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Pontine Mechanisms of Respiratory Control

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Abstract

Pontine respiratory nuclei provide synaptic input to medullary rhythmogenic circuits to shape and adapt the breathing pattern. An understanding of this statement depends on appreciating breathing as a behavior, rather than a stereotypic rhythm. In this review, we focus on the pontine-mediated inspiratory off-switch (IOS) associated with postinspiratory glottal constriction. Further, IOS is examined in the context of pontine regulation of glottal resistance in response to multimodal sensory inputs and higher commands, which in turn rules timing, duration, and patterning of respiratory airflow. In addition, network plasticity in respiratory control emerges during the development of the pons. Synaptic plasticity is required for dynamic and efficient modulation of the expiratory breathing pattern to cope with rapid changes from eupneic to adaptive breathing linked to exploratory (foraging and sniffing) and expulsive (vocalizing, coughing, sneezing, and retching) behaviors, as well as conveyance of basic emotions. The speed and complexity of changes in the breathing pattern of behaving animals implies that “learning to breathe” is necessary to adjust to changing internal and external states to maintain homeostasis and survival.

Preface

Breathing is a motor behavior, generated and controlled by the central nervous system. The neurons that generate breathing are arranged as a column in the lateral pons and ventrolateral (vl) medulla, and will be henceforth referred to as the lateral respiratory column (LRC). The LRC specifically extends from the caudal medulla to the rostral pons, aligning dorsally in the rostral pons (8). The LRC forms the principle anatomical substrate for the respiratory central pattern generator (rCPG) because anatomical integrity of the bilateral pontomedullary columns is essential to produce the basic respiratory rhythm, in other words eupnea (65, 245, 312, 322, 343, 395). By the definition proposed by Grillner and Wallen (147), the terminology CPG applies to the neuronal networks involved in appropriating a specific motor function. This would also include breathing. Therefore, it is important to note that the rCPG may involve additional nuclei apart from the LRC, particularly the nucleus tractus solitarius (NTS), which forms the dorsal respiratory group (235, 394) and the brainstem raphé neurons (262, 273, 274). In the following section, we discuss the complexity of the respiratory motor pattern generated by the rCPG as it is

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expressed by various cranial and spinal motor nerves that coordinate ventilation via pump muscles and adjust airflow resistance via valvular muscles. Following a general introduction in Section “Pontine Control of Breathing: An Overview,” the anatomical connectivity and physiological significance of the pontine nuclei of the LRC will form the core of this article.

Motor Activity Generating the Breathing Pattern Controls Airway Pressure and Resistance

Rhythmic motor behaviors such as walking, running, or flying are mediated by the contraction of antagonistic skeletal muscle pairs (e.g., extensor and flexor muscles) driven by CPGs (147, 367). Understanding the kinesiology of the movements has lead to identifying features necessary in the control of these rhythmic behaviors. For instance, the fundamental concept of “half-center oscillators,” which has evolved into CPGs, was derived from the finding that antagonistic muscle contract and relax in opposing phases independently of rhythmic afferent input (147, 367). The essential feature of half-centers is reciprocal inhibition interconnecting the two half-centers whose constituent neurons are not intrinsically rhythmic. This approach to understand motor rhythm, based on kinesiology, is common to both locomotion and respiration. The breathing pattern implies further complexity in that in addition to the opposing directions of airflow (inhalation and exhalation), both active and passive forces act on airflow.

In contrast to locomotion, the eupneic motor pattern of breathing is defined by not two but three distinct phases: inspiration (I), postinspiration (post-I), or passive expiration (termed stage 1 expiration, E1), and stage 2 (E2, late or active expiration; see Fig. 1). To understand the apparent complexity of the respiratory motor pattern, one has to consider that the rCPG controls two functionally distinct groups of muscles: those controlling thoracic pressure and those controlling airway resistance. The motoneurons for the primary pump muscles are located in the spinal cord (186, 260), while those for the muscles controlling airflow (via upper airway caliber) are located in the brainstem (26). The coordinated activities of both cranial (cranial nerves: V, IX, X, and XII) and spinal (cervical and thoracic) motor pools define the breathing pattern (102, 312, 343, 344, 356). The pattern associated with eupnea, which is “normal” breathing at rest is commonly marked by only the phrenic nerve activity that defines inspiration. However, the generation of a coordinated cranial and spinal motor output integral to eupnea depends on the integrity of the entire LRC in mammals, including man (34,102,245,290,310,312,343,344,355,356). Therefore, the definition and investigation of eupnea in anatomically reduced preparations *in vitro* presents significant conceptual barriers (312, 343, 344).

Spinal motor outputs that drive respiratory pump muscles are active only during a specific phase of the respiratory cycle (see Fig. 1). The exception is, “postinspiratory after discharge” in the crural diaphragm (370). Phrenic nerve activity in early expiration controls the relaxation of the diaphragm and helps slowing of airflow during early expiration (105). Postinspiratory activity of the diaphragm has been identified in humans, cats, dogs, rabbits, and recently in rodents (76, 105, 174, 282, 370). In contrast to spinal motor neurons, respiratory motor outputs from the cranial nerves often show biphasic discharge patterns. For example, the recurrent laryngeal nerve (RLN) is active during inspiration and post-I

because it is a mixed motor nerve whose different branches innervate either ab- or adductors of the larynx (see Fig. 1). Inspiratory activity in the RLN activates the laryngeal abductors (e.g., posterior cricoarytenoid) decreasing airway resistance during inspiration, while postinspiratory motor discharge activates laryngeal adductor muscles (e.g., thyroarytenoid muscle) (26,102,159). Laryngeal adductor activation narrows the upper airway at the glottis which then reduces expiratory air-flow and counteracts the intrinsic recoil forces exerted by the expanded lung (26, 102). As expiration progresses glottal constriction, via laryngeal adductors, maintains volume and prevents atelectasis (i.e., alveolar collapse). During eupnea, the mechanical acts of inspiration and expiration are controlled by the inspiratory pump (e.g., diaphragm) and laryngeal valvular muscles. Thus, under these conditions expiration is considered to be passive because exhalation is not driven by the activity of expiratory pump muscles. In contrast, active expiration emerges during exercise, during expulsive acts such coughing and sneezing in response to hypoxia and hypercapnia. Conditions of “forced breathing” involve the recruitment and contraction of abdominal and thoracic expiratory muscle groups. In active expiration, air is exhaled in a shorter interval (compared to eupnea), and/or below functional residual capacity of the lung often in combination with an increased tidal volume (see abdominal nerve, Fig. 1). Thus, activity in the expiratory muscles occurs under the conditions of high chemical drive for breathing (3). Depending on the species, drive to abdominal expiratory muscles is reported to be present in eupnea (Fig. 1); however this drive is most likely related to posture and maintenance of intra-abdominal pressure, and hence represents nonrespiratory input to spinal expiratory motor pools (186).

Pontine Control of Breathing: An Overview

The respiratory nuclei at the rostral end of the LRC in the dorsolateral pons are the Kölliker-Fuse nucleus (KF) and adjacent subnuclei of the parabrachial (PB) complex [see Section “The Parabrachial Complex and Kölliker-Fuse Nuclei of the Dorsolateral Pons”]. The second area is the intertrigeminal region (ITR, also termed peritrigeminal region) of the central pons. The connectivity and function of this area that is different to the KF is yet to be explored. Thus, the ITR is only discussed briefly in Section “Intertrigeminal Region of the Mediolateral Pons” of the article. The third area is the noradrenergic A5 (see Section “The A5 Cell Group in the Ventrolateral Pons”) of the caudal pons. Anatomically the most caudal pontine aspect of the LRC is the retrotrapezoidal nucleus at the pontomedullary transition. The current literature refers to a RTN/parafacial respiratory group (RTN/pFRG) that includes rhythmogenic neurons just ventral to facial motor neurons identified in neonates (278). The RTN/pFRG is hypothesized as the main area for generation of expiratory oscillations during eupnea (117, 189, 250) and is shown to have a very prominent role in central chemosensitivity (153, 155, 269, 280). The role of the RTN/pFRG in rhythmogenic mechanism and chemoreception is beyond the scope of this article and hence will be not discussed further. In addition to the nuclei of LRC, the pons also includes other brain nuclei such as the locus coeruleus (11,24,63,224,283,284), pedunculopontine tegmental nuclei which can contribute to adaptation of breathing. Detailing the physiology and anatomical connectivity of these nuclei including the Barrington’s nucleus (pontine micturition center)

would require a separate publication and are reviewed elsewhere (11, 24, 63, 177, 211, 213, 224, 283, 284).

The Parabrachial Complex and Kölliker-Fuse Nuclei of the Dorsolateral Pons

The KF nuclei including adjacent areas of the PB complex are certainly the most investigated pontine part of the LRC. The KF nuclei and the following specific PB nuclei such as the lateral-crescent, extreme-lateral nucleus, external-medial subnuclei of the lateral, and medial PB are considered to be the main respiratory areas of the PB complex. For the reason of simplification, we will refer to the KF-area in the context of respiratory control (Fig. 2). Moreover, the role of KF-area nuclei could vary with species. For instance, the medial PB is seen as a vital component of the pontine “pneumotaxic center” in the cat (34, 66, 395), whereas in rat the medial PB receives major projections from the gustatory NTS (167) and is known for its important role in taste processing and taste aversion (88). The physiologically diverse functions of the KF-area in respiratory control are supported by a complex anatomical framework.

The hallmark respiratory function of the KF-area is the regulation of the inspiratory-expiratory (IE) phase transition and the dynamic control of upper airway patency during the respiratory cycle. The latter particularly involves the control of expiratory airflow patterns. The continuous motor activity that ventilates also integrates other behaviors that use chest wall respiratory muscle and the larynx for vocalizing, sniffing, and coughing. These behaviors are “respiratory” in that airflow is controlled by changing lung volume to alter elastic recoil of the lung or by changing airway resistance in the larynx. Nonrespiratory behaviors such as swallowing or emesis also need to be coordinated with the respiratory motor pattern because both ingestion/emesis and breathing share a common route through the oropharyngeal cavity. Timing mechanisms of respiratory phase resetting, synaptic plasticity, and memory in the KF are critical to behavioral adaptation of respiratory airflow.

Synaptic plasticity is a general property of the nervous system. Brainstem structures express plasticity, for example in response to intermittent hypoxic insults during various stages of development causing long-term facilitation of respiratory motor output. Thus, synaptic plasticity in chemosensory relays such as the NTS or at level of medullary or spinal respiratory motor neuron populations is well investigated (20, 225, 254, 299). However, plasticity in the KF-area circuits reflects plasticity of premotor circuits required for adaptive breathing in response to behavior and emotion. Synaptic plasticity in the pons emerges at time points when the behavioral and emotional repertoires of mammals develop and breathing becomes a behavior. The important role of the pons and also the midbrain in coordinative functions such as feeding, chewing, swallowing, vocalizing, and breathing, is conserved phylogenetically. In amphibians and reptiles, the lower vertebrates, the dorsal midbrain-pons transitional zone plays a key role in controlling breathing pattern (252) as well bird song as an example for a learned motor pattern (330).

The developmental changes observed in the pons and in other brainstem/spinal cord structures related to breathing are linked to genetic and epigenetic regulation of the

formation and function of brain circuits. The combination of genetics and anatomy has helped identifying a variety of neurochemical markers for the specific nuclei of the LRC. The pre-Bötzinger complex, the purported locus for inspiratory rhythm generation, expresses the homeobox gene, *Dbx1*, as a marker for rhythmogenic neurons (49, 145). The primary expiratory oscillator is proposed to be located in RTN/pFRG and is characterized by the expression of the developmental transcription factor Phox2B. In turn, mutation of the Phox2B is linked to congenital central hypoventilation syndrome (CCHS) (Ondine's curse) curse (9, 10). The Phox2B expressing neurons of the RTN/pFRG have significance for controlling abdominal expiratory activity and central chemosensitivity (1, 90, 246, 280, 366). Some of the Phox2b expressing neurons in the neonatal RTN/pFRG may migrate to the A5-area that also expresses Phox2b (for details see Section "The A5 Cell Group in the Ventrolateral Pons") in the adult stage (366), and thus can serve as a genetic marker for caudal pontine LRC. For the other pontine nuclei of the LRC, preliminary data suggest that the developmental transcription factor FoxP2 could be an early developmental marker for the KF-area (144). More recently, the transcription factor Runx1 was suggested to be a selective marker for lateral PB nuclei (411). The potential significances of these transcription factors are further discussed later in the article. Finally, the genetic basis neurodevelopmental and neurodegenerative disease causing breathing disorders that occur after birth or later in children, adolescents, or adults receives special attention. Therefore, the recent evidence implication a role of the pontine respiratory nuclei in neurogenic breathing disorders is also discussed in the article. Finally, KF-area functions related to chemosensory modulation of the breathing pattern and for a variety of nonrespiratory functions are introduced. In particular, the lateral PB nuclei are associated with functions such as blood pressure and thermoregulation that affect breathing as well. The links of the PB nuclei to cardio respiratory coupling is also discussed. Besides its importance in homeostasis, a major role of the lateral PB nuclei relates to pain processing via descending regulation of the sensory gain and ascending projections, which relay pain information to the limbic system. The PB nucleus is also a pivotal center for the regulation of sodium balance (sodium appetite) and central taste pathway. However, these functions are only summarized in a few words at the end of the section.

Afferent and efferent connectivity of the KF-area

The heterogeneity of physiological functions mediated by the KF-area is reflected in its anatomy with topographical organization of specific afferent and efferent connections. Reciprocal tract tracing studies demonstrate that nuclei of the KF-area are major ascending targets of the NTS that receives inputs from various visceral sensory afferents via the vagal and glossopharyngeal nerves (167, 234, 309). The earlier studies of Norgren and Leonard (272) identified gustatory and visceral sensory relays in NTS that then targeted functionally identified PB subnuclei. Later studies of Saper and Loewy (124, 329), underpinned the subnuclear organization of the PB and KF nuclei in rat showing the topographical organization of its afferent and efferent connectivity. Several follow-up tract-tracing studies completed the picture of the complex topography of connections of the PB and KF nuclei with autonomic and limbic brain areas along the neuraxis (167, 257, 258).

The main afferent and efferent connections of the respiratory KF-area are schematically summarized in Figure 2. The KF nuclei have dense descending projections innervating the A5-area, the entire LRC in the medulla oblongata, the NTS, and the nucleus ambiguus (89, 107, 167). The distribution and density of KF descending fibers and terminals in the target nuclei within the caudal pons and medulla oblongata is depicted in Figure 3. The reciprocal anatomical connections of the KF with all other nuclei within the LRC support the KF's role as an integral part of the pontomedullary LRC. In addition to prominent descending projections to the caudal pons and medulla, investigations have identified projections to brainstem motor nuclei such as trigeminal, facial, hypoglossal nuclei, and the nucleus ambiguus (113, 167, 313, 373). In the spinal cord, the KF targets the cervical phrenic motoneurons (124, 313) and spinal motoneurons that supply the intercostal and abdominal respiratory muscles (314). Less dense caudal projections innervate the sympathetic preganglionic cells of the intermediolateral cell column in the thoracic spinal cord (124). Ascending projections of the KF target the lateral hypothalamic area, the lateral preoptic area, and the central nucleus of the amygdala (124, 329), and in particular, the midbrain periaqueductal gray (PAG) (38, 210). In turn, the KF receives somato- and viscerosensory afferent information originating in the NTS, from the spinal trigeminal nuclei and from the upper cervical cord (31, 54, 115, 167). The afferent inputs convey sensory information arising from the upper and lower airways, emphasizing the general importance of the KF for processing afferent information relevant for the adaptation of the breathing pattern. The KF-area also shows strong connectivity with nuclei of the ascending recticular activating system (ARAS) such as the locus coeruleus and medullary raphé nuclei (15, 38, 129–131, 237).

Descending forebrain projections to the KF-area are numerous. In the cat, the motor cortex, red nucleus, bed nucleus of stria terminals, and particularly the PAG are shown to project to the pontine lateral tegmental field that includes PB nuclei and KF (73, 176, 182). In the rat, descending forebrain projections to the KF-area is not well investigated, though reciprocal connectivity of the PB nuclei and KF-area with various cortical and limbic areas has been reported (328). In the rat, the KF-area clearly receives dense input from the PAG (209). Nevertheless, the topography of descending forebrain projections in the rat waits further detailing in the future. Although the role of these descending forebrain and midbrain projections are yet to be explored, they provide a platform for the concept that the KF-area is important for the gating of behavioral or emotional modulation of the breathing pattern within the rCPG circuits (97, 98). However, many of the forebrain-targeted areas in the lateral PB nuclei are largely devoid of projections toward the caudal LRC. Therefore, the unexplored intrinsic pontine connectivity between lateral, medial PB nuclei and the KF could provide a strong anatomical basis for gating higher brain input within the rCPG via intra-PB synaptic interaction.

In summary, retrograde and anterograde tract tracing provide evidence for an anatomical framework of the KF-area to function as an integral part of the LRC. The descending fore-brain inputs to the KF-area and its efferent connectivity with important sensory relay nuclei in brainstem and spinal cord supports the important role of rostral pons in the gating of adaptive breathing during behavior, emotion, and associated homeostasis.

KF-mediated control of inspiratory off-switch: A balance between afferent feedback and intrinsic synaptic mechanisms

The inspiratory off-switch (IOS), results from interplay among sensory feedback from slowly adapting pulmonary stretch receptors, and intrinsic synaptic mechanisms of the rCPG located in the KF-area (Fig. 4). Sensory feedback from the inflated lung arising from pulmonary stretch receptors is termed Breuer-Hering reflex (BHR) after the discoverers (50, 168, 212). The physiological significance of the BHR for IOS was demonstrated in numerous experiments examining the effect of diminishing the vagally mediated stretch receptor feedback with vagotomy (deafferation), cooling of the vagus nerve, preventing lung deflation, as well as mimicking vagal feedback using lung inflation and vagal stimulation. Absence of BHR feedback transforms the breathing pattern leading to a modest prolongation of inspiratory and expiratory phase durations, a significant increase in burst amplitude and a decrease in respiratory frequency (212). This obvious BHR impact on inspiratory phase duration has been confirmed in numerous studies and interpreted as BHR sensory feedback during lung inflation conveys a primary signal to initiate the IOS, and thus controls transition from inspiration to expiration. The role of the KF-area in IOS has almost as long a history as that of BHR. Pontine modulation of IOS was first demonstrated by Marckwald in 1887 (245). Marckwald showed that bilateral lesions of the dorsolateral pons and then subsequent cooling of the vagal nerves can transform the normal breathing pattern into apneusis—a breathing pattern that is characterized by severely prolonged inspiration. These results were later confirmed by Stella (352). Today apneusis after KF-area lesions or transections in vagotomized animals is seen as marker for lack of pontine control and timing of IOS (29,94,104,226,236,245,264,343,356,396). Ironically, Lumsden (236) who coined the term “pontine pneumotaxic center” challenged this interpretation holding that vagotomy was not necessary for apneusis. Other investigations have shown that chronic pneumotaxic lesion in vagi intact animals does not produce apneusis, but merely causes a small increase in the inspiratory duration (134, 362, 363). Nevertheless, a most recent investigation using spontaneously breathing, vagally intact, pontine lesioned goats concluded that KF-area is critical for the generation of eupnea (46). The dependence of the generation of apneusis on both vagotomy and inactivation of the KF-area indicates that vagal afferent input and rostral pontine input act through a common central IOS mechanism involved in the proper timing of IOS and inspiratory/expiratory phase transition (Fig. 4). The concept of vagal and pontine inputs mediating a common inspiratory inhibitory element in the rCPG has persisted through many models of the rCPG (4, 64, 235, 245, 310, 318, 322, 355, 396).

The effect of the KF-area on the medullary rCPG could be either phasic or tonic. Numerous experiments performed during the latter half of the 20th century hypothesized that the KF-area tonically modulates the threshold for IOS mediated in the medullary nuclei of the LRC (395). Curt von Euler’s conceptual model of a pontine modulated IOS by was largely based on the finding that tidal volume required for IOS to reach threshold is decreasing during the progressing inspiratory phase (61). This shows a phasic relation between centrally generated inspiratory activity and BHR feedback. In a subsequent study, lesioning the KF-area in the vagi intact cat caused a significant increase in tidal volume threshold required for BHR reflex evoked IOS, albeit the phasic relationship between central inspiratory activity and BHR remained unchanged (396). From these elegant studies, von Euler concluded that KF-

area provides important tonic excitatory drive for the gating of IOS; however he largely excluded pontine phasic descending inputs to the medullary rCPG as trigger for IOS. Around the same time, important investigations by Morton Cohen showed that phasic pontine activity can be suppressed by BHR acting to disfacilitate rhythmic input to the pons or inhibit pontine activity (66, 116, 118). Accepting these previous data, it appears that phasic BHR feedback is the primary mechanism for the initiation of IOS in an intact organism. However, recent evidence challenges this fundamental principle of respiratory physiology.

The workgroup of Chi-Sang Poon has shown that vagally mediated BHR feedback habituates (241, 342, 348). Habituation is a decrease in response strength to a repeated stimulus. Thus, if the supposedly essential BHR feedback can rapidly decrease in synaptic strength, the pontine mechanisms for IOS must provide phasic information to maintain rhythmic patterning of inspiration and expiration. The possibility of phasic inspiratory inhibitory mechanisms arising from the KF-area is further supported by stimulation experiments. Chemical or electrical stimulation of the KF-area evokes short latency phase resetting and IOS in animals whose vagi are intact (59, 60, 91, 93, 216, 217, 276, 277). A recent study expanded the previous findings of the KF-area and demonstrated that bilateral pharmacological lesion of the KF-area abolished all postinspiratory activity from upper airway motor output (94). According to current understanding, it is not feasible that the generation of a normal three phase motor pattern after vagotomy depends on tonic gating of the vital postinspiratory phase of the respiratory cycle. In all models that describe the formation of the respiratory motor pattern, the generation of the postinspiratory phase depends on phasic synaptic interaction of various types of respiratory neurons (see later). In addition, indirect evidence for phasic synaptic interaction is provided by the presence of phasic respiratory neurons in the KF-area. In 2006, Kazuhisa Ezure reported recording from 235 phasic respiratory neurons in the KF-area in vagi intact rat (111), also see references 239, 341, 359, and 374 for recordings in cats). In vagotomized animals, phasic respiratory activity appears to be even more pronounced (37,81,86,94,266). Direct evidence for an increasing phasic pontine activity after vagotomy was demonstrated in recent studies (86, 319). With the vagi intact pontine neurons express tonic activity with weak respiratory modulation, whereas after vagotomy or in the absence of lung inflation, the strength and consistency of phasic respiratory activities in the KF-area increase significantly. However, despite the existence of strong descending projections these and previous studies have been able to identify only a few monosynaptic connections between pontine and medullary neurons (36, 37, 331, 332). These data may seem to question the existence of strong phasic pontomedullary interaction. However, general experimental procedures, effect of anesthesia (e.g., ketamine as N-Methyl-D-aspartate (NMDA)-receptor antagonist) or methods of artificial ventilation impact significantly on respiratory neuron activity in KF-area. Because of these technical inadequacies, the physiological significance of identified phasic pontomedullary synaptic interactions still remains un-derappreciated. However, the role of KF-area-mediated IOS in reduced quietly breathing animals may not provide an insight into a role of the pons in behaving animals even with the vagi intact (68, 97, 98, 296).

In summary, the IOS is controlled by the interplay of the phasic sensory BHR feedback and phasic synaptic interaction of the KF-area with the rCPG. Nevertheless, other nuclei are

involved in IOS. Injection of the inhibitory neuropeptide somatostatin in the Bötzinger complex (53), blockade of glutamatergic or GABAergic neurotransmission in the NTS (72, 399, 400), or lesion of the caudal vl pons (191) can trigger changes in the breathing pattern from subtle prolongation of inspiration to apneusis. These changes are indicative of disturbed IOS mechanism and identify processing of IOS beyond the sensory-pontine loop. Thus, these studies potentially relate to degeneracy within the respiratory network that describes the ability of structurally distinct elements to generate similar function (249). Network degeneracy also explains why apneusis after KF-area lesion and vagotomy is not permanent because structures outside the primary sensory-pontine loop compensate initial lack of function (375). This important network property for IOS requires further detailing regarding a potential hierarchical organization of brain structures involved in the control of IOS.

Phasic pontomedullary synaptic interaction during inspiratory off-switch and the role of NMDA-receptor-mediated neurotransmission

The electrophysiological analysis of IOS mechanism revealed that late-inspiratory (late-I) neurons initiate IOS and subsequent activation of the post-I neurons completes the transition from inspiration to post-I. The sequential activation of late-I and post-I neurons during IOS is the essence of models of respiratory rhythm and pattern generation (34, 266, 320–322, 343, 344). Although computational models have been developed to explain possible pontine mechanisms (4,318,319,322), very little is known about intrapontine synaptic interactions, biophysical properties of pontine respiratory neurons, and their control over the primary rhythm and pattern generating circuits in the medulla. Extracellular recordings of pontine IE phase spanning neurons, situated within the KF region, support their involvement in the regulation of IOS (111, 239, 341, 359, for review see 68). In particular, data from Cohen and Shaw (2004) indicated that medullary late-I neurons receive excitatory inputs from pontine IE neurons. This shows that pontine and medullary late-I neurons are coupled synaptically providing a framework for the KF-area to control IOS. Intracellular neuronal recordings from the KF-area reveal a variety of phasic respiratory activities (12, 81, 94, 266). The majority of KF respiratory neurons exhibit either early-I (early-I, also termed decrementing inspiratory, I-dec), IE or post-I activities. In particular, the high numbers of IE phase-spanning neurons in the pons is in agreement with data from the cat and the rat *in vivo* (68, 86, 111). Based on the analysis of the membrane trajectories of intracellularly recorded KF neurons, we propose a model for IOS that depends on an *efference copy*. To understand this model, it is important to note that most previous models are almost exclusively based on reciprocal synaptic inhibition and biophysical properties (expression of subsets of ion channels) generating the alternating bursting of respiratory interneurons (310). However, to contract the respiratory muscles the rhythmic bursts of the interneurons have to be transmitted via excitatory premotor neurons to the motoneuron pools. According to more recent models, these excitatory premotor neurons are activity involved in respiratory pattern formation (322). The model for pontine mediated and efference copy-based IOS considers two paradigms. First, the primary motor pattern and rhythm is generated within the medullary LRC. Second, the KF-area has no intrinsic capacity to generate respiratory rhythm. Therefore, the generation of phasic respiratory unit activity in the KF-area depends

on the efference copy of synaptic activity of specific inspiratory units of the medullary rCPG (Fig. 5).

In this model, pontine early-I neurons are inhibitory. Both pontine and medullary early-I neurons receive synaptic drive from inspiratory-driver (I-driver) neurons (Fig. 5). I-driver neurons are neurons with conditional pacemaker properties located within the medullary pre-Botzinger complex (117, 319, 345). The pre-I neurons in integrated network models are considered to be potential I-driver cells (319, 322, 343, 344). However, more likely, the I-driver population reflects neurons providing tonic excitatory drive from peripheral and central chemoreceptors or from the reticular arousal systems. The pontine early-I cells inhibit IE phase spanning neurons and post-I neurons of the pons via local connections during the early stages of inspiration. This connectivity prevents initiation of phase transition during the early inspiratory phase (Fig. 5). With ongoing inspiration, IE neurons receive increasing input drive from excitatory augmenting-inspiratory (aug-I) premotor populations of the medullary rCPG. Both decreasing inhibition from pontine early-I and increasing excitatory drive from aug-I neurons cause onset of firing of the pontine IE cells during mid or late expiration. In turn, IE neurons are excitatory and trigger activation of medullary late-I neurons that initiate the IE phase transition. Late-I neurons deactivate the early-I neurons via synaptic inhibition. This releases inhibitory (interneurons) and excitatory (premotoneurons) post-I neurons from synaptic inhibition provided by the early-I population, reflecting the transition from inspiration to expiration as described in various reviews (34, 110, 310, 311, 344). The pontine and medullary premotor post-I populations are reciprocally coupled via excitatory connectivity. This excitatory coupling of post-I premotor neurons allows for a dynamic regulation of strength and duration of the post-I phase. The present concept for pontine mediated IOS is based on the prediction that pontine neurons receive excitatory synaptic inputs from major neuron populations such as I-driver, augmenting-I, and post-I neurons. In our model, the drive from the medullary inspiratory premotor population is adjusted by a single intrapontine inhibitory synaptic interaction, which shapes the activity pattern of I/E neurons that initiate inspiratory termination (68, 319, 322). This intrapontine connectivity remains to be experimentally verified.

The crucial excitatory inputs to the KF-area required for control of IOS involve glutamatergic neurotransmission via NMDA receptors (NMDA-R). Numerous experiments illustrate that IOS is disrupted after local blockade of NMDA-R in the KF-area or following systemic application of NMDA-R antagonists (34,43,48,71,79,99,120,121,125,127,160,161, 226,266,291–293,355). These findings are consistent with the dense expression of NMDA-Rs in KF neurons (151,207,259). Because NMDA-Rs commonly expressed postsynaptically, it is most likely that local NMDA-R blockade is suppressing glutamatergic input to KF neurons. Thus, local pontine NMDA-R blockade disrupts the postsynaptic processing of phasic excitatory synaptic input provided via the efference copy of medullary inspiratory promoting neurons and aug-I premotor neurons. Without the critical excitatory drive from medullary inspiratory neurons, the pontine IE cells cannot start firing and thus IOS is delayed and consequently the motor pattern reflects apneusis (Fig. 6). Nevertheless, it is remarkable that pharmacological blockade of NMDA-R alone disrupts neurotransmission. Normally, an α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainite receptor-mediated predepolarization is required to remove Mg^{2+} from the pore of NMDA-R

to become active in many neural systems (e.g., hippocampus). NMDA-Rs are heteromeric containing at least two different receptor subunits (74, 261). Recently, it was shown that NMDA-Rs of KF neurons express NR2D subunits (207). The presence of the NR2D subunits allows for rapid membrane depolarization following NMDA-R-mediated glutamatergic neurotransmission without AMPA/kainate-receptor-dependent predepolarization (62). These data imply that neurotransmission involves specialized NMDA-R in the KF-area.

Naturally, NMDA-Rs are not the only receptors in the KF-area. *In situ* hybridization has revealed a multitude of neurotransmitters and receptors in the PB and KF nuclei. The KF has both GABAergic and glycinergic cell populations (166, 402, 408, 409). The noradrenergic A7 cell group also overlaps with the KF. In addition to GABA, glycine, and noradrenalin receptors, various glutamate (AMPA/kainic acid, NMDA, and metabotropic receptors (59, 149–152) and cholinergic and serotonergic (5-HT) receptors are expressed in the PB and KF nuclei (103, 165, 244). Moreover, large subset of neuropeptide transmitters such as neurotensin, cholecystokinin, substance P, somatostatin, and calcitonin gene-related peptide and their associated receptors are also expressed (324–327). However, their role in mediation of IOS is not explored.

Learning to breathe: Lessons from the postnatal maturation of rCPG

In the previous sections, we introduced the theory of a balance between the sensory BHR evoked and KF-area-mediated IOS. BHR feedback from the expanded lung during inspiration initiates IOS via exactly the same mechanism: excitation of late-I and (67, 158, 206, 310, 311) and post-I neurons (157, 163, 310, 311, 322). Consistent with the balance theory KF-area-mediated activation of late-I neurons can be suppressed by BHR feedback. A series of recent studies in the cat using multielectrode arrays to record pontine respiratory activity support this theory (86,319,331). Dependent on homeostasis and general arousal the IOS mechanisms may alternate between BHR and KF-area-regulated IOS in behaving animals. Such a mechanism requires plasticity within the two convergent pathways regulating IOS (Fig. 7). In this way, KF-area pathway would be released from afferent inhibition and mediate IOS when BHR feedback habituates (97,98,240,241,348). In such situation, the rCPG would operate under a pontine-dominated IOS based on the efference copy of inspiratory activity of the rCPG. This functional state of the rCPG would permit adaption of the breathing pattern required for behaviors such as vocalizing or sniffing, etc. (described later). In contrast, during increased synaptic pulmonary stretch receptors (PSR) feedback during high tidal volume (e.g., exercise, hypoxia, and hypercapnia), then the sensory feedback would dominate IOS. In this situation, the KF-area neurons are inhibited (66,116,118) and the IOS is rather determined by the afferent feedback (Fig. 7). In a state of high metabolic demands, reflected in high tidal volume and BHR feedback adapting breathing to suit behavior is decreased due to inhibition of the KF-area. This diminished effectiveness of the pons, for example, may explain the difficulty in talking during intense exercise.

The synaptic mechanisms enabling transition from KF-area to BHR dominated IOS (or vice versa) may fulfill the dual processing theory (148). Donald Hebb in 1949 introduced the

hypothesis that synaptic memory is based on either homosynaptic facilitation or depression. These two forms of synaptic learning were extended to heterosynaptic mechanisms of synaptic facilitation and depression via modulatory interneurons acting at the presynaptic terminals (18). The heterosynaptic strengthening is called sensitization while the decrease of a behavioral (motor) response to repeated stimuli is termed “habituation.” Chi-Sang Poon adapted the dual processing theory, which is broadly used in experimental and clinical physiology and social sciences to describe BHR plasticity (reviewed in reference 296). The dual processing for BHR plasticity is the waning and waxing of habituation and sensitization of IOS within the convergent pathways of BHR and KF-area-mediated IOS. Thus, the reported habituation of BHR input can causing sensitization of the KF-mediated IOS mechanism which then dominates the respiratory pattern formation during eupnea (Fig. 7 and reference 98). The application of the perfused brainstem preparation for investigation of postnatal maturation of the rCPG starts to illuminate the postnatal emergence of synaptic mechanisms underlying the dual processing and associated synaptic plasticity of IOS.

The respiratory network serves a vital function and errors in synaptic organization during development could have fatal consequences. Extensive studies utilizing the perfused brainstem preparation of newborn the rat clearly show the eupneic neuronal rCPG activity is very similar to adults. In particular, glycinergic synaptic inhibition required for network oscillation and respiratory pattern formation is functional immediately after birth (51, 100, 102, 104, 288). Thus, most of the synaptic changes observed during postnatal development of the rCPG are likely to be related to the processing of peripheral sensory information, and behavioral or emotional commands (98). With the first breaths, the neonatal respiratory network must cope immediately sensory feedback that was absent during the embryonic stages development (146). In particular, these include the mechanical feedback from the expanded lung after birth. Moreover, basic survival behavior linked to feeding, pain, and distress are operational as well (128). Beyond doubt, neonates are immediately able to process afferent inputs and many important afferent control mechanisms are fully functional at birth. However, several studies demonstrate changes in reflex responses during ontogeny (13, 97, 99, 141, 285, 377, 379, 381, 398) indicating the postnatal maturation of synaptic pathways integrating respiratory reflexes. Most of these reflex pathways involve the KF-area. The mechanisms of neuronal reorganization of respiratory reflex pathways during ontogeny as well as the underling synaptic mechanisms are not well understood. Presently, developmental changes have been identified in the biophysical properties, histochemical profile, and neurotransmission of with the rCPG circuits and in particular, the NTS. These changes impact the processing of afferent information in the intact rCPG. Predominantly, afferents carrying the arterial chemosensory information have been investigated (see references 28, 39, 55, 142, 201, and 306). Most neonatal breathing disorders, such as “apnea of prematurity” and “sudden infant death syndrome (SIDS),” appear to be associated with an altered chemical drive (202, 286).

A small number of experimental data address the postnatal maturation of the PB and KF-area. Lesion or transection experiments of the PB and KF in *in vivo* and *in situ* preparations suggest that basic pontine mechanisms influencing the respiratory motor pattern are already present at birth (104, 126). Even superfused, neonatal *en bloc* spinal-cord preparations have

strong phasic bursting activity at the level of the KF-area that is modulated with burst of respiratory motor activity (12, 203, 279). The KF has projections to the phrenic motor nucleus and this pathway is established at birth (347) but its functional connectivity with the medullary rCPG has not been investigated. The cytoarchitecture and cell morphology of the PB and KF are substantially immature at birth (97, 205, 207, 220, 233, 308) indicating that the pontine modulation of the breathing pattern requires development in the early postnatal period. The PB complex develops its adult-like cytoarchitecture around postnatal days 12–15 in the rat (97, 208, 308). Approximately the same time as fundamental changes in the molecular composition of neurotransmitter receptors for gamma-aminobutyric acid (GABA), ##AMPA/Kainate (2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl)propanoic acid), Glycine, 5-HT, and neurokinin 1 receptor are reported for the medullary parts of the rCPG (172,228–232,404,405). Detailed investigation of the physiology of these extensive cytochemical changes in rCPG arising naturally two weeks after birth, need to be undertaken. Nevertheless, evidence accumulates that synaptic plasticity associated with BHR and pontine IOS is absent in neonates and does not emerge before postnatal days 12–14 (97–99) (Subramanian et al., Respir Physiol Neurobiol in revision). Thus, in the following paragraph, we specifically focus on the developmental changes of cellular and network plasticity in the BHR pathways (e.g., NTS) and the KF-area controlling IOS.

Several *in vitro* electrophysiological studies have shown that short- and long-term depression (STD and LTD), as a cellular bearing for habituation, were not present in the NTS of neonates (22, 23). These and other synaptic mechanisms obviously require postnatal development in the NTS (22, 23, 44, 77, 143, 275, 389, 390, 410). However, at early neonatal stages synaptic plasticity could be “unwarranted” developmentally, because the processing of unchanged sensory signals is required for physiological maturation of the developing circuits. For instance, BHR feedback is of major importance for the stabilization and maintenance of the eupneic respiratory motor pattern. Diminished or complete absence of BHR input has been shown to be life threatening for neonates (114,267,301). In a study using a NMDA-R subunit knockout mouse, an anomalous neonatal form of LTD was expressed as a cellular correlate for habituation. The neonatal form of LTD induced by the genetic manipulation triggered respiratory depression and premature death of the animals (297). Physiological studies on BHR development show that in maturing rats habituation of the BHR does not occur before postnatal days 13–15 (Subramanian et al., Respir Physiol Neurobiol in revision). HBR habituation in this study was investigated using stimulation of vagal nerve afferents to mimic the HBR inflation-withhold reflex causing a stimulus-dependent prolongation of the expiratory phase that diminished with repeated stimuli only in the juvenile animal. In accordance with the cellular findings of physiological absence of STD and LTD neonates displayed stereotyped processing of BHR feedback. Since BHR feedback is not restricted to a single breath, but is linked to rhythmic expansion of the lungs during each inspiration, a second study investigated the developmental changes in the motor response to rhythmic BHR feedback stimulation. This study showed that repetitive presentation of a rhythmic vagal stimuli or lung inflation in the perfused brainstem preparation can trigger learning and recall of respiratory patterns in juvenile, but not in neonatal rats (99). The stimulation protocol is illustrated in Figure 8A. In neonates, immediate and stereotyped 1:1 entrainment occurred during repetitive simulation trails. IOS

was triggered stereotypically by onset of stimulation trains in the late-I phase. The finding that neonatal breathing activity spontaneously aligns to the vagal IOS during the late-I phase underpins the physiological significance of the BHR in neonates (Fig. 8B). The initial stimulation trials in the juvenile rat were different, and yielded irregular 1:1 entrainment. Many of the rhythmic stimulation trains completely suppressed phrenic activity and produced skipped breaths. With repeated presentation of the stimuli the 1:1 entrainment emerged. Different to neonates the 1:1 entrainment was characterized by anticipatory IOS before the onset of an individual stimulus train which indicates the sensory signal for IOS (Fig. 8C). The occurrence of the anticipatory IOS provides the evidence that a given pattern of afferent IOS signals can be learned because breathing still entrains to the pattern and frequency of the applied sensory stimulation. Consistent with previous data the observed learning of the vagal feedback pattern perfectly coincides with the postnatal emergence of BHR habituation that triggers the release of the KF-mediated IOS from BHR-mediated synaptic inhibition (66, 118). In subsequent experiments, this scenario was further verified by showing that bilateral blockade of NMDA-R in KF-area completely prevented anticipatory IOS. In addition, following NMDA-R blockade an immediate and stereotyped 1:1 entrainment was observed which remained unchanged during repetitive stimulation, as it was seen in neonates that have an immature KF-area (99). Therefore, our studies not only provides proof that the anticipatory IOS is mediated by the KF-area but also strongly suggests that glutamatergic neurotransmission via NMDA-R in the KF-area is important for synaptic mechanisms underlying learning and memory in breathing.

The analysis of the expression profile of NMDA-R subunits revealed a strong developmental upregulation of the NR2D subunit in the KF. The characteristics of NMDA-currents in the KF match the expression of the NR2D subunit (207, see previous section). The NR2D-dependent NMDA-currents subunit had a reduced Mg^{2+} block (14) accompanied by low baseline conductance, long deactivation kinetics, and a lack of desensitization (74). The long deactivation kinetics of NR2D-mediated NMDA-current can produce a continuous background current (385). Such a continuous background current could promote learning of breathing patterns associated with multiple respiratory cycles (207). Besides the general characteristics of NMDA-currents the associated Ca^{2+} influx is an essential trigger for various intracellular signaling cascades linked to short- and long-term changes in membrane excitability and conductance of a postsynaptic neuron. These changes are prerequisite for learning and memory. In various forms of synaptic plasticity, the NMDA-R-dependent Ca^{2+} conductance is modified by the release of neuromodulators. Amongst various potential neuromodulators potentially contributing to synaptic plasticity in the KF-area only brain-derived neurotrophic factor (BDNF) has been investigated (205–208). It has been demonstrated that BDNF-application provoked a progressive, protein-kinase-C-dependent potentiation of NMDA-current in KF neurons (207). BDNF induced short-term potentiation was present in juvenile animals and was absent in neonates. The BNDF-mediated NMDA-current potentiation correlates with the developmental time window for anticipatory IOS and HBR habituation. These cellular findings support the working hypothesis that NMDA-R-dependent neurotransmission in the KF-area is not only linked to IOS but the same synapses are also associated with learning and memory of breathing patterns.

The course of the postnatal maturation of synaptic function in the KF-area is coincident with an increasing behavioral and emotional repertoire of the developing mammal. Because most developmental studies are performed in rodent models, it is important to remember that rats and mice do not see and hear until postnatal day 10–12. With these sensory systems functional, the exploratory behavior increases dramatically and subsequently the rCPG has to cope with rapid changes from eupneic to adaptive breathing linked to behaviors such as foraging and other explorative behaviors like sniffing (see Fig. 9) as well as basic emotions (e.g., fear and anxiety—flight or fight response). The dexterity of changes in the breathing patterns in behaving animals implies that learning is required to adjust respiratory control (98) to changing internal and external states to maintain homeostasis and survival (128, 371).

KF-area mediation of protective airway reflexes and upper (non) respiratory behavior such as swallowing and vocalizing

Most protective reflexes are expiratory (e.g., sneeze, cough, sensory apnea, etc.) and at the least require initially postinspiratory mediated glottal closure. The physiological significance of this is twofold. First, glottal closure protects the lower airways from aspiration (42,101,287,307) and second abdominal muscle contraction against the closed upper airway valve generates high abdominal and thoracic pressure required for compulsory reflexes and behavior (27,300,333–335,338,339).

The KF-area mediates the post-I apnea elicited by noxious stimulation of the nasal or laryngeal mucosa (91–93, 255), as well as during upper airway reflex such as sneezing (215, 247, 397) and coughing (136, 188, 294, 336, 337). Nevertheless, the important role of the KF-area in orchestration of almost all airway reflexes is consistent with data showing that excitatory postinspiratory premotor neurons of the KF control the ambiguual motoneurons that mediate glottal constriction (94). In our model for the pontomedullary synaptic interaction, descending excitatory input to inhibitory post-I neurons allows the pons to directly switch to post-I phase and activate post-I motor activity irrespective of other pontomedullary interactions (Fig. 5C). Moreover, in the medulla oblongata, post-I laryngeal motoneurons have been classified as multifunctional neurons (338,339). In this context, specific activation patterns of the laryngeal adductor motor neurons could process input from multifunctional premotor neurons that initiate oral behavior and reflexes. Taken the physiological and anatomical evidence into consideration, it is likely that a major population of these multifunctional premotor neurons is located in the KF-area (see reference 97).

The anatomical connectivity and physiological significance of the KF-area in the control of upper airway muscles also provides the platform for the mediation of upper airway related nonrespiratory behavior such as swallowing and vocalizing. During swallowing, laryngeal adductor activation is important to prevent aspiration during ingestion (35, 137, 138, 289). In addition to the essential prevention of aspiration, swallowing is also linked to tongue movement. The hypoglossal motor pool, which controls tongue movement, receives a strong modulatory input from the KF-area (47, 95, 137, 214). Thus, pontine descending inputs to the medullary hypoglossal motor and premotor pools are also potentially involved in the coordination of swallowing and breathing (35, 137). A recent study using chronic lesion of

the KF-area indeed reveal a strong modulatory influence of the KF-area for coordination of breathing and swallowing in the awake goat (47).

The biological significance of the KF-area in the mediation of multimodal afferent inputs involves the adaptation and modulation of breathing to behavior. Amongst various behaviors, vocalization is linked closely to primary motor circuits of breathing. However, most experimental data regarding vocal control circuits originated from the cat, in which the synaptic pathway for vocalization (25,175,178,368,413) and breathing (34, 310, 395) are fairly well characterized. Non-human primates have also been used for the understanding of vocalization generated in midbrain and forebrain areas (194, 196, 219, 382). In contrast, in the rat neural mechanisms of vocalization remain uncharacterized. Therefore, at the present stage, we are forced to make models based on experimental studies derived from the several species.

Vocalization in non-human primates and cats involves an innate vocal pattern attached to emotions and very elementary intraspecies communication. In cats, the innate vocal pattern can be elicited upon chemical stimulation of specific areas of the PAG (25,368,369,413). The PAG, which acts as a critical relay of the limbic system (176) represent the final common pathway for vocalization in mammals (175,369). Vocalization can be considered to be the most complex motor behavior in mammals since it requires a highly coordinated activation of laryngeal, thoracic, and abdominal muscles. Many of these muscles are accessory respiratory muscles and thus are arbitrated by the rCPG. However, it is not understood how synaptic signals arising from the PAG or other forebrain structures are integrated within the rCPG. It is known that laryngeal and abdominal pathways for vocalization are organized through the nucleus retroambiguus (NRA) (369,412). The NRA can be considered as the caudal part of the LRC as many respiratory related neurons (251) have been recorded and perturbation to the NRA causes disruption of eupnea (369). However, since post-I laryngeal adductor activation mediates vocal fold tensioning, the KF-area could be involved in adapting timing and duration of inspiration (via IOS) and expiration (via post-I regulation) for sound modulation. Thus, the KF-area could serve a critical role in reorganizing rCPG-derived eupnea into a vocal breathing pattern. The dense reciprocal connectivity of the vl column of the PAG and the KF-area provides the anatomical structure (38,209,210) to this hypothesis (Fig. 10). Physiological evidence is provided by a report that showed that during the conditioned vocalizations neurons in the KF-area in the cat change their activity (112). Recently, experiments on vocalization in the bat demonstrated a mandatory role for the KF-area in sound production (346). Bats like rodents have a similar vocal pattern in the ultrasonic spectrum, and thus it can be hypothesized that the KF in rat may be involved in vocalization too. In the cat and non-human primate experimental evidence suggests that the final conversion of the breathing pattern to a vocal pattern required laryngeal premotor populations of the NRA (195, 197, 238, 369). The NRA receives strong descending projections from the KF (135, 179) and in turn gets activated by KF stimulation (19). According to the final common pathway for vocalization (175, 369), the PAG-NRA pathway is critical for the production of sound. However, for conveyance of emotions, the sound itself needs to be modulated. The modulation of sound is dependent on the timing of inspiratory and expiratory activity, fine motor control of the upper airways and the diaphragm and sensorimotor integration of

homeostatic and vagal feedbacks. In this regard, the PAG-KF pathway could play a vital role.

Interestingly, Foxp2, a transcription factor directly linked to the development of speech (119, 383), appeared to be a selective marker for KF neurons in the developing rCPG (144). Thus, the function of the KF-area within the rCPG is also seen in the coupling of respiration to vocal behavior. However, this role of the KF-area requires future investigation.

KF-area and neurogenic breathing disorders

Studies of breathing dysfunction and the underlying synaptic pathomechanisms in the rCPG can be investigated in a number of genetically engineered animal models (132). Here, we summarize the role of the KF-area and associated pontomedullary synaptic interactions in transgenic mouse strains designed to mimic human neurological diseases.

The KF-area is explicitly identified to contribute to breathing disorders in a mouse model for a neurodevelopmental disease called Rett-syndrome (RTT). The genetic cause and neurological disorder in RTT are reviewed elsewhere (56) and detailed information on synaptic mechanisms contributing to breathing disorders in RTT can be found in references 200 and 227. In brief, RTT is an X-linked neurologic disease associated with breathing abnormalities and severe mental retardation in females. Gene mutations or gene deletions in the *MECP2* gene located on Xq28 have been identified as cause of the disease. The clinical course of RTT is characterized by a regression period, which occurs between 1 and 3 years of age accompanied by state-dependent breathing abnormalities. Respiratory disturbances during wakefulness comprise alternating periods of hyperventilation and apneusis, breath holding frequently terminated by Valsalva's maneuvers and forced and deep breathing. *Mecp2*$^{-/y}$ knockout mice develop an RTT-like respiratory disorder approximately 3–4 weeks after birth (388). The breathing disorders observed after the equivalent regression period in mice involve, impaired responses to hypoxia, hypercapnia (392), altered postsigh breathing activity (393), and pronounced breath hold accompanied by glottal closure (391). In the perfused brainstem preparation, the control of post-I activity was impaired and this impairment involved both KF-area and BHR circuits for IOS (353). Indeed, the synaptic impairment of the major control circuitry for the post-I phase correlated highly to the upper airway related neurological deficits observed in RTT patients such as apneas with laryngeal closure, loss of vocalization, and weak coordination of swallowing with breathing (2, 200, 227, 354). A detailed investigation of the breathing dysfunction in RTT not only revealed a potential synaptic impairment within the KF but, more importantly, a lack of plasticity during NTS/KF dependent processing of BHR (353). The delayed onsets of breathing disorders in both, RTT patients and the *Mecp2*$^{-/y}$ KO mouse correlate with the developmental changes in the KF-area (and elsewhere in rCPG) related to synaptic plasticity particularly required for coordinating breathing and vocalization. Therefore, genetic factors specifically involved in the maturation of synaptic plasticity in the rCPG, and in particular the KF-area can be linked to neurogenic breathing disorders in RTT.

Besides RTT, the pathology within the KF-area has implications in SIDS. Postmortem examination of infants reveals significant changes in histology including alterations in the neurochemical profile of the KF-area (221–223, 253). The abnormality of KF-area to as a

cause for SIDS remains unexplored. However, it is consistent with the mainstream hypothesis (202, 286) that, breathing failure in SIDS may involve pathophysiological changes in the serotonergic modulation of the pontine circuitry. This serotonergic modulation is provided by the interaction of medullary raphé and KF-area (172, 274).

Recent experimental evidence corroborates the KF-area to upper-airway dysfunction in neurodegenerative diseases associated with dementia. Neurodegenerative diseases, such as Alzheimer's disease are inherently associated with tauopathy. In turn, tauopathy manifests postmortem as neurofibrillary tangles and neuropil treads. Hyperphosphorylation of the microtubule associated protein tau causes tauopathy and abnormal intracellular aggregation and is evident as accumulation of Tau protein. Investigation of the transgenic mouse model P.301L expressing tauopathy at 7–8 months of age, reveal reduced post-I discharge of laryngeal motor activity (96). With high chemical drive (hypercapnia), post-I discharge is nearly absent. *In vivo* data support the hypothesis that KF-area tauopathy shifts the post-I laryngeal constrictor activity toward inspiration. This potential post-I shift has caused a significant increase in inspiratory resistive load due to glottal constriction during inspiration. Although upper airway dysfunction is not directly linked to death in dementia patients, it would be a factor for the associated vocalization disorders [e.g., primary progressive aphasia (315)], impaired swallowing and aspiration reflexes in these patients (185). Histological analysis of postmortem brains of dementia patients revealed severe tauopathy in the KF-area (317) supporting synaptic dysfunction of the pontine control of upper airway activity. Thus, KF-area dysfunction contributes to neurodegenerative disorders that involve modulation of the breathing pattern during oropharyngeal behaviors. Similar, KF-area dysfunction was also observed in transgenic mouse model of tauopathy (96). The strong overlap of tauopathy in the KF-area and the PAG as the main output relay for the limbic system (178), implies that breathing dysfunction in neurodegenerative disease are linked to the emotional and behavioral respiratory control (see previous paragraph and Fig. 10).

In summary, we conclude that pathophysiological changes involving the KF-area and PAG circuits are closely associated with breathing dysfunctions. These sustained breathing disorders have been identified within dementia (neurodegenerative) and autism spectrum diseases (neurodevelopmental). Neuropharmacological therapy for such breathing dysfunction requires an increasing understanding of the importance of midbrain-pontine interactions.

The role of the KF-area in chemical control of breathing

The KF-area receives strong projection from the carotid body afferent relays within the NTS (167), and from the RTN/pFRG (316). This anatomical connection implies a physiological role of the KF-area in the adaptation of breathing in response to activation of central or arterial chemoreceptors. Lesioning and recording studies show direct evidence that the KF-area is involved in mediating the magnitude of the arterial chemoreceptor reflex (204, 256, 273, 323). Several investigations using the immediate early gene c-Fos as a marker of neural activity have revealed strong activation of the KF-area during hypoxia, hypercapnia or carotid sinus nerve stimulation (32, 40, 108, 173, 218, 378). In the cat and the rats, bilateral lesions of the KF-area attenuated increases in respiratory minute volume during hypoxic or

hypercapnic challenges (256, 323, 364). But discrete lesions in the lateral PB nuclei within the KF-area prevent the shortening of the expiratory phase that is associated with the increase in respiratory frequency in response to hypoxia and hypercapnia (349, 350). Thus, perhaps the interaction between pontine and medullary networks contributes to respiratory frequency responses during hypoxia and hypercapnia. A potential interaction between dorsolateral pons and the caudal vl A5 region is discussed in section “The A5 Cell Group in the Ventrolateral Pons.” Finally, the processing of chemosensory information in the KF-area is also of importance during the mediation of adaptive breathing behavior to maintain and control homeostasis.

The role of the KF-area in the modulation of breathing across the sleep/wake cycle

Breathing displays distinct changes during sleep and wake-fulness (281, 282). Early studies report that chronic lesion of the KF-area in the cat change the respiratory pattern and rhythm during sleep states (21, 45, 134, 357, 360, 361). Subsequent vagotomy in these same cats exacerbated breathing instability and resulted in apneusis during rapid eye movement (REM)-sleep (21). Pontine respiratory-modulated neurons modulate their discharge pattern to arousal state alteration, specifically with a significant decrease in activity during REM-sleep (239,340). This general pattern also occurred in a Carbachol (mixed cholinergic agonist) induced REM-sleep-like state (139,140). Furthermore, the discharge frequency of expiratory modulated neuron activity was decreased considerably more compared to inspiratory unit activity (139, 140). However, tonic or weakly modulated respiratory neurons in the KF-area show heterogeneous effects, and are either activated or deactivated following Carbachol induced REM-sleep like states or during natural REM sleep (139, 140).

Unfortunately, the potential role of KF-area in sleep-related respiratory disorders, specifically obstructive or central sleep apnea is not clear. Considering that the KF-area excites upper airway motor neurons responsible for maintenance of upper airway patency (94,95,137,214,216), it would be likely that a decrease in discharge of the KF-area activity could contribute to development of upper airway atonia. Consequently, disfacilitation of upper airway activity could contribute to decreased upper airway muscle tone and obstructive sleep apnea. The reported decrease in discharge activity of expiratory units as well as the decrease in the activity of tonic KF-area units during REM-sleep could be effectively linked to the decrease in upper airway tone during REM-sleep. This may play a key role in the pathologically reduced airway patency contributing to obstructive REM-sleep apnea, in a variety of clinical settings.

The role of parabrachial and KF nuclei in the cardiovascular-respiratory coupling

Apart from their role in breathing control the PB and KF nuclei are implicated in cardiovascular regulation. This is consistent with the fact that cardiovascular and respiratory regulations are coupled (e.g., cardiac vagal, sympathetic, and phrenic activity patterns have common frequency components). This is also consistent with the strong anatomical supposition of respiratory and cardiovascular neural networks in the brainstem (75,156,268,376). In the following section, we briefly introduce the potential role of the PB and KF nuclei in cardiovascular-respiratory coupling.

Cardiovascular and respiratory activities are inherently rhythmic. Cardiovascular-respiratory coupling refers not only to the influence of respiratory activity on heartbeat (380) and sympathetic nerve activity (5) but also to the expression of the arterial-pulse pressure on respiratory activity (84, 85). Thus, cardiovascular-respiratory coupling has been shown to be reciprocal (75,80). Cardiovascular-respiratory coupling may serve systemic homeostasis by coordinating blood flow and blood gasses for optimal efficiency. Gas exchange as an integrated function is akin to studying effectors of heart rate and vascular resistance for the cardiovascular system or blood gasses and lung volume for the respiratory system.

In each respiratory cycle, the heart rate increases during inspiration, which is referred to as respiratory sinus arrhythmia, while sympathetic nerve activity increases during post-I. This coupling depends on both reflex and central mechanisms (106, 193, 198, 199), although the discrete mechanisms involved are still controversial. A central neural mechanism is evident that a sinus arrhythmia can be identified in the *in situ* preparation in which rhythmic sensory (including vagal, chemo-, and baroreceptors) inputs are blocked (17, 80). Furthermore, after dorsolateral pontine transection or bilateral lesion in the dorsolateral pons, the respiratory modulation of heart rate and of sympathetic nerve activity is attenuated (17, 263, 264). Thus, coupling, at the least, the respiratory modulated rhythm in the heart rate and in the sympathetic nerve is modulated by the pons.

Parabrachial complex-mediated modulation of breathing during pain

The lateral nuclei subnuclei of the PB complex receive both second- and higher order relay neurons for nociceptive sensory information (30, 52, 133, 190, 403). Nociceptive stimuli trigger the profound alterations in cardiorespiratory functions such as apnea/tachypnea, tachycardia/bradycardia, and rise or fall in arterial blood pressure associated with nociceptive stimuli. The specific cardiorespiratory responses depend on the strength and source of input. The PB complex plays a role in mediating these cardiorespiratory responses. Moreover, chemical stimulation of the lateral PB nuclei (59, 60, 93, 94, 216, 217, 276) may be associated directly with the processing of pain. However, so far, only a single study provides evidence that the lateral crescent PB nucleus links nociception and breathing (190). Thus, the lateral PB complex may be specifically involved in mediating the respiratory response to nociceptive stimuli.

Brief summary of additional physiological functions associated with the PB complex

The PB complex is an important relay of the central taste pathway. Particularly, nuclei of caudal PB complex relay gustatory information from the rostral nucleus of NTS to the ventrobasal nucleus of the thalamus (272). Another related role of PB nuclei is the regulation of water and sodium intake (248). In general, forebrain limbic and reward systems receive ingestion-taste-related information via the PB nuclei [for review see references 88 and 407)]. An elegant recent study showed that transgenic inactivation of GABA synthesis in the arcuate nucleus caused a loss of GABAergic signaling to the PB nucleus that resulted in voluntary starvation of the animals (406). Moreover, of particular importance is the role of PB complex in conditioned taste aversion as a propensity of learning and memory (401). The role in taste aversion underlines the role of PB complex in the expression of learned behavior (407). In addition to taste and ingestion, other related

systems are influenced by PB nuclei. The lateral PB nuclei have been implicated in thermoregulation (265, 271). The potential role of lateral PB nuclei in respiratory-thermoregulatory interaction during exercise was recently discussed but still requires experimental evidence (295). Furthermore, neurons in the KF-area are involved in defecation (122, 123, 186). Stimulation of the KF-area can also elicit sustained and rhythmic straining behavior in the decerebrate dog (122, 123). The involvement of the PB complex in straining behavior is supported by dense projections to the Barrington's nucleus, which is commonly referred to as the pontine micturition center, located in the dorsolateral pontine tegmentum (177). Finally, lesions of PB nuclei accelerate incisor growth in Long-Evans rats (270), while stimulation of the PB nuclei also evokes salivation in cats (83).

Intertrigeminal Region of the Mediolateral Pons

The ITR, also defined as peritrigeminal region, lies between the principal sensory and motor trigeminal nuclei and interconnects the rostral dorsolateral and the caudal vl pontine respiratory nuclei. Glutamate microinjected into the ITR consistently triggers brief apnea which indicates that this nucleus is an "expiratory-facilitatory" area (57, 60). Similar to the KF-area the ITR possesses reciprocal connectivity with the medullary LRC and brainstem motor nuclei (180, 181). In addition, the ITR receives synaptic input from the NTS and spinal trigeminal nuclei. A more recent study has identified anatomical connectivity connection between the ITR and the medullary raphé nuclei (384). All three of these sites, NTS, spinal trigeminal and raphé nuclei, are associated with sensory apnea; therefore, the ITR may be involved in mediating apnea. Apnea evoked by glutamate injections in the ITR could be blocked by injection of glutamate receptor antagonist (303–305). NMDA-R blockade completely abolished, while AMPA-receptor antagonism only partially attenuates the glutamate-evoked apnea (187). Furthermore, AMPA-receptor blockade did not affect vagally mediated reflex apnea induced by intravenous infusion of serotonin (187), while pharmacological blockade of metabotropic glutamate receptors exacerbated apneic responses to intravenous serotonin (365). Thus, functional apneic responses from the ITR may be mediated via NMDA-R, which are reported to be densely expressed in this pontine brain region (151). Yet, ironically unilateral lesioning of the ITR region increases the incidence of sleep apnea (302).

The ventral tip of the KF has also been identified as an apneic site (59, 60, 93, 94). Therefore, the close proximity of these structures hinders distinguishing the physiological exclusivity of the ventral parts of KF and ITR. Mapping the dorsolateral and mediolateral pons with glutamate injection provides some evidence that KF stimulation triggers a post-I protective apnea associated with strong laryngeal constriction, while the apnea evoked from the ITR region appears to occur without laryngeal constriction (94). If ITR and KF mediate functionally different types of apnea then this would provide insight into the mechanism of apnea.

The A5 Cell Group in the Ventrolateral Pons

The A5 cell group in the vl pons contains both noradrenergic and glutamatergic neurons that modulate cardiovascular and respiratory function. Anatomical studies revealed that vl pons

project caudally to the medullary cardiorespiratory centers and to the sympathetic premotor neurons in the spinal cord (6–8). However, the role of the vl pons may be species specific, because of the known differences between the rat and the cat, the two primary models studied in cardiorespiratory control. Furthermore, the anatomy of the vl pons has not been well defined into subnuclei as in the case of the PB complex. The A5 neurons, the primary structure to which the actions of the vl pons are attributed is a distributed cluster group of neurons. For the purposes of this review, we focus on the A5-area because it projects directly to the rostral ventral respiratory group and that it was well integrated in the LRC (6–8). With regards to respiratory control, vl pons like the dl pons interacts with BHR inputs to determine respiratory phase duration. Thus, these pontine areas may have interconnections (351).

A role for the vl pons in cardiovascular regulation was identified prior to its potential role in respiratory control. Retrograde labeling studies demonstrate that the noradrenaline-containing neurons of the A5 cell group project directly to the preganglionic sympathetic neurons (54). Stimulation of A5 neurons with glutamate revealed differential control of blood flow in both anesthetized rat and dog and in the unanesthetized rabbit (87,183,243). Specifically, A5-area activation increases splanchnic and renal nerve activity but usually decreases lumbar sympathetic nerve activity (87,183,243). However, blocking A5 activity with injections of muscimol does not affect resting renal sympathetic nerve activity in the unanesthetized rabbit (242). Recording A5 neurons identified via antidromic activation of their axons in the spinal cord and by its complete inactivation following systemic injections of clonidine indicates that these cells have a respiratory (post-I)-modulated activity pattern (154,184). Although many bulbo-spinal sympathetic neurons express respiratory-modulated activity, this type of activity indicates a potential role for the vl pons in respiratory as well as sympathetic control.

Subsequent studies provided extensive evidence on the vl pons modulated respiration in the rat. While bilateral electrolytic lesions in vl pons cause apneusis, experiments that involve bilateral injections of muscimol ($GABA_A$-receptor agonist) only slightly prolongs inspiration. It is to be noted that the prolongation of inspiratory duration (Ti) does not result in the profound apneusis that followed similar dl pontine intervention (191). However, as observed for the KF-area, stimulating the vagi reverses the apneusis (191) and in spontaneously breathing rats baseline-breathing patterns are also altered only slightly following vl pontine interventions in the vagi intact rat (69, 82). Activation of neurons in the vl pons with glutamate prolongs expiratory duration (Te) (192). It appears that like KF-area, ITR is also primarily an expiratory-facilitatory area. Thus, this vl pons may be interpreted as a ventrocaudal extension of the expiratory-facilitatory areas. Recording revealed respiratory modulated activity particularly post-I and E activity. These activities are responsive to hypoxia (82, 154). The expiratory-facilitatory effect evoked by stimulation of the vl pons is consistent with the recording of expiratory-modulated activity within.

The expiratory-facilitatory role of the vl pons becomes physiologically evident in the dynamic regulation of breathing during and following brief hypoxic episodes. The changes in the respiratory pattern during hypoxia depend on numerous factors including the age of the animals and the severity of the hypoxic episode, that is, the partial pressure of the

oxygen and the duration of the exposure (298). Briefly, during severe hypoxia respiratory frequency increases rapidly and then begins to slow. If the exposure persists then breathing will stop and gasping occurs. If the hypoxic exposure is stopped, breathing frequency will drop below normal and slowly return to normal. The drop in breathing frequency is referred to as posthypoxic frequency decline. Interestingly, these changes in respiratory frequency originate from the neural network rather than a result of metabolic demands because they have been observed during and following carotid sinus nerve stimulation under hyperoxic conditions also (162). The amplitude of the motor activity however follows a different course. Amplitudes increase to an asymptote and after hypoxia decreases to baseline. In the rat, both the dl and vl pons have a role in mediating the changes in respiratory frequency during and following hypoxia.

As discussed in Section “Intertrigeminal Region of the Mediolateral Pons,” in the cat, a facilitatory role has been identified for the PB complex (358). In rat, the facilitatory role of the vl pons differs from that of the KF-area. Even though bilateral interventions in either KF-area or vl pons results in a significant decrease in baseline respiratory frequency, specific elements in response to hypoxia can be affected differentially. When rats with bilateral lesions of the lateral external nucleus of the PB complex are exposed to hypoxia, expiratory duration does not decrease during hypoxia (350). The change in Te was the only alteration in the hypoxic response; Ti decreased during hypoxia and Te prolonged following hypoxia just as before the interventions (350). In contrast, when rats with bilateral vl pontine interventions were exposed to hypoxia, Ti and Te decreased with no changes in peak respiratory frequency. However, Te does not decrease after hypoxia (69,82). Thus, even though normal breathing pattern was altered following vl pontine lesions, the acute response remains during hypoxia and only the posthypoxic pattern is altered (69, 82). These data raise the possibility that interaction between the KF-area and vl pons is critical for the mediation of breathing changes in hypoxia.

Recordings show that vl pontine neurons respond to hypoxia. Further, this activity may arise from A5 neurons (204). First, selective lesioning of the noradrenergic neurons with the toxin 6-hydroxydopamine (6-OHDA) in the vl pons attenuated the sympathetic chemoreflex to the same extent as muscimol in the vl pons. Thus, neurons in the vl pons are activated during hypoxia and continue to remain activated. Expiratory neurons in the A5 region fit this profile. Their activity correlates with prolongations in Te during and following hypoxia.

Noradrenergic neurotransmission may mediate the Te prolongation associated with post hypoxic frequency decline after brief hypoxia. Noradrenaline has been demonstrated to be produced and released by A5 neurons, and activation of α2-adrenergic receptors modulates Te (41, 164). In addition, with an *en bloc in vitro* neonatal rat brainstem-spinal cord preparation, bath application of α2-antagonists increased burst frequency (170, 171). The decrease in respiratory frequency following hypoxia was not consistently blocked after administration of α2-antagonists (16,70). These data although nonlinear, do support the general working hypothesis that the vl pons acting via A5 neurons modulate breathing.

Noradrenaline function and dysfunction in breathing

In the last 25 years, the use of preparations, which are tractable to experiments in neonatal rodent models and identifying specific gene deficits that are associated with aberrant respiratory patterns, have revealed the role f the vl pons in generating a stable breathing pattern.

The *en bloc* preparation developed in the 1980s is a super-fused *in vitro* preparation consisting of the brainstem spinal cord (372). The phrenic bursts produced in this preparation are dependent on the integrity of the pontomedullary circuitry. The bursting frequency increased when the pons was removed (109). The increased rate resulted from removing a noradrenergic input located in the pons, specifically the A5 neurons in the vl pons. However, even prior to that, it was evident that action of noradrenaline was complex, with the ability to increase or decrease respiratory rate depending on the site of action (pons or medulla, dorsal or ventral, and α1- or α2-receptors) (109, 386, 387). The *en bloc* preparation indicates that the breathing pattern was modulated by pontine noradrenergic neurons even in prenatal preparations.

Subsequent work on genetic “knockouts” shows the importance of pontine noradrenaline neurons in the development of the respiratory control network (169). The HASH-1-PHOX2A-PHOX2B developmental cascade differentially controls the development of neurons Locus Coeruleus (PHOX2A), A5-area (PHOX2B), and other brainstem catecholaminergic cells with a definitive or transient noradrenaline phenotype (10, 78). Initially, mutations in the *PHOX2* and *MECP2* (discussed earlier) genes were thought to primarily affect noradrenaline-expressing neurons. Thus, a noradrenaline connection was thought to underlie the disorderly breathing patterns associated with severe respiratory disturbances such as SIDS (169), CCHS, and Rett syndrome (78). However, recent studies showed that the RTN/pFRG is perhaps the more directly affected system. Indeed, ablation of catecholamine-containing neurons (with saporin conjugated to dopamine-beta-hydroxylase) decreases breathing frequency and chemoresponsiveness in adult animals after development of the respiratory control system, but in these animals breathing arrest did not take place during sleep (224).

CCHS results from polyalanine repeat expansion mutations in the paired-like homeobox *(PHOX)2B* gene in more than 90% of cases. CCHS is characterized by sleep apnea attributed to decreased chemoreflex excitatory drive (33). However, despite the association of Phox2b with catecholaminergic neurons, in the adult rat Phox2b is not expressed in pontine noradrenaline cell groups but rather in medullary neurons involved in chemosensation directly (366). Indeed, mice with mutations like the humans (with polyalanine repeat expansion (Phox2b27Ala/+) lack Phox2b-expressing glutamatergic neurons in the parafacial region of the ventral medulla and die soon after birth from central apnea (90).

Conclusion

Compared to the rhythmogenic medullary respiratory circuits, research on pontine nuclei that shape and modulate the eupneic respiratory rhythm and pattern, still remains largely

uninvestigated. Here, we aimed to underline the physiological significance for a pontine mediated IOS for the generation of both the eupneic and adaptive breathing pattern. The IOS is not a simple termination of inspiratory motor activity, but is tightly linked to the motor act of laryngeal adduction (constriction). The dynamic regulation of the strength and duration of laryngeal adduction controls the expiratory airflow profile or primes breathing to be integrated with various oropharyn-geal motor acts, such as swallowing or vocalizing. The multimodal sensory influences, which include processing of higher behavioral and emotional commands, on the timing and dynamic of the IOS and laryngeal adduction, manifests within convergent and reciprocally connected pontomedullary rCPG circuits.

The descending inputs from the midbrain, limbic, and forebrain structures, and in turn its reciprocal connectivity with various brainstem sensory and motor nuclei illustrates that the pons function as the supramedullary control center for breathing. We coin this functionality of the pons as the “adaptive breathing center.” Adaptive breathing requires a high degree of synaptic plasticity that is linked to physiological aspects of learning and memory. The future is ripe to understand the microcircuitry and synaptic processing underlying adaptive breathing. For this breathing should be investigated as a quintessential behavior rather than stereotypic generation of rhythm.

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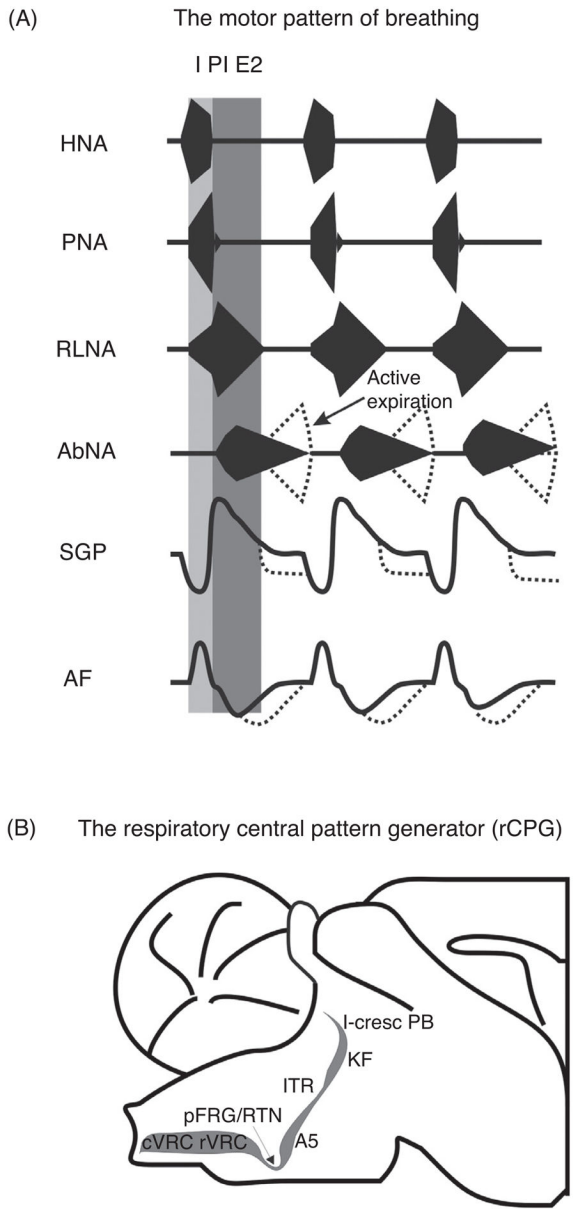

Figure 1.

(A) Respiratory motor outputs in relation to the three major phases of the respiratory cycle (I, inspiration, post-I, postinspiration, E2, late expiration). HNA, hypoglossal nerve activity; PNA, phrenic nerve activity; RLNA, recurrent laryngeal nerve activity; AbNA, abdominal nerve activity (lumbar segment 1). The lower two traces illustrate the dynamic changes in subglottal pressure (SGP) related to changes in upper airway resistance and airflow (AF). (B) Sagittal section of the anatomical organization of the lateral respiratory column (LRC) which includes the respiratory central pattern generator (rCPG) in the pontomedullary brainstem. *Abbreviations:* cVRC, caudal ventral respiratory column; rVRC, rostral ventral respiratory column; RTN/pFRG, retro-trapezoidal nucleus/parafacial respiratory group; A5, noradrenaline-containing neurons in the ventrolateral pons; ITR, intertrigeminal region; KF, Kölliker Fuse nucleus; l-cresc PB, lateral crescent nucleus of the parabrachial complex.

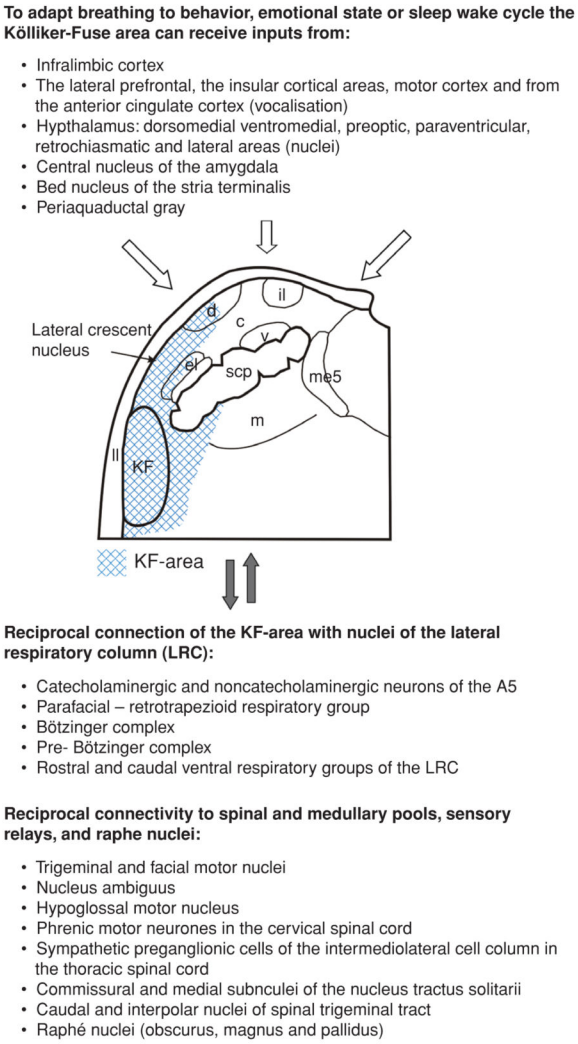

Figure 2.

The efferent and afferent connections of the primary respiratory nuclei (shaded): Kölliker-Fuse nucleus and adjacent subnuclei of the parabrachial complex of the dorsolateral pons (KF-area). *The data supporting the KF-area projecting to the parafacial nucleus are unpublished and supplied by Bellintani, Herbert, and Dutschmann. Abbreviations*: c, central subnucleus of the PB; d, dorsal subnucleus of the PB; el, external lateral subnucleus of the PB; il, internal lateral subnucleus of the PB; ll, lateral lemniscus; m, medial subnucleus of the PB; me5, mesencephalic trigeminal nucleus; scp, superior cerebellar peduncle; v, ventral subnucleus of the PB.

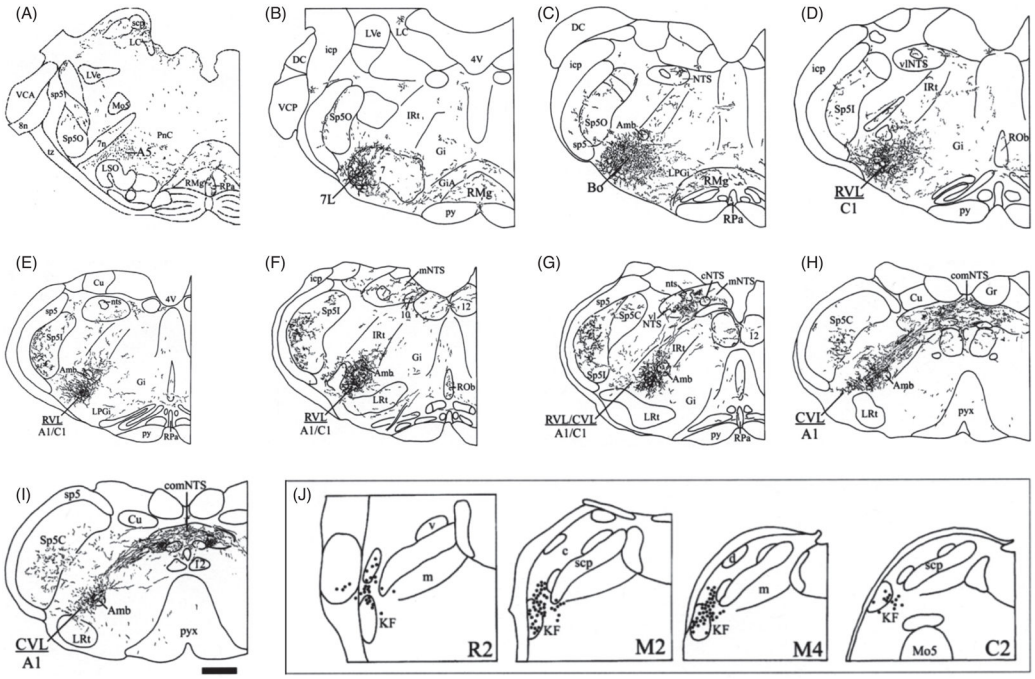

Figure 3.

Camera lucida drawings of coronal sections through the caudal pons and medulla oblongata from rostral to caudal (a–i) illustrating the pattern and distribution of anterogradely labeled descending fibers following PHA-L injection into the KF (see inset j, filled circles reflect neurons which have been filled with PHA-L, and therefore represent the probable neurons with projections). Figure published with permission of Horst Herbert, Tübingen, Germany. Orientation: *Panels a–i are from rostral to caudal transverse sections through the pontomedullary brainstem. Abbreviations*: 4V, 4th ventricle; 7, facial nucleus; 7L, lateral facial motor nucleus; 7n, facial nerve; 8n, vestibulocochlear nerve; 10, dorsal motor nucleus of vagus; 12, hypoglossal nucleus; A1, A1 noradrenergic cell group; A5, A5 noradrenergic cell group; Amb, nucleus ambiguus; AP, area postrema; Bo, Bötzinger complex; C1, C1 adrenergic cell group; CnF, cuneiform nucleus; Cu, cuneate nucleus; CVL, caudal ventrolateral reticular nucleus; DC, dorsal cochlear nucleus; DLL, dorsal nucleus of the lateral lemniscus; Gi, gigantocellular reticular nucleus; GiA, gigantocellular reticular nucleus, part alpha; Gr, gracile nucleus; icp, inferior cerebellar peduncle; IRt, intermediate reticular nucleus; KF, Kölliker-Fuse nucleus; LC, locus coeruleus; LPGi, lateral paragigantocellular nucleus; LRt, lateral reticular nucleus; LSO, lateral superior olive; LVe, lateral vestibular nucleus; me5, mesencephalic trigeminal tract; Mo5, trigeminal motor nucleus; NTS, nuclei of solitary tract; nts, solitary tract; PB, parabrachial nucleus; PnC, pontine reticular nucleus, caudal part; Pr5, principal sensory trigeminal nucleus; PrB, pre-Bötzinger complex; py, pyramidal tract; pyx, pyramidal decussation; RMg, raphé magnus nucleus; Rob, raphé obscurus nucleus; RPa, raphé pallidus nucleus; RVL, rostroventrolateral reticular nucleus; scp, superior cerebellar peduncle; sp5, spinal trigeminal tract; Sp5C, spinal trigeminal nucleus, caudal part; Sp5I, spinal trigeminal nucleus, interpolar part; Sp5O, spinal trigeminal nucleus, oral part; tz, trapezoid body; VCA, ventral cochlear nucleus, anterior part; VCP, ventral cochlear nucleus, posterior part *subnuclei of the parabrachial complex*

(PB) (same as Fig. 3): c, central lateral; d, dorsal lateral; el, external lateral; eli, inner part of extern lateral; elo, outer part of extern lateral; exl, external lateral; exm, external medial; il, internal lateral; m, medial; s, superior; v, ventral; w, waist. *Subnuclei of the nucleus of solitary tract (NTS)*: c, central; com, commissural; dm, dorsomedial; m, medial; vl, ventrolateral.

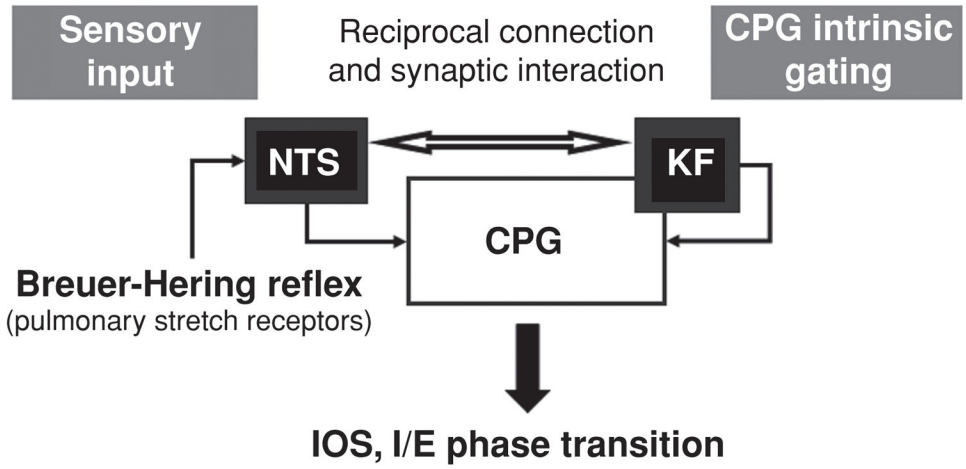

Figure 4.

Schematic drawing illustrating the two convergent pathways involved in the mediation of inspiratory off-switch (IOS) and inspiratory/expiratory (I/E) phase transition. (A) An afferent pathway mediating Breuer-Hering reflex originates from pulmonary stretch receptor input via the vagus and terminates in the nuclei of the solitary tract (NTS). (B) A central pathway that requires the Kölliker-Fuse nucleus (KF) of the pons involves reciprocal interaction between the KF and central pattern generator (CPG). Plasticity in the expression of the breathing pattern depends on intrinsic gating mechanisms (for details see text) of the CPG attributed to the KF and results from interaction between reciprocal connections of the afferent and the network pathways.

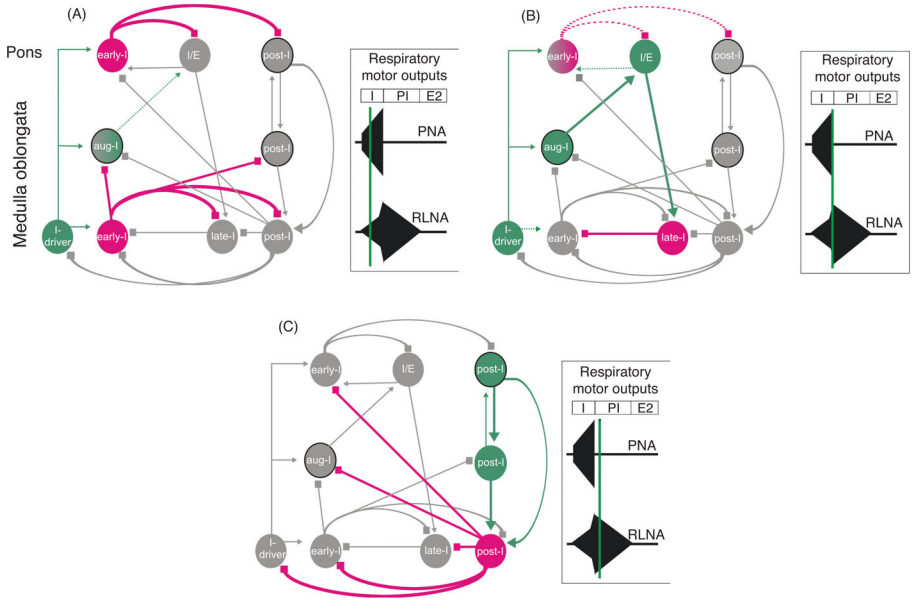

Figure 5.

Schematic illustration of the sequential phase of the pontine mediated inspiratory off-switch (IOS). The figure is adapted from Mörschel and Dutschmann 2009. Excitatory neurons and excitatory drive are highlighted in green; inhibitory neurons and interactions, red; and inactive cell populations and connections, gray. The model is based on the concept that ascending drive from the medullary respiratory neurons is required for the pontine mediated IOS. Panels on right show three time points in the cycle. (A) During the inspiratory phase, a pontine early-I population receives excitatory synaptic input (*efference copy 1*) from inspiratory driver neurons (I-driver) located in the pre-Bötzinger complex. The pontine early-I populations are inhibitory interneurons of the pons. The pontine early I neurons inhibit the pontine inspiratory/expiratory phase spanning neuron (I/E) and pontine postinspiratory premotoneurons (post-I) to prevent initiation of phase transition during early and mid-inspiration. With ongoing inspiration the pontine I/E neurons receive increasing excitatory drive (*efference copy 2*) from medullary augmenting-inspiratory premotor neurons that override the inhibition of early-I causing firing onset around late inspiration. (B) The pontine I/E neurons are excitatory pontobulbar neurons that activate the medullary late-I neurons to initiate the inspiratory/expiratory phase transition. (C) Finally, the inhibitory late-I neurons of the medulla terminate the activity of the medullary early-I neurons and release the medullary post-I population (inhibitory interneurons) from synaptic inhibition. These inhibitory post-I neurons inhibit the inspiratory populations (medullary and pontine). Consequently, the pontine and medullary postinspiratory premotor population innervating thyroarytenoid motoneurons starts firing.

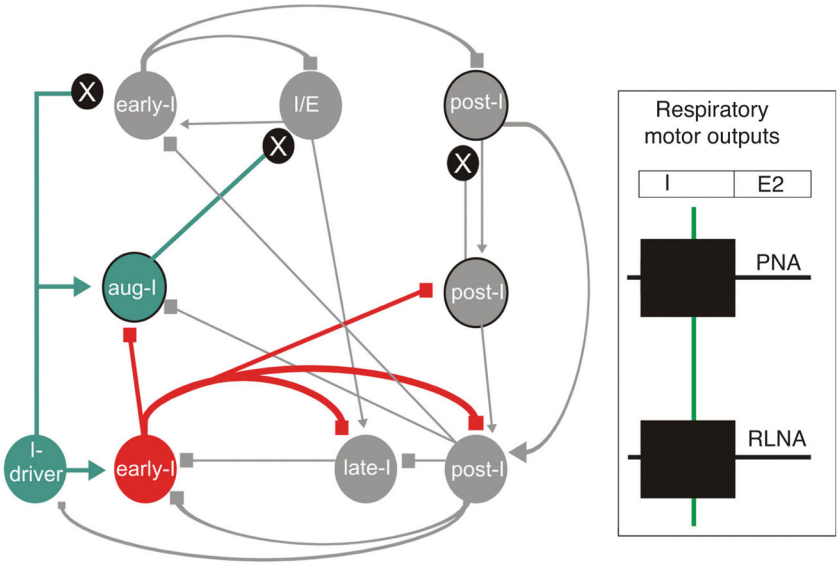

Figure 6.

Illustration of the effect of postsynaptic blockade of glutamatergic neurotransmission (e.g., NMDA-receptor antagonism) within the dorsolateral pons. Local blockade of excitatory synaptic interaction (black circles with white "x") in the pons suppresses the *efference copies 1–2* (see text and Fig. 5) causing blockade of the descending excitatory synaptic input from the pontine I/E neurons to the medullary late-I population. This abolishes the pontine mediated timing of the inspiratory/expiratory phase transition causing arrest in the inspiratory phase (apneusis). Figure adapted, with permission, from Mörschel and Dutschmann, 2009.

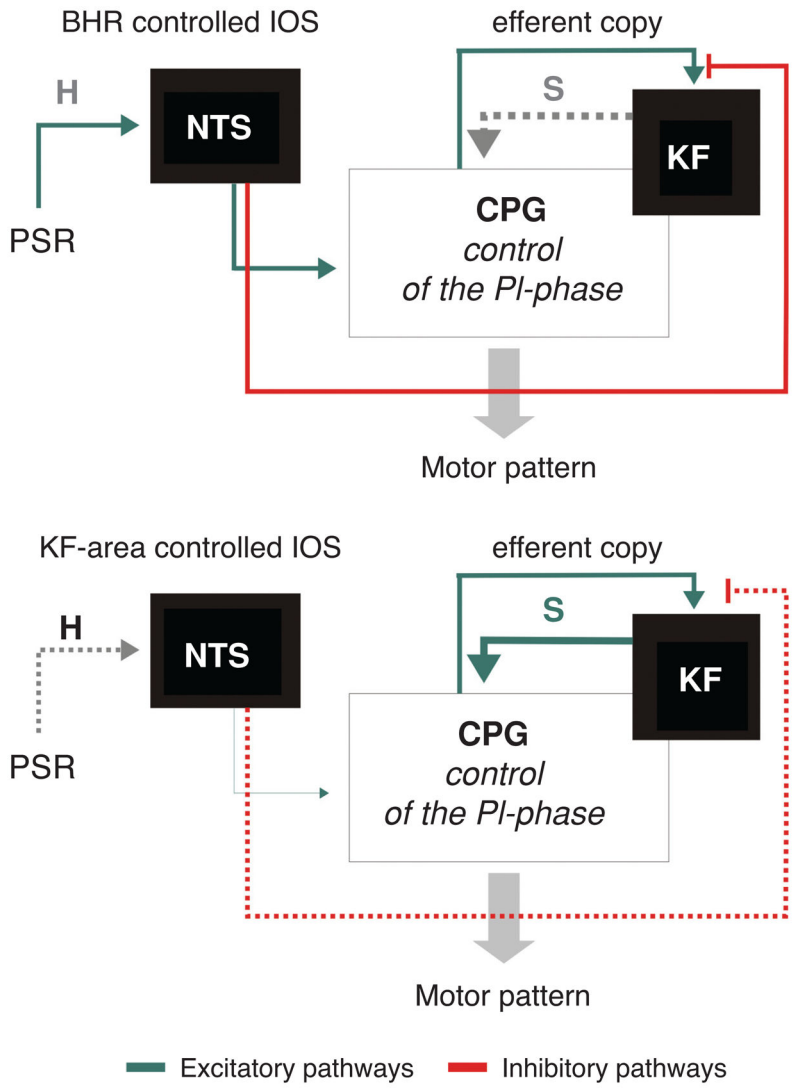

Figure 7.

Conceptual model of a dynamic switch between either Breuer-Hering reflex (BHR, pulmonary stretch receptor) or Kölliker-Fuse complex (KF) controlled inspiratory off-switch (IOS). This switch occurs naturally in the process of postnatal maturation. The concept is based on the dual processing theory and involves habituation of the PSR input at level of the nuclei of the solitary tract (NTS) and sensitization of synaptic activity of the KF-area. (A) During PSR dominance the second-order neurons that receive PSR input (pump cells) of the NTS inhibit the efference copy (see also Fig. 7) to the KF and the sensory feedback mediates the IOS. (B) During KF dominance the PSR input habituates (H) at level of the NTS and in turn sensitizes (S) the descending KF input to CPG to mediate IOS.

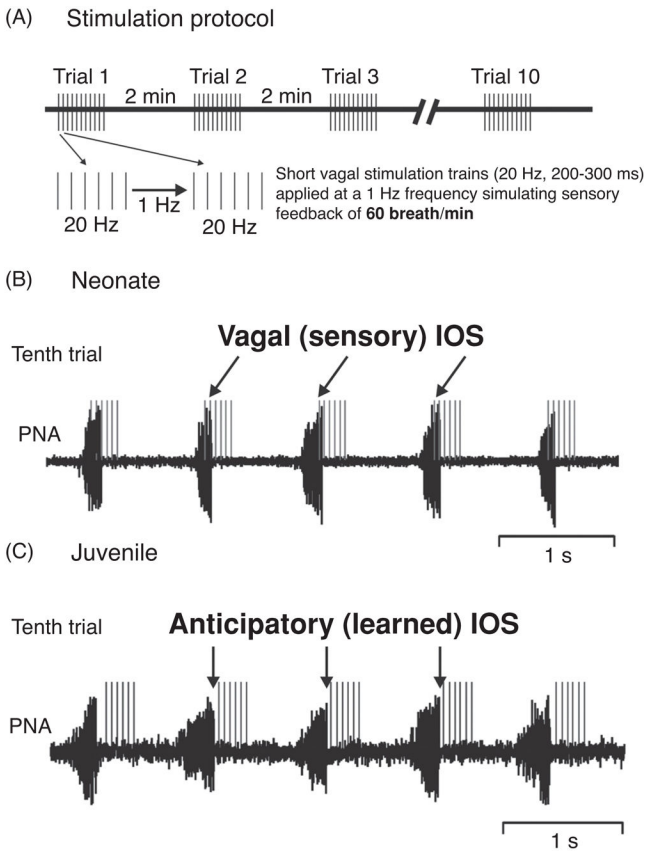

Figure 8.

(A) Illustration of the rhythmic vagal stimulation protocol. (B) Traces illustrating entrainment of phrenic nerve activity (PNA) to rhythmic vagal stimulation during the tenth stimulation trial in a neonatal perfused brainstem preparation. In the neonate, PNA entrains to stimulation trains (gray) occurring during the late inspiratory phase. Thus, the vagal stimuli provide the sensory trigger for IOS (details see reference 99). (C) Traces illustrating entrainment of phrenic nerve activity (PNA) to rhythmic vagal stimulation during the tenth stimulation trial in a juvenile rat. In juvenile rats, PNA is also entrained to the rhythmic vagal stimulation, but IOS occurs anticipatory before the onset of the stimulus train. This indicates that the KF-area has learned to pattern of vagal input and generates IOS prior to the sensory input (further details see text).

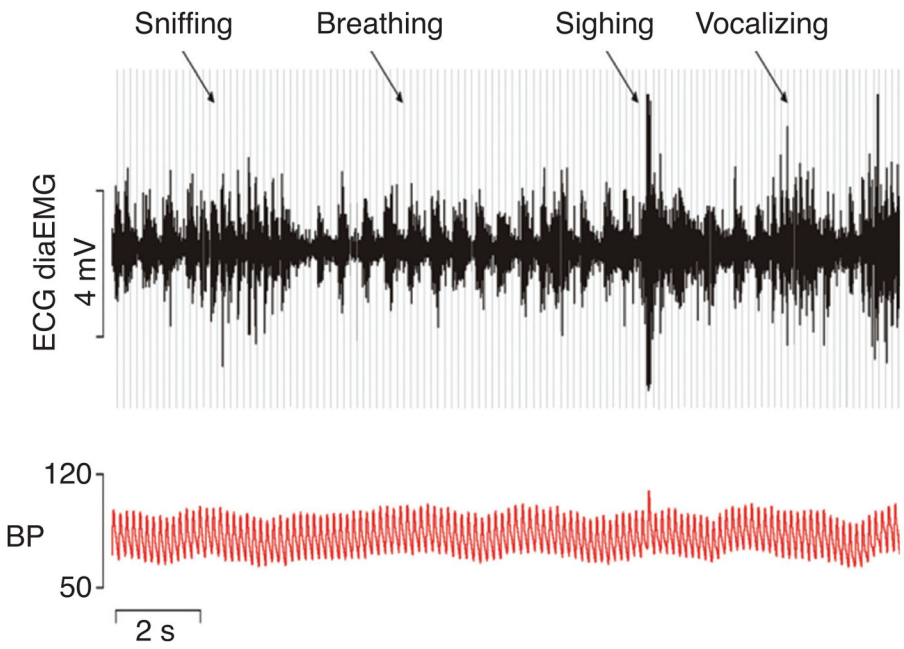

Figure 9.

Radiotelemetry recordings of electrocardiogram (ECG, gray lines), diaphragm electromyogram (DiaEMG, black) and arterial blood pressure (BP, red) in a conscious rat illustrating the continuous modulation of breathing in the context of behaviors such as sniffing, vocalizing, and sighing. Figure is published with permission of Julian Paton, Bristol.

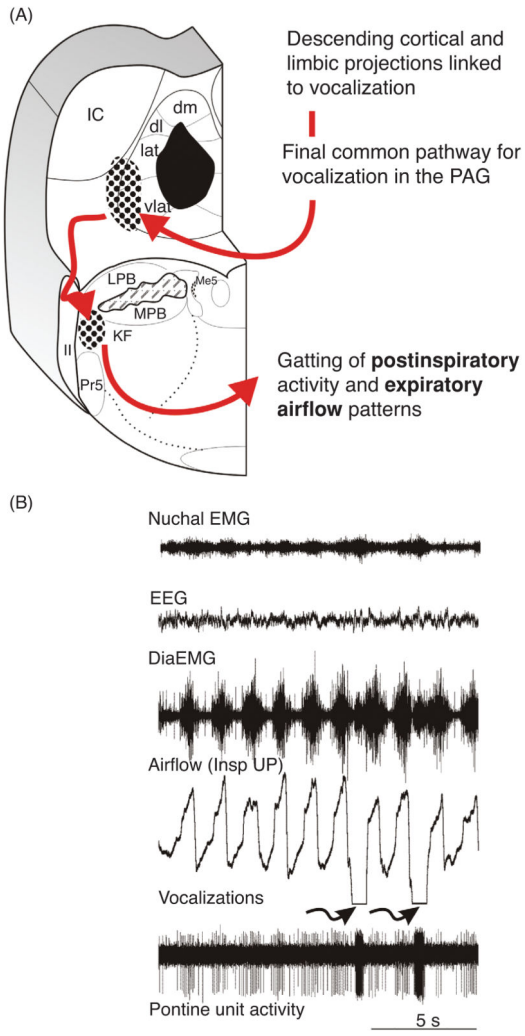

Figure 10.

(A) Schematic illustration of the proposed pathway for adaptation of the breathing pattern during vocalization. (B) Original recording of an inspiratory modulated respiratory pontine unit showing pronounced activation during vocalization. Recording was obtained from the KF-area of cat. The data are unpublished and supplied by Dick TE, Anderson C, and Orem, JM.