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A review of functional and structural components of the respiratory center involved in the arousal response

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Abstract

State-dependent changes influencing both the central chemoreceptor and vagal inputs to respiratory neurons may provide useful markers to assess some intrinsic factors of the respiratory center. In this paper we discuss the following topics from our recent experiences, and their relevance to the assessment of sleep-related phenomena. (1) 'Post-sigh' apnea appears predominantly during non-REM sleep in control subjects, and is a potential marker of respiratory dysfunction during this stage of sleep. (2) The disarranged configuration of the arcuate nucleus in Fukuyama-type congenital muscular dystrophy may represent a disturbance in the tangential migration pathway in the brainstem, and may be related to the sudden death that is common in this disorder. The maldevelopment of the arcuate nucleus in the victims of sudden infant death syndrome (SIDS) may also be related to some abnormality in the differentiation and migration of this neuronal population. (3) The onset of hypoglossal nerve activity precedes inspiratory activity of the phrenic nerve, possibly representing a latent drive from the respiratory rhythm generator. These issues are not only related to respiratory rhythmogenesis itself, but are also important in understanding the pathological conditions of arousal responses.

Keywords: Post sigh apnea; Arcuate nucleus; Hypoglossal nerve; Respiration; Leigh syndrome; Fukuyama type congenital muscular dystrophy

1. Introduction

The automatic rhythmicity of respiration results from the activities of the respiratory neurons in the brainstem. Although reciprocal inhibition of inspiratory and expiratory neurons is cardinally involved in the establishment of a respiratory rhythm, respiratory behavior is also under the control of an additional set of systems that regulate the rate and pattern of breathing. This is in accordance with the metabolic (tonic) demands as well as the somatic (phasic) inputs that evoke respiration-related reflexes such as cough, hiccup, sigh and apnea. Such systems include the central chemoreceptors and the vagal afferents, whose effects on respiratory patterns may unmask some intrinsic aspects of respiratory activity.

In this paper we refer to the 'post-sigh' type of apnea that is closely related to vagal inputs, discussing its significance in the assessment of central respiratory activity. Next, we debate the developmental aspects of the morphogenesis of the chemoreceptive structure, demonstrating the pathological condition in certain brain anomalies. Finally, we describe the difference between hypoglossal and phrenic nerve activity, suggesting that hypoglossal activity may represent a potential monitor of latent respiratory drive. We hope that some points raised here will provide clues for the research of arousal responses, particularly during the non-rapid eye movement (NREM) sleep period.

2. Theories on respiratory rhythmogenesis

The respiratory neurons are largely divided into two groups: the dorsal respiratory group (DRG) is distributed in the area of the nucleus of solitary tract (NTS) and the ventral respiratory group (VRG) is found in the vicinity of the ambiguus nucleus [1,2]. As described later, the DRG consists mainly of inspiratory neurons that are tightly regulated by vagal inputs that modify respiratory behavior. In contrast, the VRG includes many expiratory neurons (both decrementing (E-DEC) and augmenting (E-AUG) types),

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in addition to inspiratory neurons, and is responsible for the final output pathway to the respiratory muscles.

While precise details are beyond the scope of this article, the theoretical models suggest that various kinds of intrinsic properties and synaptic connections are involved in respiratory rhythmogenesis [1–3]. Although the drives from the peripheral and central chemoreceptors that respond to hypoxia and hypercapnia may activate certain populations of respiratory neurons, the nature and relative degree of direct facilitation on different types of neurons remains unclear. In patients with increased central apnea, the relative contribution of each neuronal population towards pathogenesis is also unknown. In the following sections we discuss some possible future directions for clinical and laboratory investigations that may help to answer these questions.

3. Post-sigh apnea

Leigh syndrome is a mitochondrial encephalopathy that is characterized by the involvement of the basal ganglia as well as the dorsal brainstem. Symptoms include motor and/or intellectual retardation, nystagmus, ataxia and dystonia, as well as abnormal breathing rhythm. The brainstem lesions are typically observed on T2-weighted magnetic resonance images as symmetrical high intensity areas in the bilateral tegmentum of the medulla oblongata, i.e. in the vicinity of the NTS. Our polysomnographic examinations revealed that 'post-sigh' apneic episodes are frequently observed for patients with such brainstem lesions [4]. Sighs are provoked by inputs from the lung stretch receptors through vagal afferents projecting into the NTS [5], therefore the sigh-generating system may be pathologically activated in these patients. On the other hand, Fukumizu et al. [6] report that sighs appeared more frequently during the REM period than the NREM period, despite the fact that post-sigh apnea was observed predominantly during the NREM period. Additionally, post-sigh apnea was exaggerated by hypoxia but not by hypercapnia in mice [7], in contrast to the finding that frequency of sighs is increased by hypercapnia in humans. These findings suggest that the frequency of post-sigh apnea is not necessarily dependent on the sigh appearance.

When apnea is induced by the stimulation of the laryngeal nerve [8] and pulmonary C-fibers [9], a prolonged respiratory pause is accompanied by the sustained activation of medullary expiratory neurons that inhibit inspiratory neurons. In contrast, expiratory neurons of the post-inspiratory type are not activated during the expiratory period following the sigh [10]. Thus the mechanism of post-sigh apnea remains obscure. Experiments in which lung inflation is used to induce augmented breaths [5] show a refractory period for repeated provocation, suggesting that there may be some depressant effect against the reflex augmentation of inspiratory activity after each sigh.

Interestingly, post-sigh apnea appears exclusively during the NREM sleep period, when respiratory drives from higher structures are attenuated and the metabolic drive from chemoreceptors predominates. This is reminiscent of the congenital central hypoventilation syndrome (CCHS), in which symptoms prevail during the NREM period [11,12]. In addition, the onset of symptoms of CCHS can appear during infancy, which may coincide with the establishment of the NREM sleep structure [13]. This suggests that victims of sudden infant death syndrome (SIDS) and apparent life threatening events (ALTE) may include some patients with CCHS. Taken together, the frequency and degree of post-sigh apnea may be a potential marker of disordered respiratory activity during the NREM period that may be present in some SIDS cases.

4. Tangential migration of neurons in the arcuate nucleus during development of the brainstem: observations in brains from cases of Fukuyama-type congenital muscular dystrophy

Fukuyama-type congenital muscular dystrophy (FCMD) is a disorder caused by mutations in the fukutin gene [14], and is characterized by malformations of the central nervous system including cerebral and cerebellar micropolygyria [15–17]. Based on the pathological findings in fetal FCMD cases [18,19], it is hypothesized that neurons in the cortical plate may vertically overmigrate through a fragile glia-limitans into the subarachnoid space. However, fukutin gene expression is predominantly in the migrating neurons [20,21] and not in glial cells that are involved in the formation of radial glial fibers and the glia-limitans. On the other hand, aberrant pyramidal tracts and leptomeningeal glioneuronal heterotopia (LGH) have been described in FCMD brainstems [15–17,22]. Since LGH is a nonspecific finding commonly associated with other brain malformations, and occasionally even in control subjects, it is unclear whether defects of the fukutin protein play any direct role in the morphogenesis of the brainstem.

Recently we examined ten FCMD cases neuropathologically, and found some evidence that specific neuronal structures are vulnerable to disrupted morphogenesis. Dysmorphology was consistently found at the pontine base and in three cases the pontine nucleus was protruding in a ventromedial direction. We hypothesized that the migration of neurons within the pontine nucleus is the primary defect in FCMD, and that the aberrant longitudinal and transverse fibers in the basal pons may represent secondary changes in the trajectory of corticospinal, corticopontine and pontocerebellar projections. Anatomical studies [23–25] have revealed that the immature neurons of the pontine nucleus originate from the germinal matrix in the dorsolateral medulla oblongata. These make up the 'precerebellar neuroepithelium' and migrate in a circumscribing, subpial stream that reaches the pontine flexure

ventrally. Similar tangential migration is seen during the formation of other brainstem structures including the arcuate nucleus in the ventral medulla oblongata [23], and we found that the configuration of this nucleus was disrupted in five of the FCMD cases.

Since the arcuate nucleus is thought to act as a central chemoreceptor that is sensitive to hypercapnia [26–28], the morphological disarrangement of this nucleus may play a role in the sudden death that is common in FCMD patients [22,29]. From such a viewpoint of ontogeny, the hypoplasia [30] and the decreased cholinergic receptor binding [31] of the arcuate nucleus in SIDS victims might result from disturbances in the differentiation or migration of this specific group of neurons. Further studies on the development of this nucleus may help to identify some of the intrinsic factors in the pathogenesis of SIDS. Polysomnographic observation of FCMD patients should be also encouraged.

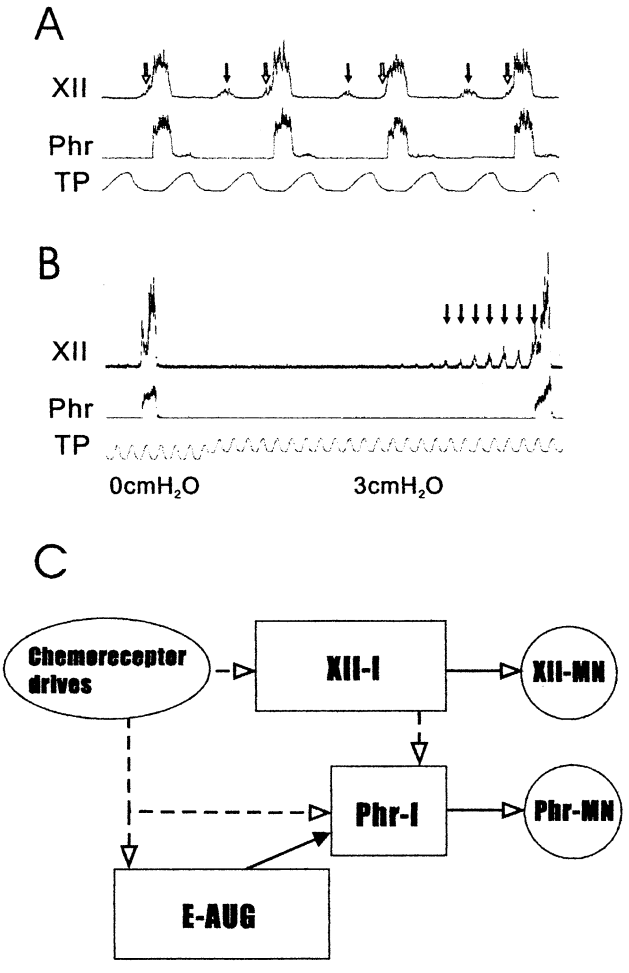

Fig. 1. Respiration-related activity of the hypoglossal nerve. (A) Hypoglossal nerve activity with onset preceding the phrenic nerve (open arrows), which can be spontaneously isolated from the phrenic activity (filled arrows). (B) Isolation of the hypoglossal nerve activity from the phrenic nerve activity, by increasing positive end-expiratory pressure (shown by arrows). (C) Possible hierarchy of inspiratory drives for hypoglossal-type, and phrenic-type neurons. E-AUG, augmenting expiratory neuron; Phr, integrated phrenic nerve activity; Phr-I, phrenic-type inspiratory neuron; Phr-MN, phrenic motoneuron; TP, tracheal pressure; XII, integrated hypoglossal nerve activity; XII-I, hypoglossal-type inspiratory neuron; XII-MN, hypoglossal motoneuron.

5. 'Latent' inspiratory activity observed in the hypoglossal motoneurons

The inspiratory activity of the hypoglossal nerve contributes to maintaining airway patency during inspiration, and its onset characteristically precedes the inspiratory burst of phrenic activity [32]. In animal experiments, we could augment this preceding component by manipulating the respirator and could distinguish such activity from the phrenic-associated bursts (Fig. 1A,B) [33]. This means that the hypoglossal and phrenic motoneurons are influenced independently by the central neural network that regulates the transition from the expiratory to the inspiratory phase. We also found that there are two types of inspiratory neurons in the DRG and VRG ('hypoglossal-type' and 'phrenic-type'), and we hypothesize that premotor neurons of the hypoglossal and other cranial motoneurons may be segregated from those of the phrenic motoneurons. This temporal segregation may result from selective inhibitory inputs during the late expiratory period from the E-AUG neurons to the phrenic-type inspiratory neurons [34]. The inspiratory neurons that fire before the overt phrenic burst, and are thought to be cardinal in respiratory rhythmogenesis [3,35], may represent hypoglossal-type inspiratory neurons. This suggests that these neurons play a more critical role in rhythm generation than the phrenic-type inspiratory neurons. Thus, hypoglossal nerve activity may be regarded as a unique window for monitoring the latent drive to the respiratory rhythm generator (Fig. 1C).

Some caveats must be remembered in the clinical application of the above idea. Firstly, central hypoglossal activity can present clinically as 'obstructive' apnea. Additionally, the REM sleep-associated suppression of hypoglossal nerve activity may be primarily mediated by non-respiratory premotor pathways rather than the inspiratory premotor neurons [36]. Considering these points, some functions related to hypoglossal nerve activity may be useful as an index of latent inspiratory activity during NREM sleep. For example, the ratio of the frequency of obstructive apnea during NREM sleep compared to REM sleep, or direct observation of respiration-related tongue movements in selected situations, such as observations on severely disabled individuals with tracheotomies.

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