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The role of the hypothalamus in modulation of respiration

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ABSTRACT

The hypothalamus is a higher center of the autonomic nervous system and maintains essential body homeostasis including respiration. The paraventricular nucleus, perifornical area, dorsomedial hypothalamus, and lateral and posterior hypothalamus are the primary nuclei of the hypothalamus critically involved in respiratory control. These hypothalamic nuclei are interconnected with respiratory nuclei located in the midbrain, pons, medulla and spinal cord. We provide an extensive review of the role of the above hypothalamic nuclei in the maintenance of basal ventilation, and modulation of respiration in hypoxic and hypercapnic conditions, during dynamic exercise, in awake and sleep states, and under stress. Dysfunction of the hypothalamus causes abnormal breathing and hypoventilation. However, the cellular and molecular mechanisms how the hypothalamus integrates and modulates autonomic and respiratory functions remain to be elucidated.

1. Introduction

The hypothalamus is the gray matter of the ventral portion of the diencephalon. Although the hypothalamus occupies less than 3% of the total brain tissue, the hypothalamus regulates a variety of autonomic brain functions that are often associated with specific regions of the hypothalamus. Probably, the best known function is neural control of endocrine function (Pang and Han, 2012). Other prominent functions of the hypothalamus include the control of sleep-wake cycle (Willie et al., 2001), circadian rhythms (Saper et al., 2005), thermoregulation (Nakamura, 2011), food intake (Yamanaka et al., 2003), energy homeostasis (Sakurai et al., 1998) and cardiovascular regulation (Dampney, 2016). Thus, the hypothalamus is seen as a major controller of body homeostasis. Moreover, as a part of the limbic system, the hypothalamus is involved in the mediation of important behavior such as flight or fight response (Dampney, 2015), reward seeking (Harris et al., 2005) and many more. Although modulation of respiration is directly or indirectly coupled with many of the above-mentioned homeostatic functions, the role of the hypothalamus in regulation of respiration is often underappreciated and, thus, the present review is exclusively focused on the respiratory functions of the hypothalamus.

2. Lesioning and transection experiments

First evidence demonstrating that the hypothalamus is a part of the central control system of respiration was provided by transection experiments. Removal of brain regions rostral to the diencephalon (i.e., decortication) increased ventilation in awake cats, suggesting that brain areas rostral to the diencephalon exert an inhibitory influence on respiration (Tenney and Ou, 1977). However, removal of the diencephalon including the hypothalamus caused a significant decrease in ventilation in awake cats (Fink et al., 1962). More recently, it was shown that ablation of the diencephalon decreased respiratory frequency in the in vitro brainstem-spinal cord preparation of the neonatal rat (Okada et al., 1998; Voituron et al., 2005) (Fig. 1). These studies suggested that the hypothalamus drives the entire respiratory network.

3. Respiratory nuclei of the hypothalamus

The more refined experimental approaches and conventional methods by electrophysiology, neuropharmacology and Fos brain mapping identified the paraventricular nucleus (PVN), perifornical area (PFA), dorsomedial hypothalamus (DMH) and lateral and posterior hypothalamus as primary nuclei of the hypothalamus that are involved

Abbreviations: CCHS, congenital central hypoventilation syndrome; DMH, dorsomedial hypothalamus; LHA, lateral hypothalamic area; NTS, nucleus tractus solitarius; PAG, periaqueductal gray; PFA, perifornical area; preBötC, pre-Bötzinger complex; PVN, paraventricular nucleus; ROHHAD, rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation; RVLM, rostral ventrolateral medulla; RVMM, rostral ventromedial medulla; SIDS, sudden infant death syndrome

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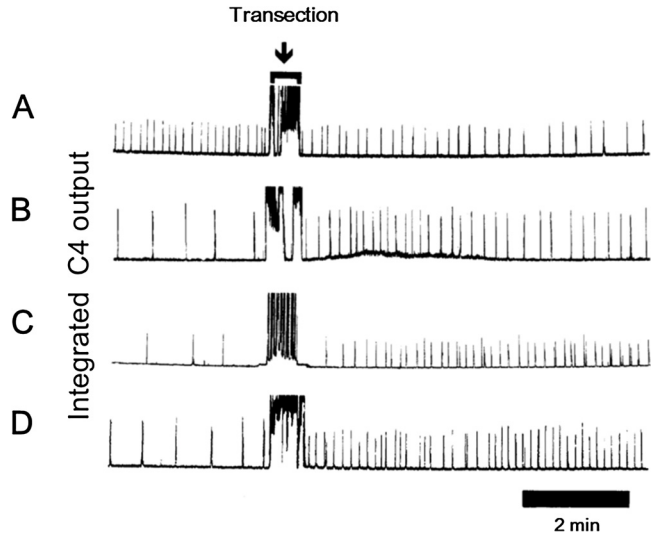

Fig. 1. The effect of brainstem transections on respiratory output (integrated 4th cervical spinal cord (C4) activity) in 4 types of preparations isolated from newborn rats; (1) the diencephalon-lower brainstem-spinal cord preparation, (2) the lower brainstem-spinal cord preparation that lacked the diencephalon but contained the midbrain, (3) the intact pons-medulla-spinal cord preparation and (4) the ventral pons-medulla-spinal cord preparation that lacked the dorsal half of the pons. **A**: Transection at the diencephalon-midbrain junction level in the diencephalon-lower brainstem-spinal cord preparation. **B**: Transection at the midbrain-pontine junction level in the lower brainstem-spinal cord preparation. Ablation of the midbrain significantly increased respiratory frequency occasionally accompanied by transient tonic C4 excitation; **C**: Transection at the ponto-medullary junction level in the intact pons-medulla-spinal cord preparation. Removal of the entire pons significantly increased respiratory frequency; **D**: Transection at the ponto-medullary junction level in the ventral pons-medulla-spinal cord preparation. Removal of the ventral pons significantly increased respiratory frequency. Ablation of the diencephalon decreased respiratory frequency (panel A), suggesting that the diencephalon has facilitatory influences on the respiratory neuronal network of the lower brainstem. On the other hand, removal of the midbrain or pons increased respiratory frequency (panels B, C, and D), indicating that both the midbrain and pons have inhibitory roles in resting respiration. Apparent difference in resting respiratory frequencies in these different types of preparations is attributed to the existence or lack of these facilitatory and inhibitory actions of the brainstem regions. Adopted from Okada et al. (1998) with permission.

in respiratory control.

3.1. Overview of the hypothalamus

The hypothalamus consists of two symmetrical halves, and its borders are anteriorly the lamina terminalis, medially the third ventricle, and posteriorly the caudal end level of the mammillary bodies. The hypothalamus consists of three zones, i.e., periventricular, medial and lateral zones, and each zone is divided into four rostrocaudal levels designated as the preoptic, anterior, tuberal and caudal (same mean as mammillary) regions (Simerly, 1995) (Fig. 2).

3.2. PVN

The PVN, located adjacently and laterally to the third ventricle in the anterior region, is a major integrative site that maintains respiratory homeostasis. The PVN contains a large population of neurons that are connected with various brain and spinal cord regions involved in respiratory control (Geerling et al., 2010). Neurons in the PVN project to the ventrolateral periaqueductal gray (PAG), pedunculopontine tegmental nucleus, dorsal raphe nucleus, pre-locus coeruleus, locus coeruleus, parabrachial nucleus, retrotrapezoid nucleus, nucleus ambiguus, A1 and caudal C1 catecholaminergic neurons, nucleus tractus solitarius (NTS), rostral ventrolateral medulla (RVLM), dorsal motor nucleus of the vagus and phrenic nucleus in the spinal cord (Zheng et al., 1995; Yeh et al., 1997; Schlenker et al., 2001; Kc et al., 2002; Geerling et al., 2010). In particular, vasopressin and oxytocin-containing PVN neurons project to the pre-Bötzinger complex (preBötC) and phrenic nucleus (Kc et al., 2002). The PVN also receives afferent fibers from other brain areas such as the NTS, DMH, hippocampus and arcuate nucleus that have been shown to participate in control of breathing (Swanson and Sawchenko, 1983; Corfield et al., 1995; Thompson et al., 1996; Schlenker et al., 1997). However, the pathways through which the PVN influences ventilation remain to be fully elucidated (Fig. 3A).

Nevertheless, it has been demonstrated that the PVN plays a role in driving baseline respiration. Electrical stimulation of the PVN in anesthetized rabbits caused an increase in respiratory frequency (Duan et al., 1997). Similarly, glutamate injection into the PVN increased electromyographic activity of the diaphragm in anesthetized rats (Yeh et al., 1997). Neural activity in the PVN of cats was altered during sigh/apnea events that were normally observed in all behavioral states (Kristensen et al., 1997). Moreover, disinhibition of the PVN with $GABA_A$ receptor antagonist bicuculline doubled respiratory frequency and increased tidal volume in conscious rats, suggesting that the activity of the PVN neurons involved in respiratory control is suppressed by GABAergic systems (Schlenker et al., 2001). Stimulation of the PVN induced respiratory modulation via oxytocinergic innervation of preBötC neurons in anesthetized rats (Mack et al., 2007), suggesting that oxytocinergic neurons of the PVN contribute to respiratory drive in room air.

The most prominent role of the PVN is its involvement in the mediation of the respiratory response to hypoxia. For instance, when carotid bodies sense hypoxia, which via the carotid sinus nerves activate the commissural nucleus of the NTS, the PVN integrates chemosensory afferent signals from the NTS in conscious cats and rats (Miller and Tenney, 1975; Schlenker et al., 2001; Reddy et al., 2005). Specifically, bilateral microinjection of lidocaine into the PVN attenuated increases in phrenic nerve activity in response to systemically administered potassium cyanide (Reddy et al., 2005). Furthermore, the role of the PVN in mediating chemoreflex may be specific to hypoxic but not to hypercapnic stimulation. Blockade of neurotransmission within the PVN had no effect on the hypercapnia-induced central chemoreflex responses in carotid body denervated animals (Reddy et al., 2005). In addition, lesions of PVN-projecting catecholaminergic neurons exhibited a slightly but statistically significant decrease in respiratory frequency during normoxia and decreased respiratory frequency and amplitude of augmented breaths during progressive hypoxia in conscious rats, suggesting that catecholaminergic inputs to the PVN contribute to baseline ventilation and that catecholaminergic neurons that project to the PVN are important in hypoxic ventilatory response (King et al., 2015). The role of the PVN may be selective for processing sympatho-excitatory and ventilatory responses evoked by peripheral but not central chemoreflex.

3.3. PFA

The PFA, located medial to the lateral hypothalamus and surrounding the fornix, is a region for mediation of respiration, arousal and other autonomic regulation. The anatomical basis for the involvement of the PFA in control of respiration is supported by direct connection from the PFA to other regions that are involved in control of respiration. Neurons of the PFA project to the NTS, RVLM, rostral ventromedial medulla (RVMM), Kölliker-Fuse nucleus, lateral and medial parabrachial nuclei, PAG, prelimbic prefrontal cortex, amygdala and spinal cord (Peyron et al., 1998; Sakurai et al., 1998; Nambu et al., 1999; Zhang et al., 2005; Carrive and Gorissen, 2008; Kuwaki, 2008; Furlong et al., 2014; Papp and Palkovits, 2014; Sakurai, 2014). The PFA also receives afferent fibers from other hypothalamic areas such as the arcuate nucleus (Thompson et al., 1996). The PFA has extensive

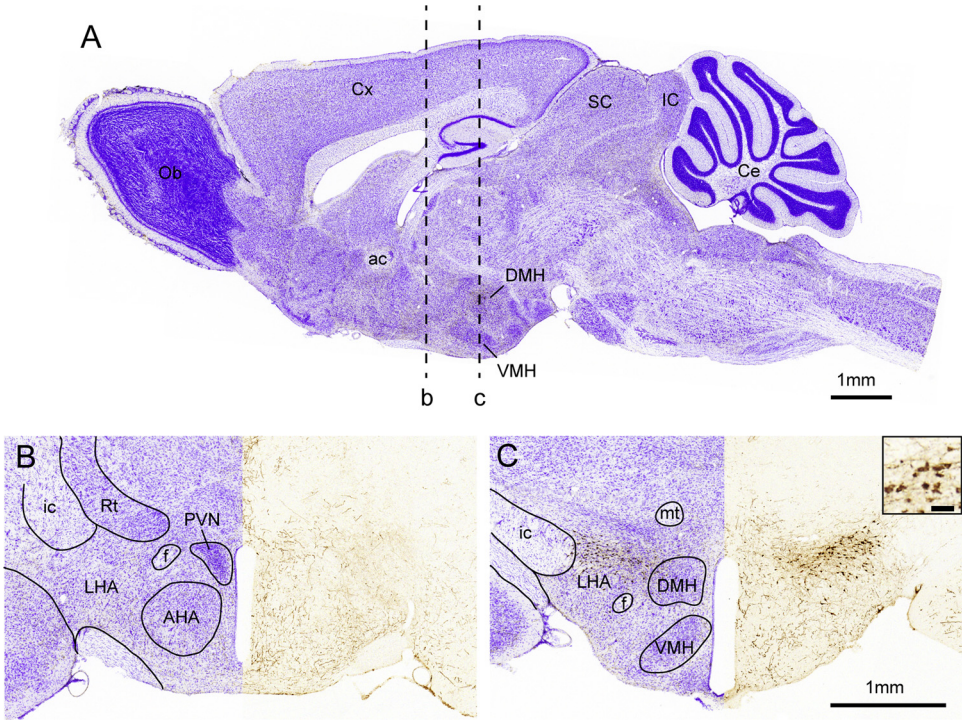

Fig. 2. The distribution of orexin-immunoreactive neurons in the hypothalamus. **A**. A Nissl-stained sagittal section of the mouse brain after orexin immunostaining. Two dashed-lines (**b** and **c**) indicate the levels of the transverse sections in panels B and C, respectively. **B** and **C**. Distribution of orexin-immunoreactive neurons and fibers at the level of the PVN and DMH, respectively. Left halves of the pictures are Nissl-stained sections, and right halves of them demonstrate orexin immunohistochemistry. Orexin-immunoreactive neurons are distributed in the DMH and LHA in the panel C. An enlarged picture of orexin-immunoreactive neurons in the LHA is displayed in the right upper corner of the panel C (horizontal bar, 50 μm). AHA, anterior hypothalamic area; ac, anterior commissure; Ce, cerebellum; Cx, cerebrum cortex; DMH, dorsomedial hypothalamus; f, fornix; IC, inferior colliculus; ic, internal capsule; LHA, lateral hypothalamic area; mt, mammillothalamic tract; Ob, olfactory bulb; Rt, reticula thalamic nucleus; PVN, paraventricular nucleus; SC, superior colliculus; VMH, ventromedial hypothalamic nucleus.

interconnections with the DMH (Thompson et al., 1996; Thompson and Swanson, 1998; Bondarenko et al., 2015), and it is likely that DMH neurons regulate autonomic and respiratory activity via projection to the PFA (Fig. 3B).

Electrical stimulation of the PFA elicited respiratory augmentation in anesthetized cats (Abrahams et al., 1960). Disinhibition of PFA neurons augmented respiratory activity in anesthetized rats (Iigaya et al., 2012). These reports indicate that the PFA is involved in regulation of basal respiration. Importantly, integrity of the PFA region seems to be essential for generation of respiratory responses to alerting stimuli and stress in conscious animals (Fortuna et al., 2009). The PFA has been known as the center for defense response, and is called the defense area. As the components of defense reaction, increases in respiratory frequency are evoked by either brief alerting stimuli or more prolonged psychological stressors in both humans and animals (Suess et al., 1980; Boiten et al., 1994; Kabir et al., 2010; Bondarenko et al., 2014, 2015).

3.4. DMH

The DMH, located in the medial zone of the tuberal region, plays roles in regulation of respiration, arousal, and other autonomic functions. The DMH has been known as the center for defense response similarly as the PFA. Neurons in the DMH project to the NTS, RVLM, RVMM, raphe pallidus, PAG, prelimbic prefrontal cortex, PVN and PFA (Thompson et al., 1996; Peyron et al., 1998; Nambu et al., 1999; Sarkar et al., 2007; Kuwaki, 2008; Tupone et al., 2011; Kataoka et al., 2014; Sakurai, 2014). Also, there are sparse projections from the DMH to the Kölliker-Fuse nucleus, and lateral and medial parabrachial nuclei (Papp and Palkovits, 2014). In contrast, there is no direct projection from the DMH to the spinal cord (Thompson et al., 1996). The majority of inputs to the DMH arise from the bed nucleus of the stria terminalis, amygdala, superior lateral parabrachial nucleus and medial prefrontal cortex (Thompson and Swanson, 1998; Vertes, 2004; Chiou et al., 2014). In contrast, direct inputs from brainstem nuclei to the DMH are sparse, except for a substantial input from the parabrachial nucleus (Thompson and Swanson, 1998). As an intermediate relay nucleus, the parabrachial nucleus receives dense projections from the preBötC and projects to the DMH (Saper and Loewy, 1980; Yang and Feldman, 2018). There is only a minor direct projection from the dorsolateral PAG to the DMH (Thompson and Swanson, 1998) (Fig. 3C). Although the DMH is immediately medial to the PFA, it is not clear whether the neurons that are critical for the integration of autonomic and respiratory responses to psychological stress and arousal are confined within the DMH or whether they extend into the PFA. It is possible that DMH neurons activated by psychological stress augment respiratory activity via connections with PFA neurons that project to brainstem respiratory neurons (Dampney, 2015) (Fig. 3B). Nevertheless the DMH is a critical region for integration of autonomic and respiratory responses to psychological stress in both humans and animals (Suess et al., 1980; Boiten et al., 1994; Kabir et al., 2010; Bondarenko et al., 2014, 2015). Microinjections of bicuculline into the DMH evoked dose-dependent increases in respiratory activity in anesthetized rats, indicating that disinhibition of neurons in the DMH increases central respiratory drive and induces hyperventilation (McDowall et al., 2007).

3.5. Lateral hypothalamic area

Several studies have suggested that the lateral hypothalamic area (LHA) (synonym of the lateral hypothalamus) plays a role in regulation of breathing. Destruction of the LHA in lightly anesthetized cats induced an immediate decrease in frequency and/or depth of respiration, and inhibition of the LHA by barbiturates also reduced respiration (Redgate and Gellhorn, 1958). It has been shown that neuronal firing frequency increased in response to hypercapnia in the LHA in lightly anesthetized rabbits (Cross and Silver, 1963). In addition, it has also been shown that focal microdialysis of CO_2 into the LHA increased breathing during wakefulness in rats, suggesting that the LHA is a central chemoreception site (Li et al., 2013). Anatomically there are projections from preBötC neurons to the LHA in mice (Yang and Feldman, 2018). We recently obtained an interesting finding in experiments using the diencephalon-lower brainstem-spinal cord preparation of newborn rat in vitro. We found respiration-coupled rhythmic activity in the LHA by voltage imaging, of which physiological significance must be clarified (Fukushi et al., 2017).

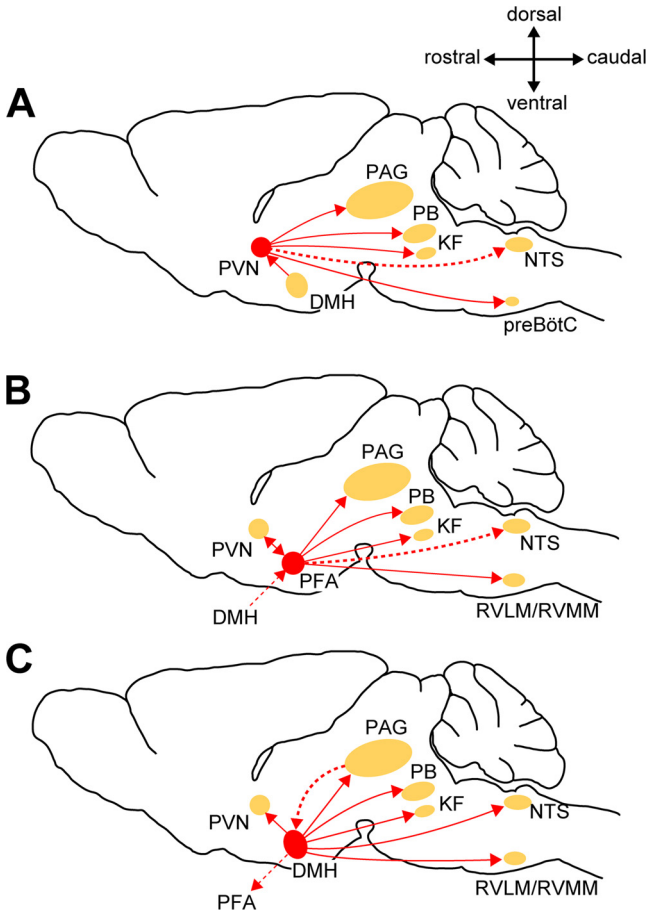

Fig. 3. Numerous nuclei in the hypothalamus make complex pathways and circuits within the hypothalamus and with nuclei in the midbrain, pons, medulla and other areas. These pathways and circuits enable the hypothalamus to play roles in various autonomic functions. **A.** The projections from/to the PVN. **B.** The projections from/to the PFA. **C.** The projections from/to the DMH. DMH, dorsomedial hypothalamus; PFA, perifornical area; PVN, paraventricular nucleus; PAG, periaqueductal gray; KF, Kölliker-Fuse nucleus; PB, parabrachial nucleus; preBötC, pre-Bötzinger complex; RVLM/RVMM, rostral ventrolateral medulla/rostral ventromedial medulla; NTS, nucleus tractus solitarius.

3.6. Caudal hypothalamus

The caudal hypothalamus occupies the caudal portion of the hypothalamus at the level of the mammillary bodies, and includes the posterior hypothalamic nuclei that are located bilaterally in the ventral portion of the caudal hypothalamus. The term “posterior hypothalamus” has been often used as synonym of the caudal hypothalamus. Thus for simplification we use the term “caudal hypothalamus” for the following paragraph. The caudal hypothalamus has extensive projections to a number of brain regions involved in respiratory control (Beitz, 1982; Beart et al., 1990; Semenenko and Lumb, 1992). Strong descending projections from the caudal hypothalamus to the PAG and ventrolateral medulla, both of which modulate respiratory outflows, were visualized by anatomical tract tracing (Vibert et al., 1979; Vertes and Crane, 1996). The descending projections to the medullary respiratory areas are reciprocal, but this is not the case for the PAG (Vibert et al., 1979; Cameron et al., 1995). The posterior hypothalamic nucleus is large, and extends from the caudal end of the hypothalamus rostrally to the DMH (Vertes and Crane, 1996). Fibers from the caudal hypothalamus distribute densely to the lateral/ventrolateral regions of the PAG, peripeduncular nucleus, dorsal raphe nucleus, laterodorsal tegmental nucleus, Barrington's nucleus, raphe magnus nucleus, raphe pallidus nucleus, RVLM and inferior olivary nucleus (Vertes and Crane, 1996).

A number of studies have shown that the caudal hypothalamus plays a role in the maintenance of baseline respiration in both conscious and anesthetized animals (Eldridge et al., 1985; Waldrop et al., 1986a). Injection of bicuculline into the caudal hypothalamus evoked dose-dependent increases in respiratory frequency in anesthetized rats (DiMicco and Abshire, 1987). On the other hand, microinjection of a GABA agonist muscimol into the caudal hypothalamus as well as electrolytic lesions of the caudal hypothalamus decreased basal respiratory activity in anesthetized cats (Redgate, 1963; Waldrop et al., 1986b, 1988).

Dillon et al. (1991) examined respiratory responses to baroreceptor activation before and after microinjection of GABA antagonists or GABA synthesis inhibitor into the caudal hypothalamus and showed that GABAergic mechanism in the caudal hypothalamus is involved in respiratory responses to baroreceptor stimulation.

The hypothalamus, in particular the caudal aspect, provides an excitatory influence over basal ventilatory drive. The caudal part of the LHA and caudal hypothalamus, both of which contain O_2-sensing neurons, have been demonstrated to facilitate respiration during hypoxia (Horn and Waldrop, 1994; Horn et al., 1999; Neubauer and Sunderram, 2004). Dillon and Waldrop (1993) also determined that a subset of neurons in the caudal hypothalamus are sensitive to hypoxia and that a large portion of these cells have respiratory related discharge patterns in anesthetized cats. It must be noted that respiratory modulation by and responses to hypoxia of these neurons were maintained even in the absence of input from the vagus and carotid sinus nerves, suggesting that peripheral chemoreceptor and baroreceptor inputs are not necessary for the respiratory modulation and hypoxic sensitivity of caudal hypothalamic neurons. Also, there was a significant increase in the density of neurons expressing Fos in the caudal hypothalamus of hypoxic compared to normoxic adult rats, which was maintained in the absence of peripheral chemoreceptors, indicating that neurons in the caudal hypothalamus are directly responsive to changes in oxygen tension (Horn and Waldrop, 1994; Horn et al., 2000a). It has been reported that more than 75% of neurons in the caudal hypothalamus were activated by hypoxia in brain slice preparations and most of these neurons maintained the response to hypoxia during perfusion with a synaptic blockade medium (Fig. 4) (Dillon and Waldrop, 1992; Horn and Waldrop, 1997). It has been suggested that sodium currents are primarily responsible for the depolarization and increased firing frequency response observed in neurons in the caudal hypothalamus during hypoxia (Horn et al., 1999; Horn and Waldrop, 2000b). It has been recently suggested that astrocytes in the brain are directly involved in the hypoxic ventilatory response as an oxygen sensor (Angelova et al., 2015; Fukushi et al., 2016; Pokorski et al., 2016; Marina et al., 2016; Gourine and Funk, 2017; Sheikhbahaei et al., 2018). Thus, in the hypothalamus, both neurons and astrocytes may be involved in sensing of hypoxia for regulation of respiration. However, a critical role of hypothalamic glia-neuron interaction during oxygen sensing needs further validation.

Several studies have demonstrated that the caudal hypothalamus also modulates respiratory responses to hypercapnia in both conscious and anesthetized animals (Tenney and Ou, 1977; Nielsen et al., 1986; Hayashi and Sinclair, 1991; Waldrop, 1991: Peano et al., 1992; Dillon and Waldrop, 1993). Microinjection of GABA antagonists or a GABA synthesis inhibitor into the caudal hypothalamus accentuates respiratory responses to hypercapnia in anesthetized cats and rats (Waldrop, 1991; Peano et al., 1992). Electrophysiological studies have provided evidence that hypercapnia exerts an excitatory effect on neurons in the caudal hypothalamus. Thus, neurons in the caudal hypothalamus receive GABAergic input that modulates the ventilatory response to hypercapnic stimulation. Hypercapnia have roughly additive effects on the discharge of the chemical stimulation of caudal hypothalamic neurons at all levels of CO_2. The chemical stimulation of caudal hypothalamic neurons are a source of excitatory drive to the

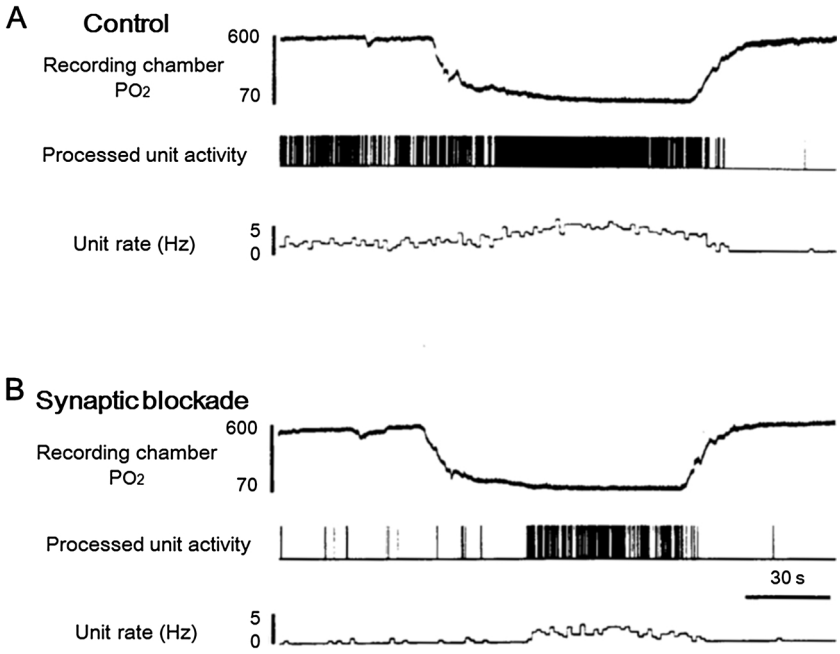

Fig. 4. The effect of synaptic blockade on hypoxic response in neuronal firing frequency in slices of the caudal hypothalamus of adult rats. **A**: Response of a hypothalamic neuron to 10% O_2 while perfused control medium. **B**: Response is maintained even when synaptic transmission is blocked. Note the decrease in spontaneous firing frequency. Responses to hypoxia are not dependent on synaptic input, indicating that the effect is intrinsic in caudal hypothalamic neurons. Adopted from Dillon and Waldrop (1992) with permission.

central respiratory pattern generator (Fortuna et al., 2009). Blockade of GABA synthesis in the caudal hypothalamus augments the respiratory response to hypercapnia but does not alter the response to hypoxia (Peano et al., 1992).

During exercise, ventilation augments to support increased oxygen demands of working muscles. The increases in respiratory activity that occur during exercise are due to both the feed-forward mechanism, i.e., central command, as well as the feedback from receptors in exercising muscles (Eldridge and Waldrop, 1991). Central command is the mechanism, in which signals from the higher central nervous system including the hypothalamus activate both somatomotor and respiratory brain areas (Eldridge et al., 1981, 1985; Eldridge, 1994). Stimulation of the caudal hypothalamus elicits locomotion and simultaneously augments respiration, suggesting that there is a parallel activation of locomotion and respiratory outflow that compensates for the immediate oxygen demands (Orlovskii, 1969). Studies using Fos expression have also shown that exercise is associated with an increase in neuronal activity in the posterior hypothalamic nucleus as well as in the adjacent DMH in rats (Ichiyama et al., 2002; Soya et al., 2007). The increases in respiration during stimulated locomotion can be elicited in a paralyzed, ventilated animal, in which feedback from pulmonary and muscle afferents are absent (Eldridge et al., 1981, 1985; Waldrop et al., 1988). These studies indicate the presence of a central command mechanism in the caudal hypothalamus that induces the feed-forward activation of respiration during locomotion. In addition, studies of locomotion evoked by electrical or chemical stimulation of the paraventricular hypothalamic locomotor region showed that increases of respiration were correlated with the speed or magnitude of locomotion (Eldridge et al., 1985). Microinjection of bicuculline into the posterior hypothalamic locomotor region of anesthetized cats evoked increases in ventilation, as well as limb locomotor movements (Shekhar and DiMicco, 1987; Waldrop et al., 1988). In these studies the microinjection sites in the caudal hypothalamus were within a region just caudal to the DMH as well as within the posterior hypothalamic nucleus.

3.7. A special role of hypothalamic orexinergic neurons in modulation of breathing

Orexin is a neuropeptide expressed only in the hypothalamus (Sakurai et al., 1998) and plays an important role in multiple physiological functions, including the respiratory regulation (Peyron et al., 1998; Zhang et al., 2005; Sakurai, 2007; Dutschmann et al., 2007; Yokota et al., 2016). Neurons containing orexin are located within the PFA, DMH and LHA (Peyron et al., 1998). The PFA and DMH are the areas with the highest density of orexinergic neurons (Fig. 2) (Peyron et al., 1998; Sakurai et al., 1998; Date et al., 1999).

The orexinergic neurons in the PFA projecting to the autonomic and respiratory centers in the brainstem may generate the respiratory responses. However, the orexinergic neurons constitute only a minority of the projection neurons from the PFA and DMH (Tupone et al., 2011). For example, only 20% of perifornical neurons projecting to the NTS and RVMM contain orexin (Tupone et al., 2011; Zheng et al., 2005). Disinhibition of the amygdala by bicuculline evoked significant respiratory responses in wild-type mice but not in orexinergic neuron-ablated mice under anesthesia (Zhang et al., 2009). However, disinhibition of the PFA/DMH evoked significantly smaller respiratory responses in orexin knockout mice than in wild-type mice (Kayaba et al., 2003), suggesting that the orexin system of the PFA/DMH could be involved in mediating respiratory responses to arousing and stressful stimuli (Bondarenko et al., 2015).

Orexinergic neurons in the LHA are sensitive to CO_2/H^+ changes both in vitro and in vivo (Williams et al., 2007; Sunanaga et al., 2009). It has been reported that orexinergic neurons in the LHA project to respiration-related regions, such as the preBötC, hypoglossal and phrenic nuclei and NTS (Fung et al., 2001; Krout et al., 2005; Young et al., 2005). However, only 0.5% and 2.9% of orexinergic neurons innervate the preBötC and phrenic nucleus, respectively (Williams and Burdakov, 2008). We interpret these results that there are not significant direct projections from orexinergic neurons to the medullary or spinal cord respiratory neurons (Young et al., 2005; Williams and Burdakov, 2008). On the other hand, it has been reported that orexinergic neurons send their fibers to Kölliker-Fuse nucleus neurons that project to the rostral ventral respiratory group and phrenic nucleus (Yokota et al., 2016) and that orexinergic neurons control breathing through indirect projection to the medullary and spinal cord respiratory neurons (Williams and Burdakov, 2008; Yokota et al., 2016). Dutschmann et al. (2007) reported that injection of orexin-B into the Kölliker-Fuse nucleus provoked prolonged pre-inspiratory discharge of the hypoglossal nerve in rats. Also, the parabrachial complex receives descending projections from the LHA in rodents (Moga et al., 1990; Veening et al., 1987; Tokita et al., 2009). It must be noted that projection targets and functions of orexinergic neurons are different among

the subpopulations. For example, arousal and psychological stress activates orexinergic neurons in the PFA and DMH, but not those in the LHA (Furlong et al., 2009).

Leptin is an adipocyte-derived peptide hormone and induces leptin receptor-mediated inhibition of orexigenic peptides release in the hypothalamus. Previously the central effects of leptin were thought to be primarily mediated via its direct action on hypothalamic neurons. However recent evidence suggests that some of these effects are mediated by astrocytes. Astrocytes express several splice variants in leptin receptors, and leptin receptors are responsible for leptin-induced calcium signaling in primary cultured astrocytes from the mouse hypothalamus (Hsuchou et al., 2009). Moreover, leptin improves baseline respiratory activity and ventilatory responses to hypercapnia in leptin deficient mice (Bassi et al., 2014). However, it remains to be elucidated whether effects of leptin on the respiratory responses result from its direct actions on the respiratory neuronal circuits or secondary to the responses elicited by leptin in neighboring astrocytes (Marina et al., 2018).

4. Postnatal development

The increase in firing frequency and membrane depolarization elicited by hypoxia in hypothalamic neurons is age dependent. An increase in the density of Fos-expressing caudal hypothalamic neurons was not observed during hypoxia in rats less than 12 days old (Horn et al., 2000a), although significant differences were not found in the magnitude of the inward current responses to moderate or severe hypoxia between neonatal and juvenile caudal hypothalamic neurons (Horn et al., 1999). As mentioned before, transection of the hypothalamus decreased respiratory frequency in the in vitro neonatal rat preparation (Okada et al., 1998; Voituron et al., 2005), indicating that already at birth the hypothalamus is functioning as a part of the respiratory control system and drives the respiratory neuron network in the lower brainstem.

5. Implication of the hypothalamus in neurogenic breathing disorders

Dysfunction of the hypothalamus is linked to various neurogenic breathing disorders in humans. For instance, congenital central hypoventilation syndrome (CCHS) is a disorder of central respiratory control often characterized with mutation of *PHOX2B* gene in a subset of patients with hypothalamic dysfunction, resulting in alveolar hypoventilation and absence of ventilatory response to hypercapnia and hypoxia, especially during non-rapid eye movement sleep (Ize-Ludlow et al., 2007; Patwari et al., 2010; Trang et al., 2014; Amiel et al., 2003; Ramanantsoa et al., 2011; Moreira et al., 2016). CCHS patients fail to arouse from sleep despite progressive hypercapnia or hypoxia (Moreira et al., 2016). Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD) syndrome is a poor prognosis, late and rapid-onset pediatric disease, exhibiting obesity, hypothalamic endocrine dysfunction, hypoventilation and sleep disordered breathing with pathological changes in the hypothalamus such as focal inflammation. Respiratory disorders in ROHHAD syndrome is likely due to diminished hypoxic/hypercapnic ventilatory responsiveness in the hypothalamus (Carroll et al., 2015; Chow et al., 2015; Reppucci et al., 2016). Infants at risk of sudden infant death syndrome (SIDS) have dysfunctional sleep and poor arousal thresholds. Hunt et al. (2015) suggested the causal relationship between hypothalamic disorder and SIDS. They reported that in SIDS infants orexin-immunoreactive neurons were significantly decreased in the PFA, DMH and LHA compared to non-SIDS. Reduction of orexin-immunoreactive neurons in the hypothalamus of SIDS victims may be associated with sleep dysfunction, impaired arousal and sudden death during sleep. Also, in animal experiments, lesioning of the hypothalamus (bilateral subthalamic locomotor regions) produced a fall in resting levels for respiratory frequency and ventilation (Waldrop et al., 1986b).

6. Conclusion and outlook

A number of studies have shown that the hypothalamus plays a vital role in modulation of respiration. Particularly, the PVN, PFA, DMH, lateral and caudal hypothalamus are the primary nuclei of the hypothalamus critically involved in respiratory control. Neurons in these regions have extensive interconnectivity and have substantial connection with other respiratory brain regions in the midbrain, pons, medulla and spinal cord. These regions of the hypothalamus are involved in the maintenance of basal ventilation, modulation of respiration in hypoxic and hypercapnic conditions, during dynamic exercise, in awake and sleep states, and under stress. Dysfunction of the hypothalamus causes abnormal breathing and hypoventilation. However, the cellular and molecular mechanisms of how the hypothalamus integrates and modulate autonomic and respiratory functions remain to be elucidated. Most of the findings reviewed in this article originated from cats and rodents, and we should be cautious in extrapolation of them to other animal species and humans. Further clarification of these issues would contribute to better understanding of the hypothalamic role in respiratory control and pathophysiology of respiratory disorders associated with hypothalamic dysfunction.

Conflict of interest

The authors declare no competing financial interests.

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