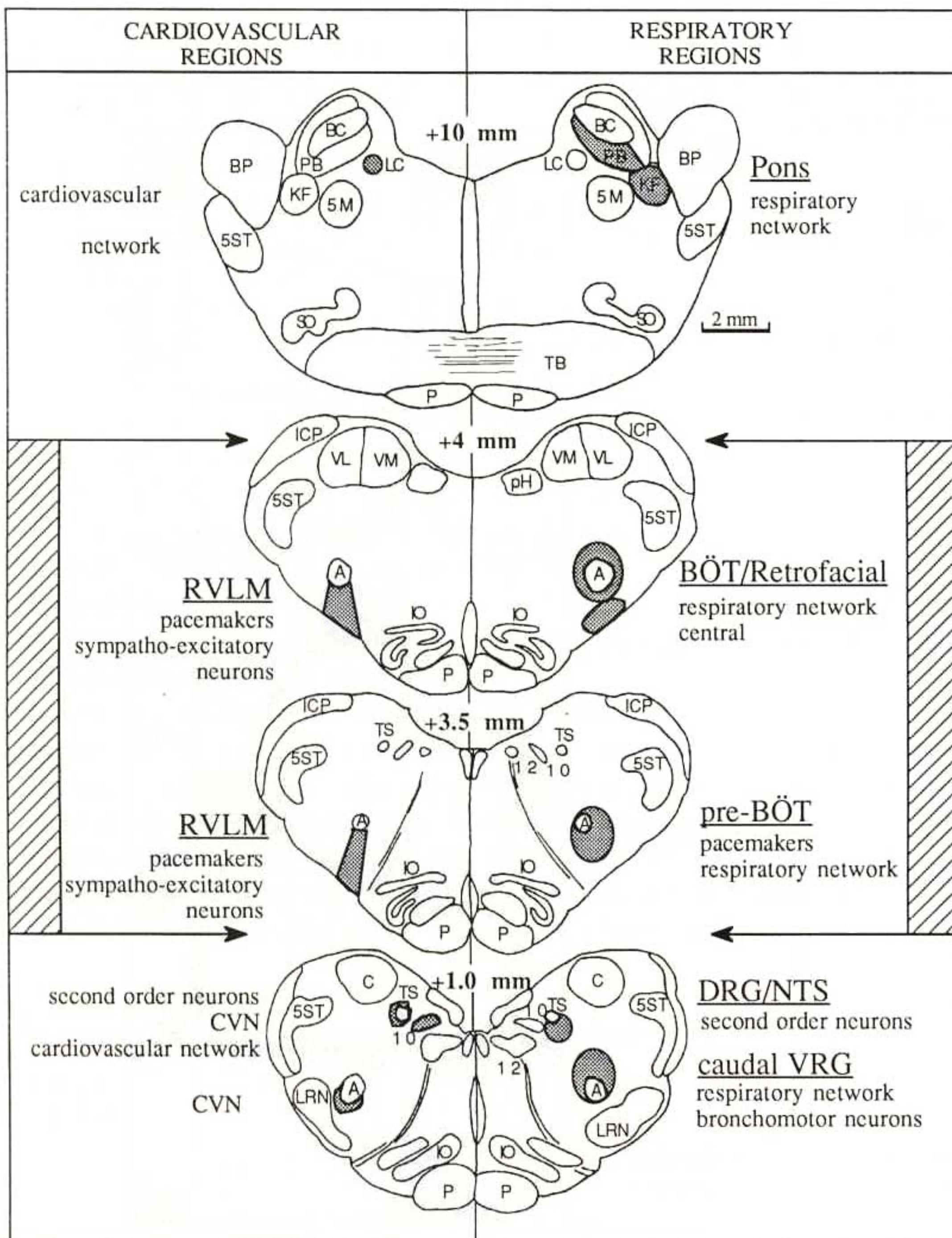
during this initial period of expiration. Passive exhalation of air does not occur rapidly, because the lung volume is held by an actively controlled relaxation of the diaphragm. This can be recognized by a postinspiratory “after-discharge” in the phrenic nerves (Fig. 105.1) [145,150]. Expiratory airflow is retarded additionally during normal breathing and during speech by the contraction of laryngeal adductor muscles (e.g., thyroarytenoid muscle) and loss of activity in laryngeal abductor muscles (e.g., posterior cricoarytenoid muscles), which increases the resistance to expiratory air flow and allows vocalization [16]. During the final period of exhalation, expiratory airflow can be increased by active contraction of expiratory intercostal and abdominal muscles (Fig. 105.1). This phase is called stage 2 of expiration, the *E-2* phase, following as it does the initial phase of passive exhalation (*PI* phase or stage 1 expiration). Phrenic and inspiratory intercostal nerve activities are silent during this *E-2* phase of the respiratory cycle (Fig. 105.1).

During quiet breathing, a total respiratory cycle ( $T_{tot}$ ) lasts for approximately 3–4 s (Fig. 105.1) and inhalation ( $T_I$ ) is slightly shorter than exhalation ( $T_E$ ). During exhalation, the *PI* phase normally occupies 70%–90% of  $T_E$  [168]. The *E-2* phase can be absent; this occurs

- Occasionally during normal breathing
- During thermoregulation in panting animals
- During activation of the defense area in the hypothalamus [10]
- During lung edema, when pulmonary J receptors (juxtagapillary) are activated (see Table 105.1) [44,131]. Under these conditions, the expiratory interval is shorter and rhythmic breathing occurs in only two antagonistic neural phases, i.e., inspiration and post-inspiration [10,147], resulting in rapid shallow breathing or panting.

### 105.3 Medullary Respiratory Network

In mammals, the efferent neural activity to the various respiratory muscles is ultimately controlled by a neuronal network located in the lower brain stem, specifically in and near the ambiguous nucleus and the Pre-Bötzinger and Bötzinger complexes, which areas comprise the ventral respiratory group (VRG) [5,22,25,46,56,57,124,164,171,170]. Presynaptic neurons in the rostroventrolateral medulla [76,110], bronchomotor neurons, cardiac



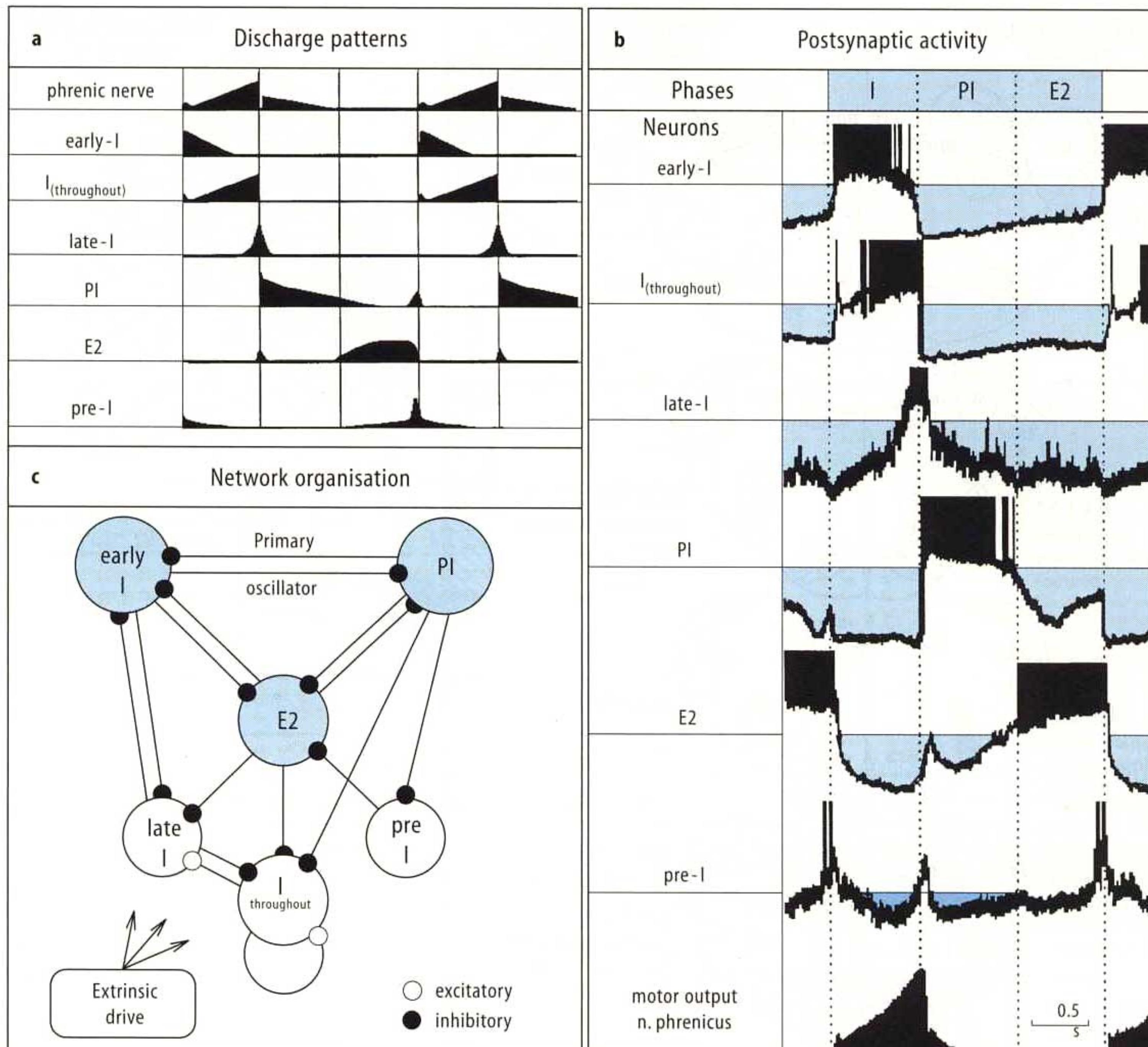
**Fig. 105.2.** Cardiorespiratory regions. Location of various types of neurons and networks controlling respiratory (*right column*) and cardiovascular (*left column*) functions within the pons and the medulla oblongata of mammals. Specific regions are shown as *shaded areas* and neighboring structures are shown as *white areas*. The location of neurons is indicated unilaterally, but in fact is bilateral, and there is considerable overlap, especially if the dimensions of the dendritic trees of neurons are taken in account. The types of neurons located at the different levels of the brain stem are listed on both sides of the diagram. *BC*, brachium conjunctivum; *BP*, branchium pontis; *LC*, locus ceruleus; *PB*, nucleus parabrachialis; *5M*, motor nucleus of the trigeminal nerve;

*KF*, Kölliker-Fuse nucleus; *5ST*, spinal trigeminal tract; *SO*, superior olive; *TB*, trapezoid body; *P*, pyramidal tract; *pH*, nucleus praepositus hypoglossi; *VM*, medial vestibular nucleus; *VL*, lateral vestibular nucleus; *12*, hypoglossal nucleus; *10*, dorsal vagal motor nucleus; *TS*, solitary tract; *ICP*, inferior cerebellar peduncle; *A*, nucleus ambiguus; *IO*, inferior olive; *C*, cuneate nucleus; *LRN*, lateral reticular nucleus; *BöT*, Bötzinger complex, retrofacial nucleus; *pre-BöT*, pre-Bötzinger complex; *DRG*, dorsal respiratory group; *NTS*, nucleus of the solitary tract; *VRG*, ventral respiratory group; *RVLM*, rostroventrolateral medulla; *CVN*, cardiac vagal neurons [70,84] and central chemosensitive regions [104] all coexist in this area (Fig. 105.2).

The bulbar respiratory network consists of various populations of neurons which are identified by the timing and pattern of their discharge relative to phrenic nerve activity [43,55,59,89,97,113,114,123,126, 127,145,148,162,170]. These patterns of discharge are comparable to the patterns of postsynaptic activities in identified reticulospinal output neurons [145]. Six types of neurons have been classified in *in vivo* mature mammals

(Fig. 105.3) [145,150,154,163,164]. Respiratory neurons are:

- Early-inspiratory (during early I phase)
- Inspiratory (throughout I phase)
- Late-inspiratory (during late I phase)
- Postinspiratory (during PI phase)
- Expiratory (during E2 phase)
- Pre-inspiratory (pre-I phase).



**Fig. 105.3a–c.** Respiratory neurons and network. Respiratory neurons have been identified by their discharge profile and the temporal relation of the discharge profile to phrenic nerve activity. Three types of neurons discharge during inspiration: early-inspiratory (early-I), inspiratory ( $I$ , discharging throughout the inspiratory phase) and late-inspiratory (late-I) neurons. Postinspiratory (PI) neurons discharge during the after-discharge of phrenic nerves, and expiratory (E2) neurons discharge during the pause in phrenic nerve activity. Preinspiratory (pre-I) neurons discharge in a characteristic phase-spanning manner between inspiration and expiration. Membrane potential trajectories of

medullary respiratory neurons (depolarization upward, hyperpolarization downward). Shading indicates various types of inhibitory synaptic processes. The fluctuations of membrane potential of neurons are related (in normalized form) to the motor output in the phrenic nerve. Phrenic nerve activity is illustrated in its “averaged” form in the bottom trace. Medullary respiratory neurons interact synaptically. A presumed connectivity model (white circles indicate excitatory and black circles, inhibitory connections) is assumed on the basis of analyses of the discharge profiles (a) and postsynaptic activities (b). The primary rhythm generator is made up of early-I and PI neurons

## 105.4 Postsynaptic Activities in Respiratory Neurons

Medullary respiratory neurons of neonatal and adult mammals reveal rhythmic fluctuations of their membrane potential that are synaptically induced [8,9,14,25,60,65,78, 79,80,91,97,99,123,126,127,128,138,139,145,164,171,172]. Continuous synaptic bombardment through all phases of the respiratory cycle precludes determination of a resting membrane potential for these neurons. When the neurons are silent, they receive inhibitory synaptic inputs (IPSPs), the underlying conductances shunting all other excitatory

inputs (EPSPs), and when active, they receive a combination of excitatory or excitatory and inhibitory synaptic inputs. Figure 105.3 shows the synaptic inputs to each cell type during the respiratory cycle:

*Early-I neurons* undergo a rapid membrane depolarization leading to action potential discharge at, or shortly before, onset of inspiratory activity in the phrenic neurogram. Thereafter, the frequency of action potential discharge declines and early-I neurons normally cease discharging during the second half of inspiration. This decline of activity seems to depend largely on intrinsic mechanisms (see below) [113,140,149,154,156] and also on synaptic inhibition [96]. During the PI phase, early-I neurons are inhibited

maximally and they remain inhibited during the E2 phase (Fig. 105.3).

*I neurons* depolarize at the beginning of inspiration and then continue to depolarize throughout inspiration. Some of them depolarize rapidly to a plateau potential and others depolarize almost linearly (Fig. 105.3) [59,145]. A steadily augmenting depolarization results from the integration of excitatory inputs arriving throughout inspiration and inhibitory synaptic inputs during the early-I period. Many propriobulbar I neurons are maximally inhibited during the PI phase and remain inhibited during the E2 phase.

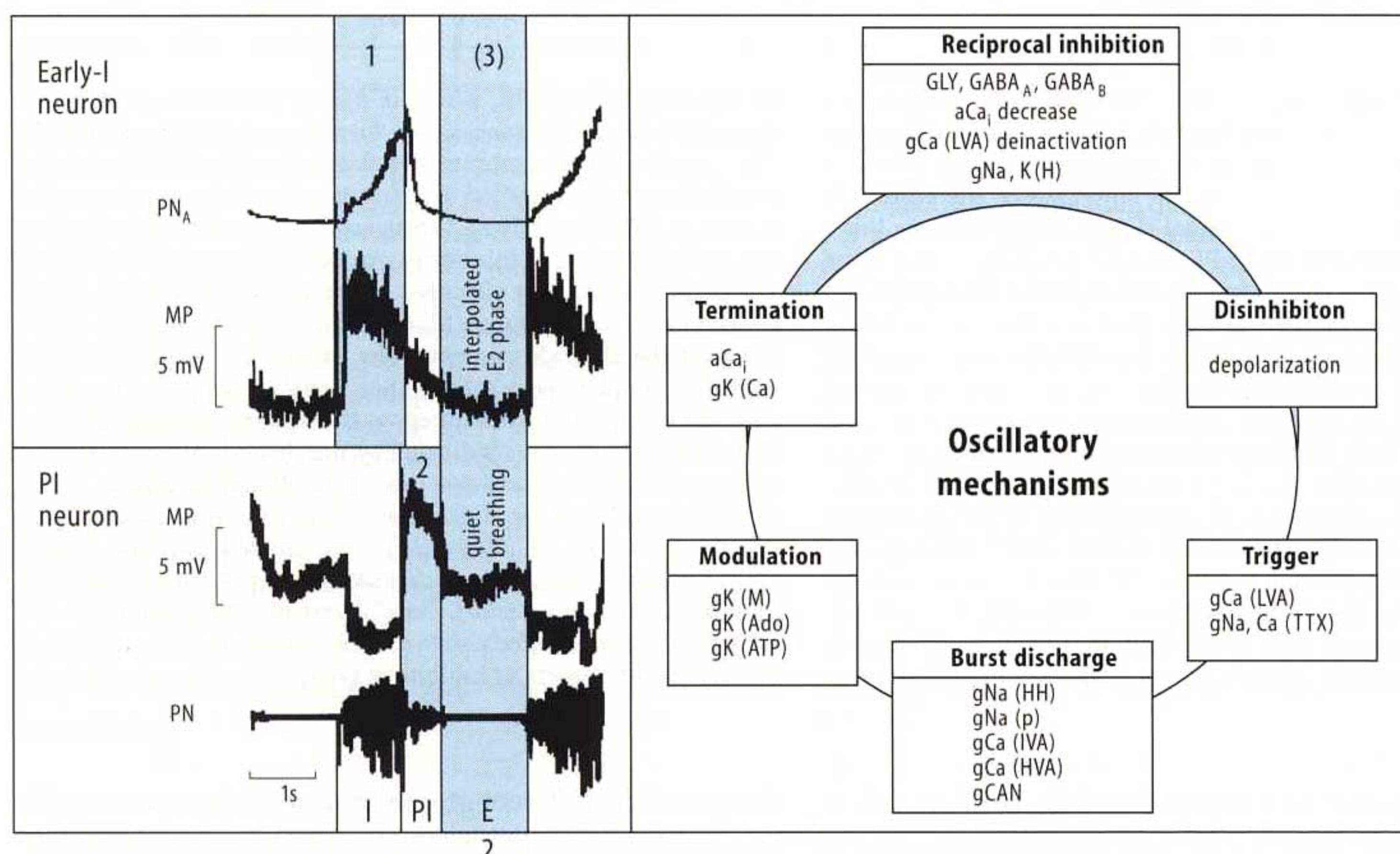
*Late-I neurons* do not discharge action potentials before the second half of inspiration. The late onset results from an early-I inhibition, which is stronger than the inhibition received by steadily depolarizing I neurons (Fig. 105.3; cf. Fig. 105.5). The inhibitory input during the early-I period effectively shunts the excitatory drive that arrives throughout the I phase [145]. Late-I neurons are synaptically inhibited during the PI and E2 phases.

*PI neurons*, which constitute bulbar respiratory interneurons and also cranial motor output neurons [184], depolarize rapidly and discharge their first action potentials shortly after inspiration (Fig. 105.3). The rapid changes are partly due to rebound excitation [154,175] following the release from inspiratory inhibition (Fig. 105.5). Later in the PI phase, the action potential discharge de-

clines, and the neurons normally cease firing before the end of the expiratory interval. PI neurons adapt spontaneously [140] and receive weak synaptic inhibition during the E2 phase (Figs. 105.3, 105.4). Therefore, they often show a secondary membrane depolarization together with a secondary burst of spike discharge shortly before the end of the E2 phase (Fig. 105.6). PI neurons are then maximally inhibited during inspiration.

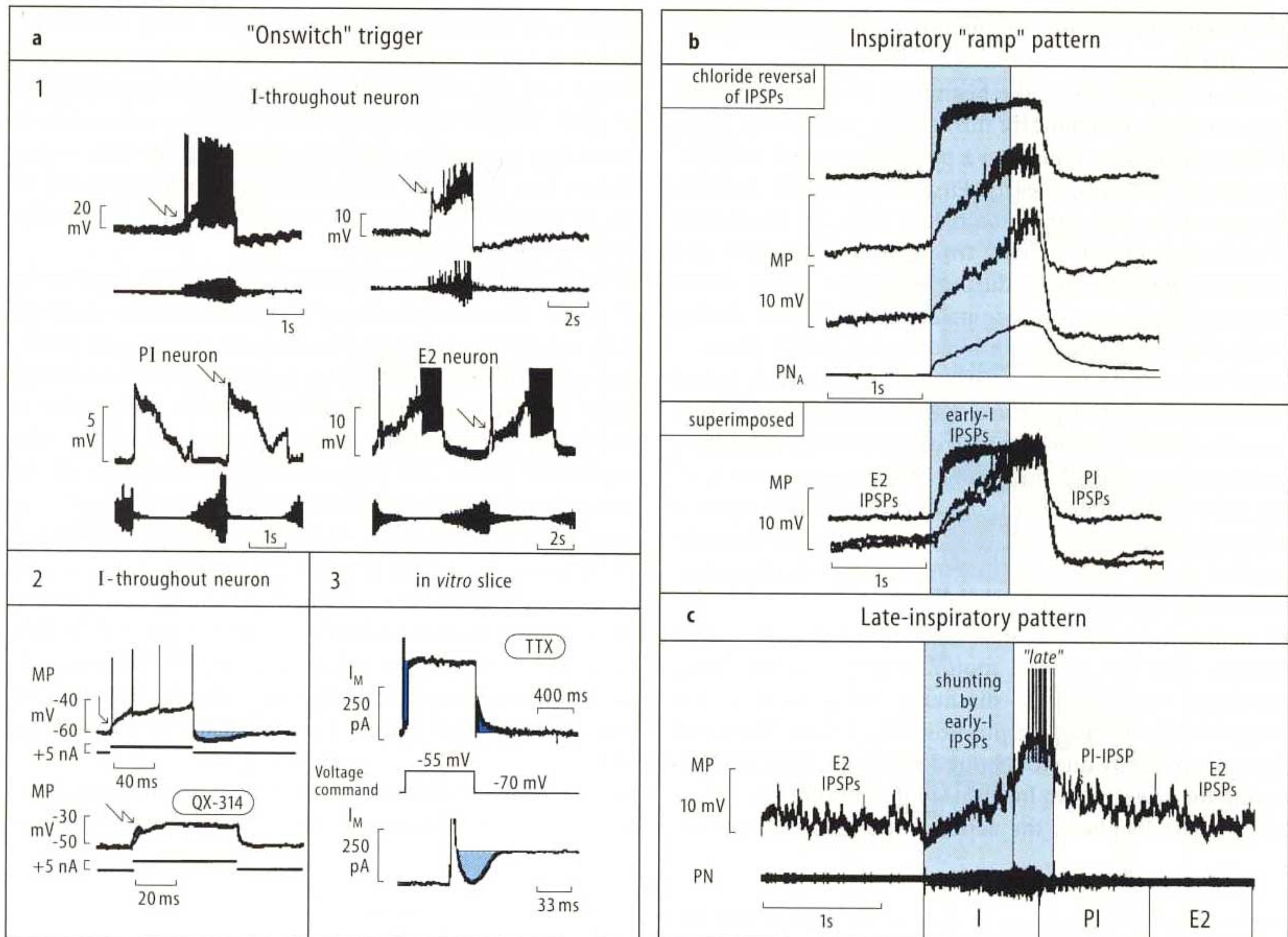
*E2 neurons* start to depolarize at the end of inspiration (Fig. 105.3) and may discharge one to two action potentials (Fig. 105.5). Thereafter, the neurons are synaptically inhibited again during the PI phase. Action potential discharge starts gradually as this PI inhibition fades and reaches a steady discharge frequency during the later part of the expiratory phase. The augmentation of discharge at the beginning of the E2 phase, therefore, appears to result from a declining pattern of (postinspiratory) synaptic inhibition [145] rather than from a ramp-like pattern of excitation [55,59]. E2 neurons are inhibited maximally during early inspiration. An additional enhancement of synaptic inhibition can become apparent during late inspiration [4]. Termination of the expiratory discharge also is controlled by synaptic inhibition during the end of the E2 phase (Fig. 105.6) [91].

*Pre-I neurons* reveal a prominent membrane depolarization and burst of action potentials during late expiration



**Fig. 105.4.** The primary oscillator. *Left side:* membrane potential trajectories (depolarization upward, hyperpolarization downward) of an early-I and a PI neuron. Both neurons respond with a rapid membrane depolarization when they are released from inhibitory synaptic membrane hyperpolarization. After this “rebound” depolarization, the neurons start to hyperpolarize again (as indicated by the shaded columns) before there is any sign of synaptic inhibition. Synaptic inhibition occurs later on, e.g., in the PI neuron during the E2 phase (3). This feature indicates that these two types of neurons may act as a primary oscillator within the

network of respiratory neurons in the adult mammal. The respiratory rhythm proceeds in two or potentially in three phases: I (1), PI (2), and E2 (3) phases. *Right side:* the processes of respiratory rhythm generation appear to be dependent on the dynamics of both synaptically induced membrane potential changes and intrinsic membrane properties of neurons. Synaptic inhibition, which occurs during antagonistic phases (shaded crescent) allows restoration of ionic homeostasis and resetting of membrane conductances. The sequence of events should be read clockwise



**Fig. 105.5a–c.** Respiratory “on” switch and inspiratory patterning. **a** 1 Inhibitory membrane hyperpolarization of respiratory neurons reactivates low-voltage activated calcium conductances. This becomes obvious in the lowering of the threshold (arrow) of the first action potential during a spontaneous burst discharge as illustrated for I, PI, and E2 neurons. 2 The same feature (arrow) is seen when an I neuron is artificially depolarized from hyperpolarized potential levels by a positive current pulse. The underlying mechanism seems to be a rebound depolarization (arrow), which becomes evident when the  $\text{Na}^+$  conductances of the neuron are blocked by intracellular injection of a local anesthetic (QX 314). The repetitive discharge is followed by an after-hyperpolarization owing to activation of (charybdotoxin-sensitive) calcium-dependent  $\text{K}^+$  conductances. 3 The underlying membrane properties can be studied in more detail under *in vitro* conditions in neurons from the area of the nucleus of the solitary tract. The mechanism is identified as a transient, low-voltage-activated  $\text{Ca}^{2+}$  current that is resistant to TTX but sensitive to cobalt (not illustrated). Membrane depolarization is followed by

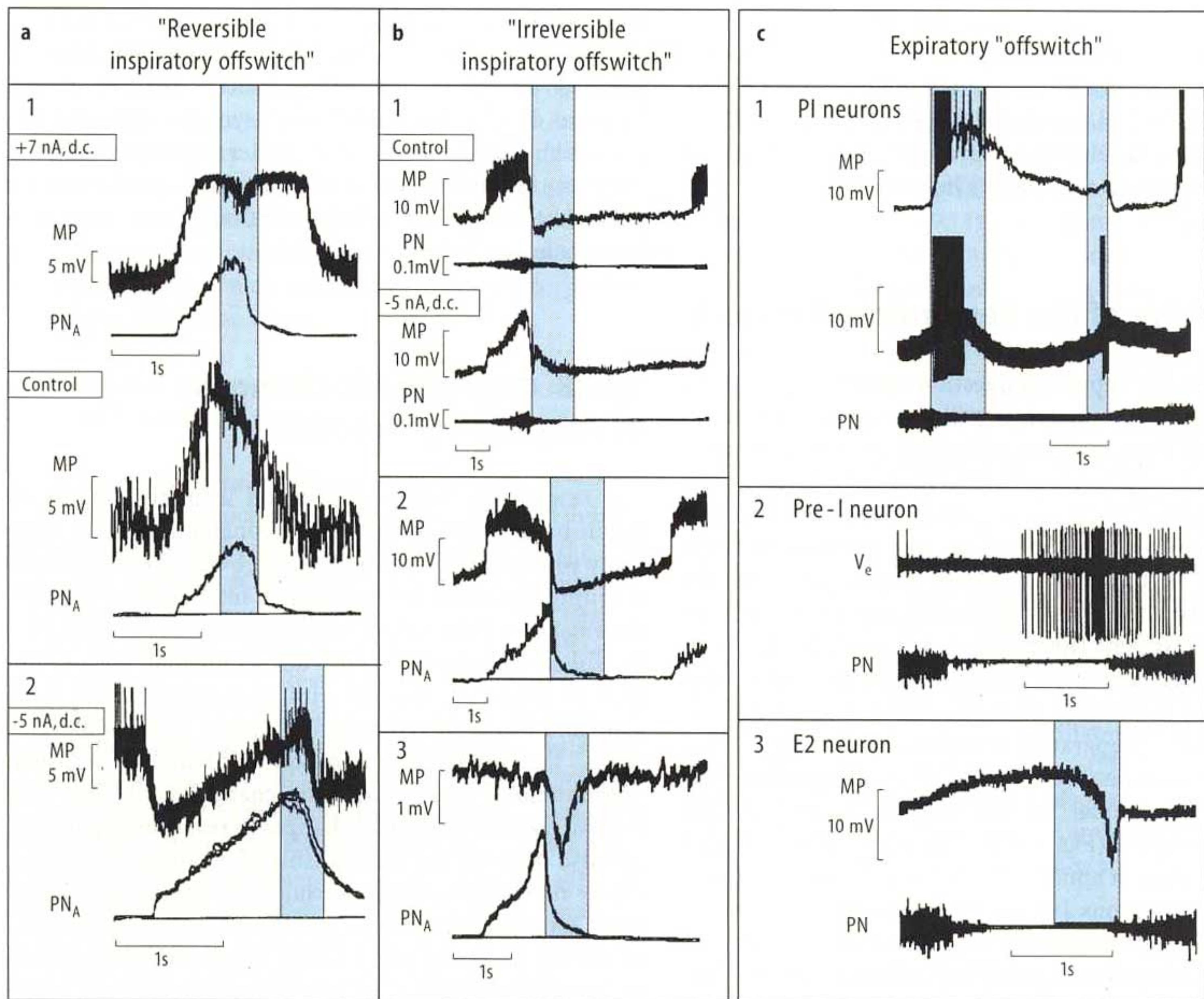
an outward tail current, which is due to activation of calcium-dependent  $\text{K}^+$  conductances. For further explanation see text. **b** The linearly rising membrane depolarization of certain I neurons results from the integration of a barrage of excitatory postsynaptic potentials (EPSPs) arriving throughout inspiration and a declining, early-I pattern of inhibitory postsynaptic potentials (IPSPs). The pattern of IPSPs is obscured under control conditions, but is revealed after intracellular chloride injection, which results in reversal of the chloride currents. The progress of IPSP reversal is shown in single sweeps (taken after variable delay) in the *upper* part and in superimposed sweeps at the *bottom*. Note that besides early-I IPSP reversal, as indicated by the *shaded columns*, there is also reversal of IPSPs arriving during the PI and E2 phases. **c** The delayed membrane depolarization of late-I neurons results from effective shunting of EPSPs (*left-hand shaded column*) during early-I periods. The neurons depolarize steeply after this early-I inhibition ends and a short, “late” burst of action potentials results (*right-hand shaded column*). The neuron is also modulated by various other sorts of inhibitory synaptic inputs as indicated

and continue to fire into inspiration (Figs. 105.3, 105.6). A second, although weaker, activation may occur during the late-I period [164,170].

## 105.5 Synaptic Interaction Within the Respiratory Network

A hypothetical connectivity scheme of the respiratory network was derived by comparing the action potential dis-

charges of the different groups of respiratory neurons with the postsynaptic activities in other groups of neurons (Fig. 105.3) [114,150,154]. Many of the presumed connections between neurons have been verified by the results obtained by cross-correlating the discharges of pairs of different neurons [72,89,105,166] and by spike-triggered averaging of postsynaptic potentials in dual cell recordings [4,59,123,127]. Only some inferred connections between respiratory neurons remain to be demonstrated. For instance, the connections between pre-I, early-I and late-I neurons have not been investigated thoroughly, because



**Fig. 105.6a–c.** Respiratory “off” switch mechanisms. **a** Reversible inhibition of inspiration is produced by synaptic inhibition. Such inhibition of I neurons (**a1, a2**) is produced by IPSPs arriving during late inspiration (*shaded column*). These IPSPs diminish the neuron input resistance and shunt the voltage effect of positive current flow across the membrane (*upper trace in 1*) and EPSPs (*lower trace in 1*). The IPSPs become visible after intracellular chloride injection and reversal of IPSPs (*shaded column in 2*). **b** Irreversible termination (switching off) of inspiration occurs by effective synaptic inhibition during the PI phase (*shaded columns* in **1–3**). These IPSPs become visible by reversal of their polarity in an I neuron after chloride injection (*lower trace in 1*). Membrane hyperpolarization is combined with effective shunting of postsynaptic noise activity, as shown for an early-I neuron in **2**. Some primarily nonrespiratory neurons are also inhibited during

the PI phase, which makes them respiratory modulated (**3**). **c** Switching off of E2 neurons is also produced by synaptic inhibition. The IPSPs terminating the discharge of E2 neurons are difficult to detect under normal conditions of quiet breathing. Under conditions of enforced breathing, these late-expiratory IPSPs become evident in peak inhibition shortly before onset of the next I phase (*shaded column in 3*). The late-expiratory IPSPs seem to originate from pre-I neurons whose discharge (**2**) corresponds well with the pattern of synaptic inhibition of E2 neurons. PI neurons, which normally show a secondary membrane depolarization shortly before inspiration (*upper trace in 1*) and often a secondary burst of pre-inspiratory action potential discharge (*lower trace in 1*) may also contribute to this inhibition of E2 neurons

they are small interneurons and therefore difficult to record from.

## 105.6 Neurotransmitters and Neuromodulators

The body of information available on the transmitters used by the neurons of the respiratory network is growing. Synaptic activation seems to be mediated mainly by glutamate acting via AMPA receptors [65,73], and also NMDA receptors [47,67–69,90,138,139]. Specifically, the inspiratory off-switch, which acts through PI neurons,

seems to be highly sensitive to NMDA receptor blockers [67,139].

Most of the inhibitory synaptic events in respiratory neurons are mediated by glycine- and GABA<sub>A</sub>-receptor-activated, chloride-permeable channels [38,79,80,126,135], which also have a significant permeability for HCO<sub>3</sub><sup>-</sup> ions, resulting in acidification of the cytosol [13]. Only some inhibitory processes seem to involve GABA<sub>B</sub> receptor-activated, K<sup>+</sup>-permeable channels [136,147]. Synaptic inhibition of inspiratory neurons during the PI phase seems to be strychnine sensitive, indicating glycinergic inhibitory synapses [38]. There is also some indication for glycinergic early-I inhibition of late-I neurons [136]. All these synaptic activities are influenced by endogenous

neuromodulators, such as intracellular ATP/ADP concentrations [137,177], adenosine [107,157,161], serotonin [45,53,94,95,118,143,158], noradrenaline [37,52,58], cholecystokinin [31], substance P [143,183], opioids [119], and thyrotropin-releasing hormone [17] acting via intracellular second messengers [6,35,36,100].

and inhibitory synaptic interaction. The respiratory rhythm is greatly disturbed when synaptic inhibition is blocked by GABA<sub>A</sub> receptor blockers [81] or during hypoxic blockade of inhibitory synaptic transmission [152,161]. This indicates that, under *in vivo* conditions, synaptic inhibition rather than rhythmic excitation via pacemaker cells is essential for rhythmogenesis in mature mammals (see below).

## 105.7 Drive of the Respiratory Network

The functionally important question concerning the drive of the respiratory network is still unresolved despite increasing data from *in vivo*, *in situ* and *in vitro* experiments [14,64,81,122,125,134,145,154,159,170–172,180]. It is still unclear whether the drive originates from endogenously active pacemaker neurons [63,64] that produce tonically beating or rhythmically bursting activity or from the reticular formation that is spontaneously active under *in vivo* conditions [85]. The pacemaker theory, already developed in the last century, was supported by the finding that spontaneous respiratory activity continued in an isolated brain stem slice preparation of neonatal rat [171,172]. This preparation contains the so-called pre-Bötzinger complex, a region just caudal to the retrofacial nucleus and Bötzinger complex (Fig. 105.2). The preparation contains an accumulation of almost all categories of medullary respiratory interneurons [46,164,170] and obviously several types of pacemaker neurons. When the neurons were depolarized, endogenous capacity to produce bursts of action potentials (burster cells) was observed in

- PI neurons (originally labelled preinspiratory) [125]
- Inspiratory neurons [171; Ramirez J-M, Quellmalz U, Richter DW, *in preparation*]
- Late-inspiratory [185]
- Expiratory neurons [185]
- Nonrespiratory neurons [171]

This behavior seems to originate from a intermediate voltage activated P-type Ca<sup>2+</sup> conductance, which is activated when the neurons are depolarized to -40 mV [2,12]. Similar burst-firing behavior of neurons was observed in brain stem cultures [27] or could be provoked in a variety of neurons when they were treated with NMDA or neuropeptides [66,176]. Tonically active (beater) cells were identified as

- Presynaptic neurons in the rostroventrolateral region [76,174]
- Neurons in the region of the nucleus of the solitary tract [39,66,133]
- Tonically active central chemoreceptive neurons [51,104]

However, endogenous bursting pacemaker properties were not discerned in any of the respiratory neurons of adult mammals *in vivo*. Here, rhythmicity of respiratory neurons seems to depend entirely on the integrity of excitatory

## 105.8 Ontogenetic Changes of Respiratory Neurons

The respiratory rhythm generation in mature mammals might be different from that in neonatal mammals, especially when they are as immature at birth as rats, in which respiratory activity still resembles fetal activity [74,154]. Pacemaker cell activation of the respiratory rhythm could be functional during early developmental stages, but may be modified strongly with maturation of the brain stem and finally be redundant or absent in the adult. This raises the interesting question of whether transient neurohumoral and ontogenetic changes could not only explain the developmental changes in respiratory patterns, but also underlie the mechanisms of disturbance of respiratory rhythm generation during early postnatal development. Ontogenetic changes seem to involve disappearance of electric synapses which could synchronize respiratory neurons in neonates. Gap junctions were observed in the neonatal, though not in the adult brain stem [142]. Other developmental changes observed involve ion transporters [42,99,178], voltage- and ligand-activated membrane channel properties (e.g., [169]) and the chemical or pharmacological sensitivity of neurons (e.g., [11,32,41,77,112]).

## 105.9 Primary Respiratory Oscillations in Mature Mammals

Normal breathing movements are never exactly the same under *in vivo* conditions. This aspect has led to the assumption that the respiratory rhythm might derive from a hybrid of network and pacemaker properties [63,172]. This means that a potential bursting pacemaker-controlled mechanism is strongly modified and normally completely suppressed by synaptic inputs to allow dynamic adjustment of respiratory frequency and pattern to the voluntary or obligatory demands of the organism. That is, network functions determine the respiratory rhythm during all stages of development.

Where does the respiratory rhythm originate in mature mammals? Within the respiratory network, there are two types of reciprocally connected interneurons, the early-I and the PI neurons, which seem to constitute a simple network with oscillatory capacity when they are activated externally (Fig. 105.4). These neurons could well be re-

mainders of those neurons that express pacemaker properties during early development. The two types of neurons are characterized by a rapid onset and then a declining pattern of activity, which results from the interaction of postsynaptic activity and specific membrane properties (Fig. 105.4). Synaptic inhibition over a long (in the range of seconds) period produces membrane hyperpolarization, which seems to be essential for resetting of intrinsic membrane properties of mature neurons. Thus the long periods of synaptic inhibition allow:

- Resetting of intrinsic membrane properties of neurons
- Control of ion homeostasis.

The primary oscillating network is synaptically connected with E2 neurons, which modulate and slow the rhythm. E2 neurons, however, do not seem to be essential for the generation of rhythmic activity, as the respiratory oscillations continue at higher frequencies during rapid shallow breathing or panting, when the inhibitory effect of E2 neurons is absent [10,147]. Resetting and modulation of intrinsic properties of neurons by synaptic interactions means the following. Whenever the action potential discharge declines in one of two antagonistically interconnected early-I and PI neurons, the postsynaptic inhibition diminishes in the other. Thus, the membrane potential of the latter neuron is no longer hyperpolarized and starts to depolarize. Within a certain voltage range, i.e., below the normal threshold of excitation, this disinhibition will lead to activation of a low-voltage-activated  $\text{Ca}^{2+}$  conductance  $g\text{Ca(LVA)}$  [34,179] or a tetrodotoxin (TTX)-sensitive  $\text{Ca}^{2+}$  conductance  $g\text{Na,Ca(TTX)}$  [1]. This results in a “rebound” membrane depolarization (Fig. 105.5), which activates the fast inactivating  $g\text{Na(HH)}$  [83] and the persistent  $\text{Na}^+$  conductances  $g\text{Na(p)}$  [115,173], thus triggering repetitive action potential discharge. This activity brings the membrane potential into the voltage range in which the intermediate-voltage-activated  $g\text{Ca(IMV)}$  [2,12] and high-voltage-activated  $\text{Ca}^{2+}$  conductance  $g\text{Ca(HVA)}$  [179] and nonspecific cation conductances  $g\text{CAN}$  [132] are activated. Repetitive discharge at high frequencies results in a prominent  $\text{Ca}^{2+}$  influx into the neurons and, possibly, release of  $\text{Ca}^{2+}$  from intracellular stores, leading to significant accumulation of intracellular  $\text{Ca}^{2+}$  ions. Intracellularly accumulated  $\text{Ca}^{2+}$  functions as an activity-dependent mechanism to activate  $\text{Ca}^{2+}$ -dependent  $\text{K}^+$  conductances  $g\text{K(Ca)}$  (Fig. 105.5), which induce repolarization of the membrane and adaptation of discharge without synaptic inhibition [108,140,156]. Decline of discharge frequency leads to disinhibition and rebound excitation of the antagonistic neurons. Antagonistic inhibition and membrane hyperpolarization of the neurons then allows deactivation of the inactivated  $\text{Ca}^{2+}$  and  $\text{Na}^+/\text{Ca}^{2+}$  conductances and sequestration and transportation of intracellular  $\text{Ca}^{2+}$ . In essence, synaptic inhibition seems to play an important role in respiratory rhythm generation by enabling adequate control of ionic homeostasis and resetting of endogenous membrane properties in respiratory neurons of mature mammals [151].

Modulatory effects on these processes may be produced by adenosine-controlled  $\text{K}^+$  conductances  $g\text{K(Ado)}$  [161], a  $\text{K}^+$  conductance  $g\text{K(ATP)}$  controlled by intracellular ATP/ADP levels [137], acetylcholine acting on a muscarinic  $\text{K}^+$  conductance  $g\text{K(M)}$  [33,36,40,117], and a mixed  $\text{Na}^+$  and  $\text{K}^+$  conductance  $g\text{Na,K(H)}$  activated by membrane hyperpolarization [109,111]. Another voltage-dependent  $\text{K}^+$  conductance  $g\text{K(A)}$  [28,40,48] does not seem to have a functional significance under normal conditions of quiet breathing [149].

## 105.10 Respiratory Rhythm and Pattern Generation in Mature Mammals

The mechanisms of respiratory rhythm and pattern generation were ascribed to separate “central rhythm generating” and “central pattern generating” networks [63]. In the mature mammal, however, both functions seem to be organized by the same network (Fig. 105.3) [154]. The rhythm generator or primary oscillator seem to organize the “switching on” and “switching off” of inspiratory and postinspiratory activities, and it also contributes to shaping the discharge patterns of inspiratory and expiratory neurons. Respiratory rhythmogenesis seems to occur in the following sequence:

- Inspiration is switched on.
- The inspiratory pattern is generated.
- Inspiration is reversibly switched off.
- Inspiration is irreversibly switched off.
- Expiration is switched on.
- Expiration is switched off.

**Respiratory Drive.** The network is activated tonically by an unpatterned excitatory input from as yet unknown sources.

**Inspiration Is Switched On.** The release from inhibition triggers rebound excitation of early-I and I neurons through activation of low-voltage-activated  $\text{Ca}^{2+}$  conductances (Fig. 105.5).

**Inspiratory Pattern Is Generated.** Postsynaptic integration of recurrent excitation within the population of I neurons [61,128,182] and inhibition by early-I neurons [8,59] results in a linearly rising membrane depolarization and ramp-like activation of reticulospinal I neurons (Fig. 105.5). This activity is transmitted to inspiratory spinal motoneurons via the reticulospinal output [103,141] and finally produces a steadily increasing lung volume.

**Phase-Switch of the Primary Oscillator.** The discharge of early-I neurons accommodates owing to the activity-dependent, intracellular  $\text{Ca}^{2+}$  accumulation and to activation of  $\text{Ca}^{2+}$ -dependent  $\text{K}^+$  conductances, which repolarizes the neurons (Fig. 105.4) [115,140,150,156].

**Inspiration Is Reversibly Switched Off.** Accommodation of early-I neurons is followed by disinhibition and delayed excitation of late-I neurons. Late-I neurons therefore start to discharge at high frequency during late inspiratory periods (Fig. 105.5). This evokes a short, but clearly identifiable, late-I inhibition of I neurons that shunts activating inputs to the inspiratory network (Fig. 105.6) [8,121,145].

**Inspiration Is Irreversibly Switched Off.** Decrease of inspiratory inhibition of PI neurons leads to rebound excitation of PI neurons (Figs. 105.4, 105.5) through activation of the low-voltage-activated  $\text{Ca}^{2+}$  conductances [149,175]. This rapid onset of PI discharge produces phase switching in the primary oscillator and irreversibly terminates inspiration (Fig. 105.6) [148,150]. PI activity also delays onset of stage 2 expiration and allows gradual passive exhalation. (It is important to note that an excitatory postinspiratory activity component seems to be added again to the inspiratory output neurons of the network [148]. This produces the postinspiratory “after-discharge” in phrenic motoneurons.)

**Expiration Is Switched On.** Activity-dependent, intracellular  $\text{Ca}^{2+}$  accumulation and activation of  $\text{Ca}^{2+}$ -dependent  $\text{K}^+$  conductances [140] produce repolarization and accommodation of PI neurons (Fig. 105.4), leading to disinhibition of E2 neurons, which become active [9,145] and inhibit not only early-I and PI neurons, but also I and late-I neurons [150].

**Expiration Is Switched Off.** The late expiratory discharge of pre-I neurons, which are not inhibited during the E2 phase, and the secondary discharge of PI neurons, which are weakly inhibited by E2 neurons (Fig. 105.3), act together to terminate the discharge of E2 neurons, thus enabling phase switching to inspiration (Fig. 105.6) [20,43,59,91].

Based on such a description of the respiratory network function, several laboratories have tried to model the respiratory rhythm [29,71,120]. When activated by an unpatterned external drive, the model network was able to develop rhythmic activities similar to those observed *in vivo*. The models also predict various disturbances to the rhythm that have been seen experimentally, such as rapid shallow breathing [10,147], hypoxic apneusis [19] and postinspiratory apnea [98,144] or hypoxic apnea [152,157].

## 105.11 A Common Cardiorespiratory Network

The data on the nervous control of the physiologically relevant adjustment of the respiratory and cardiovascular control (cf. Chap. 106) can be summarized as essentially matching respiratory minute volume to cardiac output. This prompts the question as to whether the combined “cardiorespiratory” function may be controlled by a “common cardiorespiratory” network that is part of both respi-

ratory and cardiovascular control systems in the brain stem [84,153]. Regarding the neural basis of interactions between the cardiovascular and respiratory control systems, it is interesting to note that the structures are located close together in almost identical regions of the brain stem (see Fig. 105.2) [21,76,84,110,153,171,174].

A review of the patterns of discharge that are characteristic of various sorts of sympathetic and vagal outflows to the heart, vascular beds, pupil and kidney shows that these “autonomic” activities are also rhythmic and strongly modified in synchrony with central respiratory activity. Central respiratory activity also has the ability to influence the performance of several basic cardiovascular reflexes, and by altering their efficacy affects the discharge of the respective autonomic outputs (for details see Chap. 107). The tight coupling between the two systems partly explains sinus arrhythmia, the respiration-related variations in heart rate and blood pressure. This modulation has been attributed to several mechanisms, including one resulting from a common “cardiorespiratory network” consisting of early-I, I and PI neurons [70,153]. That is, a common cardiorespiratory network controls the combined cardiorespiratory function.

## 105.12 Reflex Control of Central Respiratory Activity

Information about ventilatory mechanics, but also about chemical stimuli and temperature, is transmitted via afferent fibers of various diameters running in the olfactory, trigeminal, glossopharyngeal, and vagal nerves. This provokes various reflexes, such as termination of inspiration (Hering-Breuer reflex), sneezing, aspiration, coughing or vomiting, and also behavioral reactions, such as sniffing and inhibition of motor activity during heavy working load (Table 105.1) [16,23,75,131,160].

Afferents from glossopharyngeal and vagal nerves terminate in a specific relay nucleus of the brain stem, the nucleus of the solitary tract (NTS; Fig. 105.7; see also Fig. 105.2). The ventrolateral portion of the NTS contains the dorsal group of respiratory neurons (DRG) [21], which also are relay neurons that are not essential for respiratory rhythm generation [5,171].

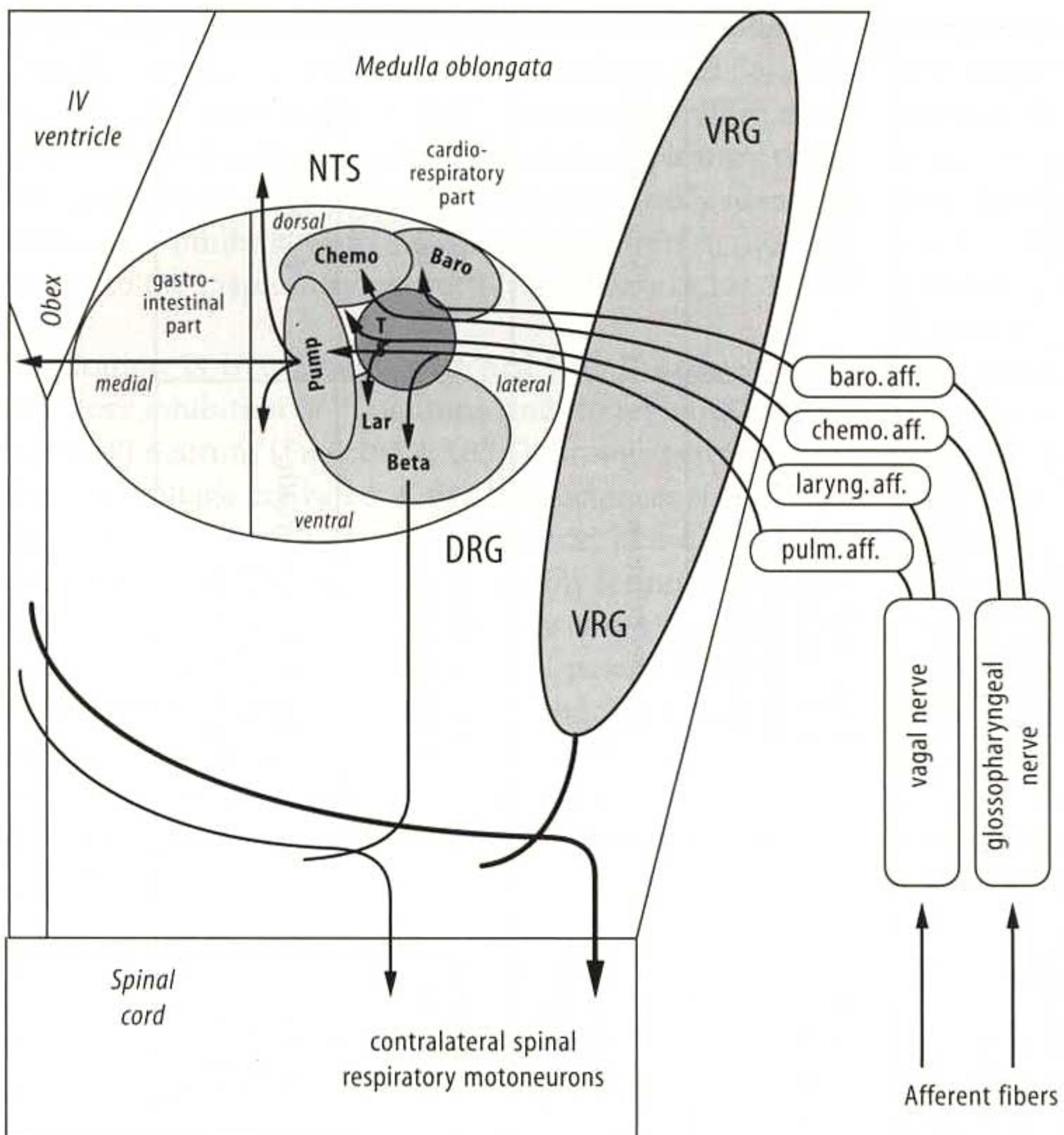
### 105.12.1 Central Processing of Slowly Adapting Pulmonary Afferents

Two types of neurons have been identified as target neurons of afferents from slowly adapting “pulmonary stretch” receptors. These are

- Inspiratory  $\beta$ -neurons ( $I_\beta$ ), which are depolarized during the I-phase and with lung inflation [181]
- “Pump” (P) neurons [19], which are depolarized with every lung inflation but are not modulated by the central respiratory rhythm.

Table 105.1. Reflexes from the airways

Receptors	Receptor localization	fiber diameter, cond. velocity	Afferent nerves	Appropriate stimulus	Reflex effects	Function
Nasal	Submucosal	1–4 $\mu\text{m}$ 4–26 m/s	trigeminal n. olfactory n.	Mechanical, chemical	Increase insp., increase exp., decrease HR	Sneezing, sniffing
	Submucosal	1–4 $\mu\text{m}$ 4–26 m/s	glossopharyngeal n.	Mechanical	Increase insp., bronchodilatation, decrease BP	Aspiration
Epi-pharyngeal	Subepithelial	1–4 $\mu\text{m}$ 4–26 m/s	vagal n.	Mechanical, chemical, cold	Increase insp., increase exp., increase BP, bronchoconstriction	Coughing
	Subepithelial	1–4 $\mu\text{m}$ 4–26 m/s	vagal n.	Mechanical (chemical)	Increase insp., increase exp., increase BP, bronchoconstriction	Coughing
Tracheal	Subepithelial	1–4 $\mu\text{m}$ 4–26 m/s	vagal n.	Mechanical, chemical, smelling salt	Hyperventilation	Deflation reflex
	Subepithelial, interepithelial	1–4 $\mu\text{m}$ 4–26 m/s	vagal n.	Mechanical, chemical	Decrease insp., increase exp	Hering-Breuer inflation reflex
Bronchial “irritant receptors”	Lamina propria	4–6 $\mu$ 25–60 m/s	vagal n.			“J reflex”
Alveolar J receptor C fibers	juxtagapillary wall	$\leq 1 \mu\text{m}$ 1 m/s	vagal n.	Mechanical, chemical, edema	Rapid shallow breath, apnea inhibit motor activity	



**Fig. 105.7.** Afferent projections to the nucleus of the solitary tract. Drawing representing a dorsal view of one half of the brain stem (without cerebellum). The nucleus of the solitary tract (NTS) is located bilaterally in the medial part of the brain stem. In the illustration, the NTS has been rotated around a horizontal axis to show dorsal parts upwards and ventral parts downwards. In its caudal extension, the lateral part of the NTS receives afferent inputs from the cardiovascular and respiratory systems, whereas the medial part of the NTS receives afferent inputs from the gastrointestinal tract. The two types of neurons that receive vagal afferent fibers from slowly adapting “pulmonary stretch” receptors are:  $I_\beta$  neurons and P neurons. The  $I_\beta$  neurons are located in the ventrolateral subnucleus of the NTS, and their axons project to the contralateral spinal cord without branching of medullary collaterals. P neurons are located directly dorsomedial and

ventromedial to the solitary tract (TS). Their axons have medullary collaterals projecting to the ipsi- and contralateral NTS and to more rostral regions of the central nervous system. In the medial parts of the NTS, neurons are activated by vagal afferents from rapidly adapting pulmonary receptors. Afferent fibers in the superior laryngeal nerve from laryngeal receptors project to the ventrolateral and medial NTS. Afferent fibers in the glossopharyngeal nerve from arterial chemoreceptors project to the dorsomedial NTS. Afferent fibers in the glossopharyngeal and vagal nerves from arterial baroreceptor terminate in the dorsolateral areas of the NTS. The details of the connections between second-order relay neurons and the respiratory network in the ventral respiratory group (VRG) are still unknown. DRG, dorsal respiratory group.

$I_\beta$ -neurons are located in the ventrolateral nucleus of the NTS (Fig. 105.7), and their dendritic tree extends into the ventrolateral and intermediate region of the NTS. Thus, their dendritic tree reaches areas where lung stretch receptor afferent fibers of vagal nerves terminate bilaterally [87,92] and monosynaptic contacts between  $I_\beta$ -neurons and these afferent fibers have been demonstrated [3,7]. The axons of  $I_\beta$ -neurons do not have any medullary collateralization [3,130], and the stem axons descend to the spinal cord, where they excite phrenic motoneurons [101]. These findings disprove the original proposal [181] that  $I_\beta$  neurons represent interneurons that inhibit reticulospinal inspiratory  $I_\alpha$ -neurons.

P neurons are located mainly in the dorsomedial and ventromedial parts of the NTS (Fig. 105.7) [163], and their dendritic arbor extends into the ventrolateral NTS, where afferents from slowly adapting pulmonary receptors [87]

and laryngeal receptors [18] terminate. The axons of P neurons terminate ipsilaterally with local collaterals in the ventrolateral NTS [162] and project to the contralateral NTS, terminating in its medial part [49,50]. Therefore, P neurons seem to be proper candidates for transmitting lung stretch receptor-related information to both ipsilaterally and contralaterally located  $I_\beta$ -neurons. Another possible target of P neurons are PI neurons in the caudal medulla and in the Bötzinger complex, which show an excitatory input in response to lung inflation [20,106]. These PI neurons could then inhibit inspiratory ventral respiratory group neurons [60,106] and explain the inspiratory-inhibitory and the expiratory-facilitatory components of the Hering-Breuer reflex [82].

Histological data also show prominent projections of pulmonary afferents to the nucleus parabrachialis medialis (PBM) and Kölliker-Fuse nuclei (KF; see Fig. 105.2)

[61,182], producing effective alteration of pontine respiratory activity [54,62,106,129,167]. The pontine outflow may involve respiratory neurons projecting to the dorsal and ventral respiratory groups in the medulla [24,166].

In sum, the Hering-Breuer reflex seems to be more complex than was thought in the past, and to involve more than just NTS neurons.

### 105.12.2 Central Processing of Other Afferent Fibers

A variety of nonrespiratory NTS neurons relay other sensory inputs: in the medial parts of the NTS, neurons are activated by rapidly adapting pulmonary afferents, which become active during hyperinflation or deflation of the lungs [88,101]. Bronchopulmonary C-fibers project to the commissural subnucleus of the NTS (and to the area postrema) [30,93]. Neurons in the ventrolateral NTS receive inputs from the superior laryngeal nerve [18], and neurons in the dorsomedial NTS are the target of afferents from arterial chemoreceptors [86,96]. Neurons in the dorsolateral NTS receive afferent inputs from arterial baroreceptors (see Chap. 107). The specific connectivity of all these relay neurons with the respiratory network is still unknown, but their axonal projections seem to be widespread. Afferent inputs from arterial chemoreceptors, for example, produce oligosynaptic activation of I, PI and E2 neurons, but inhibition of early-I neurons [96]. Respiratory neurons are also affected by baroreceptor afferent activity. Inspiratory neurons are inhibited and E2 neurons are disinhibited during early inspiration [147]. Additional influences become visible in late-I neurons, in which early-I inhibition is reduced and PI inhibition is enhanced during baroreceptor activation. These findings indicate that baroreceptor afferents affect the primary respiratory oscillator, which might explain respiratory depression during arterial hypertension. The baroreflex itself reveals respiratory modulation in its effectiveness [147]. The reflex is most effective during the PI phase and almost ineffective during the early-I period. This demonstrates that cardiorespiratory functions are controlled by a tight coupling between respiratory and cardiovascular networks, which together might constitute a “common cardiorespiratory network” [147,153].

### 105.13 Disturbances of the Respiratory Rhythm

Of particular interest for the analysis of central respiratory activity are the processes that lead to disturbance of the rhythm. Any reflex or direct perturbation of the primary oscillator or of its interaction with the network must have pathophysiological consequences: (i) Activation of PI activity by afferents from the larynx [98,144,150] or pulmonary C-fibers [131] results in respiratory arrest (reflex

apnea). (ii) Prolonged inspiratory phases (apneusis) result whenever synaptic inhibition is reduced [95]. (iii) This culminates in apnea when synaptic inhibition is blocked. Such reactions were observed under hypoxia or ischemia [14,19,146,152,155]. Thus, there are two possible causes of apnea:

- Reflex activation of postinspiratory activity
- Hypoxic blockade of synaptic inhibition within the network.

Such perturbations of the respiratory oscillator are fairly dramatic in neonatal mammals and might contribute to the sudden infant death syndrome [98,153,165].

### References

1. Akaike N, Takahashi K, Morimoto M (1991) Heterogeneous distribution of tetrodotoxin-sensitive calcium-conducting channels in rat hippocampal CA1 neurons. *Brain Res* 556:135–138
2. Alonso A, Llinás RR (1992) Electrophysiology of the mammillary complex in vitro. II. Medial mammillary neurons. *J Neurophysiol* 68:1321–1331
3. Anders K, Ohndorf W, Dermietzel R, Richter DW (1990) Synaptic contacts between lung stretch receptor afferents and beta-neurones in cat. *Pflügers Arch* 415:R91
4. Anders K, Ballantyne D, Bischoff AM, Lalley PM, Richter DW (1991) Inhibition of caudal medullary expiratory neurones by retrofacial inspiratory neurones in the cat. *J Physiol (Lond)* 437:1–25
5. Arata A, Onimaru H, Homma I (1993) Respiration-related neurons in the ventral medulla of newborn rats in vitro. *Brain Res Bull* 24:599–604
6. Arata A, Onimaru H, Homma I (1993) Effects of cAMP on respiratory rhythm generation in brainstem-spinal cord preparation from newborn rat. *Brain Res* 605:193–199
7. Backman SB, Anders K, Ballantyne D, Röhrig N, Camerer H, Mifflin S, Jordan D, Dickhaus H, Spyer KM, Richter DW (1984) Evidence for a monosynaptic connection between slowly adapting pulmonary stretch receptor afferents and inspiratory beta neurones. *Pflügers Arch* 402:129–136
8. Ballantyne D, Richter DW (1984) Post-synaptic inhibition of bulbar inspiratory neurones in the cat. *J Physiol (Lond)* 348:67–87
9. Ballantyne D, Richter DW (1986) The non-uniform character of inhibitory synaptic activity in expiratory bulbospinal neurones of the cat. *J Physiol (Lond)* 370:433–456
10. Ballantyne D, Jordan D, Spyer KM, Wood LM (1988) Synaptic rhythm of caudal medullary expiratory neurones during stimulation of the hypothalamic defence area of the cat. *J Physiol (Lond)* 405:527–546
11. Ballanyi K, Kuwana S, Völker A, Morawietz G, Richter DW (1992) Developmental changes in the hypoxia tolerance. *Neurosci Lett* 148:141–144
12. Ballanyi K, Onimaru H, Richter DW (1994) Calcium-mediated responses of respiratory neurons in the in vitro medulla of neonatal rats. *Pflügers Arch* 426:R137
13. Ballanyi K, Mückenhoff K, Bellingham MC, Okada Y, Scheid P, Richter DW (1995) Activity-related pH changes in respiratory neurones and glial cells of cats. *NeuroReport* 6:33–36
14. Ballanyi K, Völker A, Richter DW (1995) Anoxia induced functional inactivation of neonatal respiratory neurones in vitro. *NeuroReport* 6:165–168
15. Barillot JC, Grèlot L, Reddad S, Bianchi AL (1990) Discharge patterns of laryngeal motoneurones in the cat: an intracellular study. *Brain Res* 509:99–106

16. Bartlett D (1989) Respiratory functions of the larynx. *Physiol Rev* 69:33–57
17. Bayliss DA, Viana F, Berger AJ (1992) Mechanisms underlying excitatory effects on thyrotropin-releasing hormone on rat hypoglossal motoneurons in vitro. *J Neurophysiol* 68:1733–1745
18. Bellingham MC, Lipski J (1992) Morphology and electrophysiology of superior laryngeal nerve afferents and postsynaptic neurons in the medulla oblongata of the cat. *Neuroscience* 48:205–216
19. Bellingham MC, Schmidt C, Windhorst U, Richter DW (1991) The inspiratory off-switch is disturbed during hypoxia. *Pflügers Arch* 418:R16
20. Bellingham MC, Schmidt C, Richter DW (1992) Postinspiratory neurons – a possible integrator of the Hering-Breuer reflex? In: Elsner N, Richter DW (eds) *Rhythmogenesis in neurons and networks*, Proceedings of the 20th Göttingen Neurobiology Conference. Thieme, Stuttgart, p 67
21. Berger AJ (1977) Dorsal respiratory group neurons in the medulla of cat: spinal projections, responses to lung inflation and superior laryngeal nerve stimulation. *Brain Res* 135:231–154
22. Bianchi AL, Barillot JC (1982) Respiratory neurons in the region of the retrofacial nucleus: pontile, medullary, spinal and vagal projections. *Neurosci Lett* 3:277–282
23. Bianchi AL, Grélot (1989) Converse motor output of inspiratory bulbospinal premotoneurons during vomiting. *Neurosci Lett* 104:298–302
24. Bianchi AL, St John WM (1982) Medullary axonal projections of respiratory neurons of pontile pneumotaxic center. *Respir Physiol* 48:357–373
25. Bianchi AL, Grélot L, Iscoe S, Remmers JE (1988) Electrophysiological properties of rostral medullary respiratory neurones in the cat: an intracellular study. *J Physiol (Lond)* 407:293–310
26. Bianchi AL, Denavit-Saubié M, Champagnat J (1995) Neurobiology of the central control of breathing in mammals: neuronal circuitry, membrane properties and neurotransmitters involved. *Physiol Rev* (in press)
27. Bingmann D, Baker RE, Ballantyne D (1991) Rhythm generation in brainstem cultures grown in a serum-free medium. *Neurosci Lett* 132:167–170
28. Bossu JL, Dupont JL, Feltz A (1985)  $I_A$  current compared to low-threshold calcium current in cranial sensory neurons. *Neurosci Lett* 62:249–254
29. Botros SM, Bruce EN (1990) Neural network implementation of the three-phase model of respiratory rhythm generation. *Biol Cybern* 63:143–153
30. Boxham AC, Joad JP (1991) Neurones in commissural nucleus tractus solitarius required for full expression of the pulmonary C fibre reflex in rat. *J Physiol (Lond)* 441:95–112
31. Branchereau P, Champagnat J, Roques BP, Denavit-Saubié M (1992) CCK modulates inhibitory synaptic transmission in the solitary complex through CCK<sub>B</sub> sites. *NeuroReport* 3:909–912
32. Brockhaus J, Ballanyi K, Smith JC, Richter DW (1993) Microenvironment of respiratory neurons in the in vitro brainstem-spinal cord of neonatal rats. *J Physiol (Lond)* 462:421–445
33. Brown DA (1988) M-currents: an update. *Trends Neurol Sci* 11:294–299
34. Carbone E, Lux HD (1987) Kinetics and selectivity of a low-voltage-activated calcium current in chick and rat sensory neurones. *J Physiol (Lond)* 386:547–570
35. Champagnat J, Richter DW (1993) Second messengers-induced modulation of the excitability of respiratory neurones. *NeuroReport* 4:861–863
36. Champagnat J, Richter DW (1994) The roles of  $K^+$  conductance in expiratory pattern generation in anaesthetized cats. *J Physiol (Lond)* 479:127–128
37. Champagnat J, Denavit-Saubié M, Henry JL, Leveil V (1979) Catecholaminergic depressant effects on bulbar respiratory mechanisms. *Brain Res* 160:57–68
38. Champagnat J, Denavit-Saubié M, Moyanova S, Rondouin G (1982) Involvement of amino acids in periodic inhibitions of bulbospinal respiratory neurones. *Brain Res* 237:351–365
39. Champagnat J, Denavit-Saubié M, Siggins GR (1983) Rhythmic neuronal activities in the nucleus of the tractus solitarius isolated in vitro. *Brain Res* 280:155–159
40. Champagnat J, Jaquin T, Richter DW (1986) Voltage-dependent currents in neurones of the nuclei of the solitary tract of rat brainstem slices. *Pflügers Arch* 406:372–379
41. Cherubini E, Ben-Ari Y, Krnjevic K (1990) Periodic inward currents triggered by NMDA in immature CA3 hippocampal neurones. In: Ben-Ari Y (ed) *Excitatory amino acids and neuronal plasticity*. Plenum, New York, pp 147–150
42. Cherubini E, Gaiarsa JK, Ben-Ari Y (1991) GABA: an excitatory transmitter in early postnatal life. *Trends Neurol Sci* 14:515–519
43. Cohen MI (1979) Neurogenesis of respiratory rhythm in the mammal. *Physiol Rev* 59:1105–1173
44. Coleridge HM, Coleridge JCG, Roberts SM (1983) Rapid shallow breathing evoked by selective stimulation of airway C-fibres in dogs. *J Physiol (Lond)* 340:415–433
45. Connelly CA, Ellenberger HH, Feldman JL (1989) Are there serotonergic projections from raphe and retrotrapezoid nuclei to the ventral respiratory group in the rat? *Neurosci Lett* 105:34–40
46. Connelly CA, Dobbins EG, Feldman JL (1992) Pre-Bötzinger complex in cats: respiratory neuronal discharge patterns. *Brain Res* 590:337–340
47. Connelly CA, Otto-Smith MR, Feldman JL (1992) Blockade of NMDA receptor-channels by MK801 alters breathing in adult rats. *Brain Res* 596:99–110
48. Connor JA, Stevens CF (1971) Voltage-clamp studies of a transient outward membrane current in gastropod neural somata. *J Physiol (Lond)* 213:21–30
49. Davies RO, Kubin L, Pack AI (1986) Contralateral projections of pump neurones of the nucleus of the solitary tract in the cat. *J Physiol (Lond)* 371:118
50. Davies RO, Kubin L, Pack AI (1987) Pulmonary stretch receptor relay neurones of the cat: location and contralateral medullary projections. *J Physiol (Lond)* 383:571–585
51. Dean JB, Lawing WL, Millhorn DE (1989)  $CO_2$  decreases membrane conductance and depolarizes neurons in the nucleus tractus solitarius. *Exp Brain Res* 76:656–661
52. Di Pasquale E, Monteau R, Hilaire G (1992) In vitro study of central respiratory-like activity of the fetal rat. *Exp Brain Res* 89:459–464
53. Di Pasquale E, Morin D, Monteau R, Hilaire G (1992) Serotonergic modulation of the respiratory rhythm generator at birth: an in vitro study in the rat. *Neurosci Lett* 143:91–95
54. Dick TE, Bellingham MC, Richter DW (1994) Pontine respiratory neurons in anaesthetized cats. *Brain Res* 636:259–269
55. Duffin J, Aweida D (1990) The propriobulbar respiratory neurons in the cat. *Exp Brain Res* 81:213–220
56. Ellenberger HH, Feldman JL (1990) Brainstem connections of the rostral ventral respiratory group of the rat. *Brain Res* 513:35–42
57. Ellenberger HH, Feldman JL (1990) Subnuclear organization of the lateral tegmental field of the rat. I. Nucleus ambiguus and ventral respiratory group. *J Comp Neurol* 294:202–211
58. Errchidi S, Monteau R, Hilaire G (1991) Noradrenergic modulation of the medullary respiratory rhythm generator in the newborn rat: an in vitro study. *J Physiol (Lond)* 443:477–498
59. Ezure K (1990) Synaptic connections between medullary respiratory neurons and considerations on the genesis of respiratory rhythm. *Prog Neurobiol* 35:429–450
60. Ezure K, Manabe M (1988) Decrementing expiratory neurons in the Bötzinger complex. II. Direct inhibitory synaptic

- linkage with ventral respiratory group neurons. *Exp Brain Res* 72:159–166
61. Feldman JL (1986) Neurophysiology of breathing in mammals. In: Bloom FE (ed) *Handbook of Physiology, Section I, The nervous system*, American Physiological Society, Bethesda, pp 463–524
  62. Feldman JL, Cohen MI, Wolotsky P (1976) Powerful inhibition of pontine respiratory neurones by pulmonary afferent activity. *Brain Res* 104:341–346
  63. Feldman JL, Smith JC, Ellenberger HH, Connelly CA, Liu G, Greer JJ, Lindsay AD, Otto MR (1990) Neurogenesis of respiratory rhythm and pattern: emerging concepts. *Am J Physiol* 259:R879–R886
  64. Feldman JL, Smith JC, Liu G (1991) Respiratory pattern generation in mammals: in vitro en bloc analyses. *Curr Opin Neurobiol* 1:590–594
  65. Feldman JL, Windhorst U, Anders K, Richter DW (1992) Synaptic interaction between medullary respiratory neurones during apneusis induced by NMDA-receptor blockade in cat. *J Physiol (Lond)* 450:303–323
  66. Fortin G, Branchereau P, Araneda S, Champagnat J (1992) Rhythmic activities in the rat solitary complex in vitro. *Neurosci Lett* 147:89–92
  67. Foutz AS, Champagnat J, Denavit-Saubié M (1988) N-Methyl-D-aspartate (NMDA) receptors control respiratory off-switch in cat. *Neurosci Lett* 87:221–226
  68. Foutz AS, Champagnat J, Denavit-Saubié M (1989) Involvement of N-Methyl-D-aspartate (NMDA) receptors in respiratory rhythogenesis. *Brain Res* 500:199–208
  69. Foutz AS, Pierrefiche O, Denavit-Saubié M (1994) Combined blockade of NMDA and non-NMDA receptors produces respiratory arrest in the adult cat. *NeuroReport* 5:481–484
  70. Gilbey M, Jordan D, Richter DW, Spyer KM (1984) Synaptic mechanisms involved in the inspiratory modulation of the vagal cardioinhibitory neurones in the cat. *J Physiol (Lond)* 356:65–78
  71. Gottschalk A, Ogilvie MD, Richter DW, Pack AI (1994) Computational aspects of the respiratory pattern generator. *Neural Comp* 6:56–68
  72. Graham K, Duffin J (1981) Cross-correlation of medullary expiratory neurons in the cat. *Exp Neurol* 73:451–464
  73. Greer JJ, Smith JC, Feldman JL (1991) Role of excitatory amino acids in the generation and transmission of respiratory drive in neonatal rat. *J Physiol (Lond)* 437:727–749
  74. Greer JJ, Smith JC, Feldman JL (1992) Respiratory and locomotor patterns generated in the fetal rat brain stem-spinal cord in vitro. *J Neurophysiol* 67:996–999
  75. Grélot L, Milano S, Portillo F, Miller AD, Biachni AL (1992) Membrane potential changes of phrenic motoneurons during fictive vomiting, coughing and swallowing in the decerebrate cat. *J Neurophysiol* 68:2110–2119
  76. Guyenet PG (1990) Role of the ventral medulla oblongata in blood pressure regulation. In: Loewy AD, Spyker KM (eds) *Central regulation of autonomic function*, Oxford University Press, Oxford, 145–167
  77. Haddad GG, Donnelly DF (1989) Maturation of hypoglossal neuronal response to hypoxia in rats. In-vitro intracellular studies. *Fed Proc* 3:A403
  78. Haji A, Takeda R (1993) Variations in membrane potential trajectory of postinspiratory neurons in the ventrolateral medulla of the cat. *Neurosci Lett* 149:233–236
  79. Haji A, Remmers JE, Connelly C, Takeda R (1990) Effects of glycine and GABA on bulbar respiratory neurons of cat. *J Neurophysiol* 63:955–965
  80. Haji A, Takeda R, Remmers JE (1992) Evidence that glycine and GABA mediate postsynaptic inhibition of bulbar respiratory neurons in the cat. *J Appl Physiol* 73:2333–2342
  81. Hayashi F, Lipski J (1992) The role of inhibitory amino acids in control of respiratory motor output in an arterially perfused rat. *Resp Physiol* 89:47–63
  82. Hering E (1868) Die Selbststeuerung der Atmung durch den Nervus vagus. *Sitzungsber Akad Wiss Wien* 57(2):672–677
  83. Hodgkin AL, Huxley AF (1952) Currents carried by sodium and potassium ions through the membrane of the giant axon of *Loligo*. *J Physiol (Lond)* 116:449–472
  84. Hopkins DA (1987) The dorsal motor nucleus of the vagus nerve and the nucleus ambiguus; structure and connections. In: Hainsworth R, McWilliam PN, Many DAG (eds) *Cardiogenic reflexes*, Oxford University Press, Oxford, pp 185–203
  85. Hugelin A, Cohen MI (1963) The reticular activating system and respiratory regulation in the cat. *Ann NY Acad Sci U S A* 109:586–603
  86. Izzo PN, Lin RJ, Richter DW, Spyker KM (1988) Physiological and morphological identification of neurones receiving arterial chemoreceptive afferent input in the nucleus tractus solitarius of the cat. *J Physiol (Lond)* 399:31P
  87. Kalia M, Richter DW (1985) Morphology of physiologically identified slowly adapting lung stretch receptor afferents stained with intra-axonal HRP in the nucleus of the tractus solitarius of the cat. I. A light microscopic analysis. *J Comp Neurol* 241:503–520
  88. Kalia M, Richter DW (1988) Rapidly adapting pulmonary receptor afferents. I. Arborization in the nucleus of the tractus solitarius. *J Comp Neurol* 274:560–573
  89. Kashiwagi M, Onimaru H, Homma I (1993) Correlation analysis of respiratory neuron activity in ventrolateral medulla of brainstem-spinal cord preparation isolated from newborn rat. *Exp Brain Res* 95:277–290
  90. Kashiwagi M, Onimaru H, Homma I (1993) Effects of NMDA on respiratory neurons in newborn rat medulla in vitro. *Brain Res Bull* 32:65–69
  91. Klages S, Bellingham MC, Richter DW (1993) Late expiratory inhibition of stage 2 expiratory neurons in the cat – a correlate of expiratory termination. *J Neurophysiol* 70:1307–1315
  92. Kubin L, Davies RO (1987) Bilateral convergence of pulmonary stretch receptor inputs on I $\beta$ -neurons in the cat. *J Appl Physiol* 62:1488–1496
  93. Kubin L, Kimura H, Davies RO (1991) The medullary projections of afferent bronchopulmonary C-fibres in the cat as shown by antidromic mapping. *J Physiol (Lond)* 435:207–228
  94. Lalley PM, Bischoff AM, Richter DW (1993) 5HT-1A receptor-mediated modulation of medullary expiratory neurones in the cat. *J Physiol (Lond)* 476:117–130
  95. Lalley PM, Bischoff AM, Richter DW (1994) Serotonin 1A-receptor activation suppresses respiratory apneusis in the cat. *Neurosci Lett* 172:59–62
  96. Lawson EE, Richter DW, Ballantyne D, Lalley PM (1989) Peripheral chemoreceptor inputs to medullary inspiratory and postinspiratory neurons of cats. *Pflügers Arch* 414:523–533
  97. Lawson EE, Richter DW, Bischoff A (1989) Intracellular recordings of respiratory neurons in the lateral medulla of piglets. *J Appl Physiol* 66(2):983–988
  98. Lawson EE, Richter DW, Czyzyk-Krzeska MF, Bischoff AM, Rudesill RC (1991) Respiratory neuronal activity during apnea and other breathing patterns induced by laryngeal stimulation. *J Appl Physiol* 70:2742–2749
  99. Lawson EE, Schwarzacher SW, Richter DW (1992) Postnatal development of the medullary respiratory network in cat. In: Elsner N, Richter DW (eds) *Rhythogenesis in neurons and networks* Thieme, Stuttgart, p 69
  100. Ling L, Karius DR, Fiscus RR, Speck DF (1992) Endogenous nitric oxide required for an integrative respiratory function in the cat brain. *J Neurophysiol* 68:1910–1912
  101. Lipski J, Kubin L, Jodkowski J (1983) Synaptic action of R-beta neurons on phrenic motoneurons studied with spike-triggered averaging. *Brain Res* 288:105–118
  102. Lipski J, Ezure K, Wong She RB (1991) Identification of neurons receiving input from pulmonary rapidly adapting receptors in the cat. *J Physiol (Lond)* 443:55–77
  103. Liu G, Feldman JL (1992) Quantal synaptic transmission in phrenic motor nucleus. *J Neurophysiol* 68:1468–1471

104. Loeschke HH (1982) Central chemosensitivity and the reaction theory. *J Physiol (Lond)* 332:1–24
105. Long S, Duffin J (1986) The neuronal determinants of respiratory rhythm. *Prog Neurobiol* 27:101–182
106. Manabe M, Ezure K (1988) Decrementing expiratory neurons of the Bötzinger complex. I. Response to lung inflation and axonal projection. *Exp Brain Res* 72:150–158
107. Marks JD, Donnelly DF, Haddad GG (1993) Adenosine-induced inhibition of vagal motoneuron excitability: receptor subtype and mechanisms. *Am J Physiol* 264(8):L124–L132
108. Marty A (1983)  $\text{Ca}^{2+}$ -dependent  $\text{K}^+$  channels with large unitary conductance. *Trends Neurol Sci* 6:262–265
109. Mayer ML, Westbrook GA (1983) A voltage-clamp analysis of inward (anomalous) rectification in mouse spinal sensory ganglion neurones. *J Physiol (Lond)* 340:19–45
110. McAllen RM (1987) Central respiratory modulation of subretrofacial bulbospinal neurones in the cat. *J Physiol (Lond)* 388:533–545
111. McCormick DA, Pape HC (1990) Properties of a hyperpolarization-activated cation current and its role in rhythmic oscillation in thalamic relay neurones. *J Physiol (Lond)* 431:291–318
112. McDonald JW, Silverstein FS, Johnson MV (1988) Neurotoxicity of N-methyl-D-aspartate is markedly enhanced in developing rat central nervous system. *Brain Res* 459:200–203
113. Merrill EG (1974) Finding a respiratory function for the medullary respiratory neurons. In: Bellairs R, Gray EG (eds) *Essays on the nervous system*, Clarendon Oxford, pp 451–486
114. Merrill EG, Lipski J, Kubin L, Fedorko L (1983) Origin of the expiratory inhibition of nucleus tractus solitarius inspiratory neurones. *Brain Res* 263:43–40
115. Mifflin SW, Richter DW (1987) Effects of QX-314 on medullary respiratory neurones. *Brain Res* 420:22–31
116. Monteau R, Hilaire G (1991) Spinal respiratory motoneurons. *Prog Neurobiol* 37:83–144
117. Monteau R, Morin D, Hilaire G (1990) Acetylcholine and central chemosensitivity: in vitro study in the newborn rat. *Respir Physiol* 81:241–254
118. Morin D, Hennequin S, Monteau R, Hilaire G (1990) Serotonergic influences on central respiratory activity: an in vitro study in the newborn rat. *Brain Res* 535:281–287
119. Morin-Surun MP, Boudinot E, Fournie-Zaluski MC, Champagnat J, Roques BP, Denavit-Saubié M (1992) Control of breathing by endogenous opioid peptides: possible involvement in sudden infant death syndrome. *Neurochem Int* 20:103–107
120. Oglivie MD, Gottschalk A, Anders K, Richter DW, Pack AI (1992) A network model of respiratory rhythmogenesis. *Am J Physiol* 263:R962–R975
121. Oku Y, Tanaka I, Ezure K (1992) Possible inspiratory off-switch neurones in the ventrolateral medulla of the cat. *NeuroReport* 3:933–936
122. Onimaru H (1995) Studies of the respiratory center using isolated brainstem-spinal cord preparations. *Neurosci Res* 21:183–190
123. Onimaru H, Homma I (1992) Whole cell recordings from respiratory neurons in the medulla of brainstem-spinal cord preparations isolated from newborn rats. *Pflügers Arch* 420:399–406
124. Onimaru H, Arata A, Homma I (1987) Localization of respiratory rhythm-generating neurons in the medulla of brainstem-spinal cord preparations from newborn rats. *Neurosci Lett* 78:151–155
125. Onimaru H, Arata A, Homma I (1989) Firing properties of respiratory rhythm generating neurons in the absence of synaptic transmission in rat medulla in vitro. *Ext Brain Res* 76:530–536
126. Onimaru H, Arata A, Homma I (1990) Inhibitory synaptic inputs to the respiratory rhythm generator in the medulla isolated from newborn rats. *Pflügers Arch* 417:425–432
127. Onimaru H, Homma I, Iwatsuki K (1992) Excitation of inspiratory neurons by preinspiratory neurons in rat medulla in vitro. *Brain Res Bull* 29:879–882
128. Onimaru H, Kashiwagi M, Arata A, Homma I (1993) Possible mutual excitatory couplings between inspiratory neurons in caudal ventrolateral medulla of brainstem-spinal cord preparation isolated from newborn rat. *Neurosci Lett* 150:203–206
129. Otake K, Sasaki H, Ezure K, Manabe M (1988) Axonal projections from Bötzinger expiratory neurons to contralateral ventral and dorsal respiratory groups in the cat. *Exp Brain Res* 72:167–177
130. Otake K, Sasaki H, Ezure K, Manabe M (1989) Axonal trajectory and terminal distribution of inspiratory neurons of the dorsal respiratory group in the cat's medulla. *J Comp Neurol* 286:218–230
131. Paintal AS (1973) Vagal sensory receptors and their reflex effects. *Physiol Rev* 53:159–227
132. Partridge LD, Swandulla D (1988) Calcium-activated non-specific cation channels. *Trends Neurol Sci* 11:69–72
133. Paton JFR, Rogers WT, Schwaber JS (1991) Tonically rhythmic neurons within a cardiorespiratory region of the nucleus tractus solitarius of the rat. *J Neurophysiol* 66:824–838
134. Paton JFR, Ramirez J-M, Richter DW (1994) Functionally intact in vitro preparation generating respiratory activity in neonatal and mature mammals. *Pflügers Arch* 428:250–260
135. Paton JFR, Ramirez J-M, Richter DW (1994) Mechanisms of respiratory rhythm generation change profoundly during early life in mice and rats. *Neurosci Lett* 170:167–170
136. Pierrefiche O, Foutz A (1993) Effects of  $\text{GABA}_B$  receptor agonists and antagonists on the bulbar respiratory network in the cat. *Brain Res* 605:77–84
137. Pierrefiche O, Richter DW (1994)  $\text{K}^+$ -ATP channels are active in the respiratory network of cats. *Pflügers Arch* 426:R136
138. Pierrefiche O, Foutz AS, Champagnat J, Denavit-Saubié M (1992) The bulbar network of respiratory neurons during apneusis induced by a blockade of NMDA receptors. *Exp Brain Res* 89:623–639
139. Pierrefiche O, Foutz AS, Champagnat J, Denavit-Saubié M (1994) NMDA and non-NMDA receptors may play distinct roles in timing mechanisms and transmission in the feline respiratory network. *J Physiol (Lond)* 474.3:509–523
140. Pierrefiche O, Champagnat J, Richter DW (1995) Calcium-dependent conductances control neurones involved in termination of inspiration in cats. *Neurosci Lett* 184:101–104
141. Portillo F, Grélot L, Milano S, Bianchi AL (1994) Brainstem neurons with projecting axons to both phrenic and abdominal motor nuclei: a double fluorescent labeling study in the cat. *Neurosci Lett* 173:50–54
142. Quattrochi JJ, Rho JH (1985) Three-dimensional tissue reconstruction reveals integrative structural features among neurons within central respiratory centers of the brain stem. In: Bianchi AL, Denavit-Saubié M (eds) *Nuerogenesis of central respiratory rhythm*. MTP, Lancaster, pp 431–437
143. Rampin O, Pierrefiche O, Denavit-Saubié M (1993) Effects of serotonin and substance P on bulbar respiratory neurons in vivo. *Brain Res* 622:185–193
144. Remmers JE, Richter DW, Ballantyne D, Bainton CR, Klein JP (1986) Reflex prolongation of the stage I of expiration. *Pflügers Arch* 407:190–198
145. Richter DW (1982) Generation and maintenance of the respiratory rhythm. *J Exp Biol* 100:93–107
146. Richter DW, Acker H (1989) Respiratory neuron behavior during medullary hypoxia. In: Lahiri S (ed) *Chemoreceptors and reflexes in breathing: cellular and molecular aspects*. Oxford University Press, Oxford, pp 267–274
147. Richter DW, Spyker KM (1990) Cardio-respiratory control In: Loewy AD, Spyker KM (eds) *Central regulation of autonomic function*. Oxford University Press, Oxford, pp 189–207
148. Richter DW, Ballantyne D, Remmers JE (1986) Respiratory rhythm generation: a model. *NIPS* 1:109–112

149. Richter DW, Champagnat J, Mifflin SW (1986) Membrane properties involved in respiratory rhythm generation. In: von Euler C Lagercrantz H (eds) *Neurobiology of the control of breathing*. Raven, New York, pp 141–147
150. Richter DW, Ballantyne D, Remmers JE (1987) The differential organization of medullary post-inspiratory activities. *Pflügers Arch* 410:420–427
151. Richter DW, Champagnat J, Mifflin SW (1987) Membrane properties of medullary respiratory neurones of the cat. In: Sieck GC, Gandevia SC, Cameron WE (eds) *Respiratory muscles and their neuromotor control*. Wiley, New York, pp 9–15
152. Richter DW, Bischoff A, Anders K, Bellingham M, Windhorst U (1991) Response of the medullary respiratory network of the cat to hypoxia. *J Physiol (Lond)* 443:231–256
153. Richter DW, Spyer KM, Gilbey MP, Lawson EE, Bainton CR, Wilhelm Z (1991) On the existence of a common cardio-respiratory network. In: Koepchen HP, Huopaniemi T (eds) *Cardiorespiratory and motor coordination*, Springer, Berlin, Heidelberg, New York pp 118–130
154. Richter DW, Ballanyi K, Schwarzacher S (1992) Mechanisms of respiratory rhythm generation. *Curr Opin Neurobiol* 2:788–793
155. Richter DW, Bellingham M, Schmidt C (1992) Maintenance of the respiratory rhythm during normoxia and hypoxia. In: Honda Y, Miyamoto Y, Konno K, Widdicombe JG (eds) *Control of breathing and its modeling perspective*. Plenum, New York, pp 7–13
156. Richter DW, Champagnat J, Jacquin T, Benacka R (1993) Calcium and calcium-dependent potassium currents in medullary respiratory neurones. *J Physiol (Lond)* 470:23–33
157. Richter DW, Schmidt C, Bellingham M, Schmidt P (1993) Hypoxia and central respiratory neurons. In: Scheid P (ed) *Respiration in health and disease: lessons from comparative physiology*, Fischer, Stuttgart pp 303–312
158. Rudolph T, Schwarzacher SW, Herbert H, Richter DW (1992) Serotonergic innervation of cat's medullary respiratory neurones: intracellular HRP-labeling and 5HT-immunocytochemistry. In: Elsner N, Richter DW (eds) *Rhythmodogenesis in neurons and networks*. Thieme, Stuttgart p 71
159. Salmoiraghi GC, Baumgarten R von (1961) Intracellular potentials from respiratory neurones in brain-stem of cat and mechanism of rhythmic respiration. *J Neurophysiol* 24:203–218
160. Sant'Ambrogio G (1982) Information arising from the tracheobronchial tree of mammals. *Physiol Rev* 62:531–569
161. Schmidt C, Bellingham MC, Richter DW (1995) Adenosinergic modulation of respiratory neurones and hypoxic responses in the anaesthetized cat. *J Physiol (Lond)* 483:769–781
162. Schwarzacher SW, Wilhelm Z, Anders K, Richter DW (1991) The medullary respiratory network in rats. *J Physiol (Lond)* 435:631–644
163. Schwarzacher SW, Maschke M, Anders K, Richter DW (1995) Morphology of respiration-related "pump" neurones in cat brainstem: a light- and electronmicroscopic analysis
164. Schwarzacher SW, Smith JC, Richter DW (1995) Pre-Bötzinger complex in the cat. *J Neurophysiol* 73: (in press)
165. Schweitzer P, Fortin G, Beloeil JC, Champagnat J (1992) In vitro study of newborn rat brain maturation: implication for sudden infant death syndrome. *Neurochem Int* 20:109–112
166. Segers LS, Shannon R, Lindsey BG (1985) Interactions between rostral pontine and ventral medullary respiratory neurones. *J Neurophysiol* 54:318–334
167. Shaw C, Cohen MI, Barnhardt R (1989) Inspiratory-modulated neurons of the rostral-lateral pons: effects of pulmonary afferent input. *Brain Res* 485:179–184
168. Shee CD, Loysongsang Y, Milic-Emili J (1985) Decay of inspiratory muscle pressure during expiration in conscious humans. *J Appl Physiol* 58:1859–1865
169. Shinohara K, Nishikawa T, Yamazaki K, Takahashi K (1989) Ontogeny of strychnine-insensitive (<sup>3</sup>H)glycine binding sites in rat forebrain. *Neurosci Lett* 105:307–311
170. Smith JC, Greer JJ, Liu G, Feldman JL (1990) Neural mechanisms generating respiratory pattern in mammalian brain stem-spinal cord in vitro. I. Spatiotemporal patterns of motor and medullary neuron activity. *J Neurophysiol* 64:1149–1169
171. Smith JC, Ellenberger H, Ballanyi K, Feldman JL, Richter DW (1991) Pre-Bötzinger complex: a brainstem region that may generate respiratory rhythm in mammals. *Science* 254:726–729
172. Smith JC, Ballanyi K, Richter DW (1992) Whole-cell patch-clamp recordings from respiratory neurons in neonatal rat brainstem in vitro. *Neurosci Lett* 134:153–156
173. Stafstrom CE, Schwindt PC, Chubb MC, Crill WE (1985) Properties of persistent sodium conductance and calcium conductance of layer V neurons from cat sensorimotor cortex in vitro. *J Neurophysiol* 53:153–170
174. Sun MK, Young BS, Hackett JT, Guyenet PG (1988) Reticulospinal pacemaker neurons of the rat rostral ventrolateral medulla with putative sympathoexcitatory function: an intracellular study in vitro. *Brain Res* 442:229–239
175. Takeda R, Haji A (1993) Mechanisms underlying post-inspiratory depolarization in post-inspiratory neurons of the cat. *Neurosci Lett* 150:1–4
176. Tell F, Jean A (1991) Activation of N-methyl-D-aspartate receptors induces endogenous rhythmic bursting activities in nucleus tractus solitarius neurons: an intracellular study on adult rat brainstem slices. *Eur J Neurosci* 3:1353–1365
177. Trapp S, Ballanyi K, Richter DW (1994) Spontaneous activation of  $K_{ATP}$  current in rat dorsal vagal neurones. *NeuroReport* 5:1285–1288
178. Trippenbach T, Richter DW, Acker H (1990) Hypoxia and ion activities within the brainstem of newborn rabbits. *J Appl Physiol* 68:2494–2503
179. Tsien RW, Lipscombe D, Madison DV, Bley KR, Fox AP (1988) Multiple types of neuronal Ca channels and their selective modulation. *Trends Neurosci* 11:431–438
180. Völker A, Ballanyi K, Richter DW (1995) Anoxic disturbance of the isolated respiratory network of neonatal rats. *Exp Brain Res* 103:9–19
181. von Baumgarten R, Kanzow E (1958) The interaction of two types of inspiratory neurones in the region of the tractus solitarius of the cat. *Arch Ital Biol* 96:361–373
182. von Euler C (1986) Brain stem mechanisms for generation and control of breathing pattern. In: Fishman AP, Cherniack NS, Widdicombe JG, Geiger SR (eds) *Handbook of physiology*, Section III, The respiratory system, American Physiological Society, Bethesda, pp 1–67
183. Yamamoto Y, Onimaru H, Homma I (1992) Effect of substance P on respiratory rhythm and pre-inspiratory neurons in the ventrolateral structure of rostral medulla oblongata: an in vitro study. *Brain Res* 599:272–274
184. Zheng Y, Barillot JC, Biachi AL (1991) Are the post-inspiratory neurons in the decerebrate rat cranial motoneurons or interneurons? *Brain Res* 551:256–266

#### Important Reference Published Recently

185. Johnson SM, Smith JC, Funk GD, Feldman JL (1994) Pacemaker behavior of respiratory neurons in medullary slices from neonatal rat. *J Neurophysiol* 72:2598–2608