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Orexinergic modulation of breathing across vigilance states

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ABSTRACT

Basal respiration and respiratory reflex regulations are considerably different during the awake and sleep states. Tidal volume and respiratory frequency diminish during sleep, and hypoxic and hypercapnic ventilatory responses also decline during sleep. Reduced metabolic demand during sleep cannot completely explain these phenomena because $PaCO_2$ increases during sleep. In this review, I will summarize our recent discovery of the possible contribution of orexin, a hypothalamic neuropeptide, to the vigilance state-dependent adjustment of central respiratory regulation. Orexin-deficient mice show an attenuated hypercapnic ventilatory response during the awake but not during the sleep period, whereas basal ventilation remained normal, irrespective of the vigilance state. Orexin supplementation remedied the defect, and the administration of an orexin receptor antagonist to wild-type mice mimicked the abnormality. Orexin-deficient mice also showed frequent sleep apneas and loss of repetitive intermittent hypoxia-induced ventilatory long-term facilitation. Hence, it is possible that the orexin system is one of the essential modulators required for coordinating the circuits controlling respiration and behavior.

1. Introduction

1.1. Respiratory modulation across vigilance states

Basal respiration and respiratory reflex regulations are considerably different during the awake and sleep states (Douglas, 2000; Krieger, 2000). Tidal volume is largest during awake periods, decreases by 20–30% during slow-wave sleep (SWS), and decreases further during rapid-eye-movement (REM) sleep (Fig. 1). Respiratory frequency decreases during SWS and is lower than that during quiet wakefulness (QW); however, respiratory frequency does not decrease during REM sleep. Consequently, the rank order of minute ventilation is QW > SWS ≥ REM (Fig. 2). In addition, both the rhythm and amplitude of ventilation are extremely regular during SWS. Reduced metabolic demand during sleep cannot explain the diminished minute ventilation because partial pressure of arterial CO_2 ($PaCO_2$) increases during sleep (Krieger, 2000). It is possible that sleep-related neuronal mechanisms actively suppress ventilation, since minute ventilation decreases during sleep even in a hypercapnic environment (Fig. 2). During SWS, airway resistance markedly increases due to decreased tonus of the upper airway muscles, whereas decreases in the contraction of intercostal muscles and of the diaphragm are small (Krieger, 2000). Therefore, sleep affects the neurons regulating the upper airway and those controlling the thorax in different manners.

Hypoxic and hypercapnic ventilatory responses are also vigilance state-dependent (QW > SWS > REM and refer to Fig. 3). The pulmonary stretch receptor reflex and irritant receptor reflex are also suppressed during sleep, and hence, cough develops only after arousal from sleep (Douglas, 2000). Although these phenomena are well known, the underlying mechanism remains to be elucidated.

1.2. Orexin

Orexins (orexin-A and -B), also known as hypocretins (hypocretin 1 and hypocretin 2, respectively), were identified as ligands for a G-protein-coupled orphan receptor in 1998. They are cleaved from a common precursor molecule, namely, prepro-orexin (130 residues), forming orexin-A (33 amino acids) and orexin-B (28 amino acids) (Sakurai et al., 1998; Willie et al., 2001). The orexin-1 receptor (the original orphan receptor) has a 10-fold selectivity for orexin-A whereas the orexin-2 receptor, which was identified by database search with amino acid sequence of the orexin-1 receptor, binds to orexin-A and -B with equal affinity (Sakurai et al., 1998; Willie et al., 2001). The location of orexin-containing cell bodies is restricted to the lateral hypothalamus, perifornical area (PFA), and dorsomedial hypothalamus (DMH). Conversely, orexin-containing nerve terminals and receptors are widely distributed in the hypothalamus, thalamus, cerebral cortex, circumventricular organs, brain stem, and spinal cord, suggesting that orexinergic neurons have widespread connections with other regions in the brain (Elias et al., 1998; Nambu et al., 1999). This

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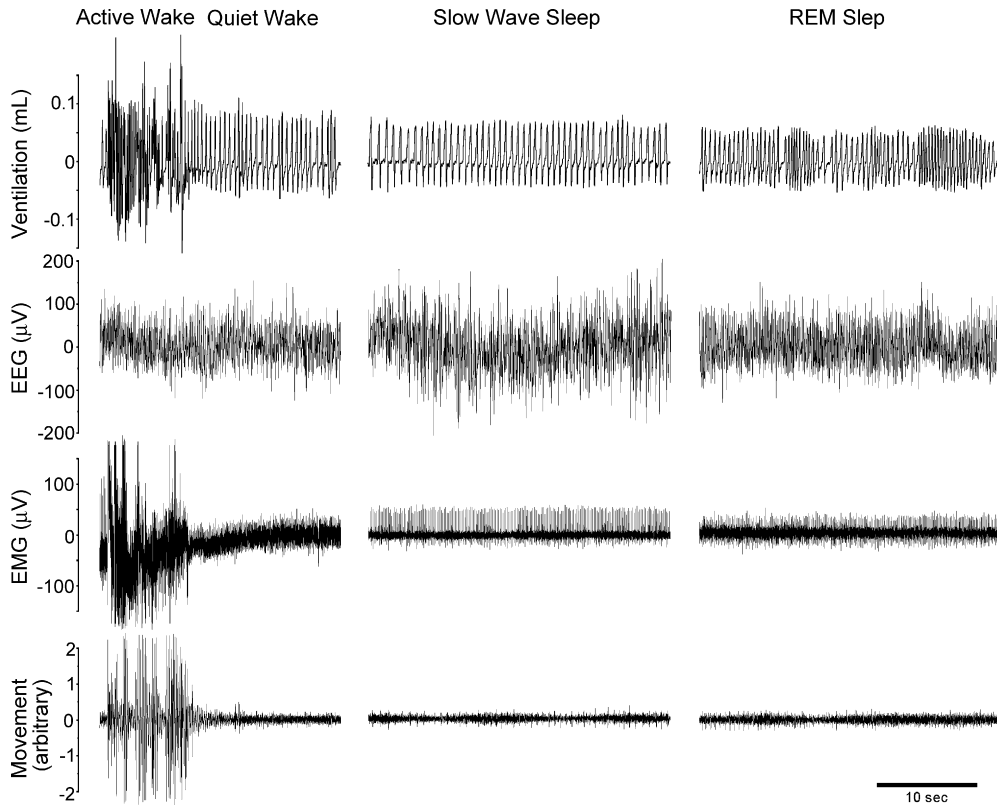

Fig. 1. Examples of vigilance state-dependent changes in ventilation observed in a mouse. Ventilation in a freely moving mouse was recorded by whole-body plethysmography and a cortical electroencephalogram (EEG), nuchal electromyogram (EMG) were also obtained; further, body movement was also recorded.

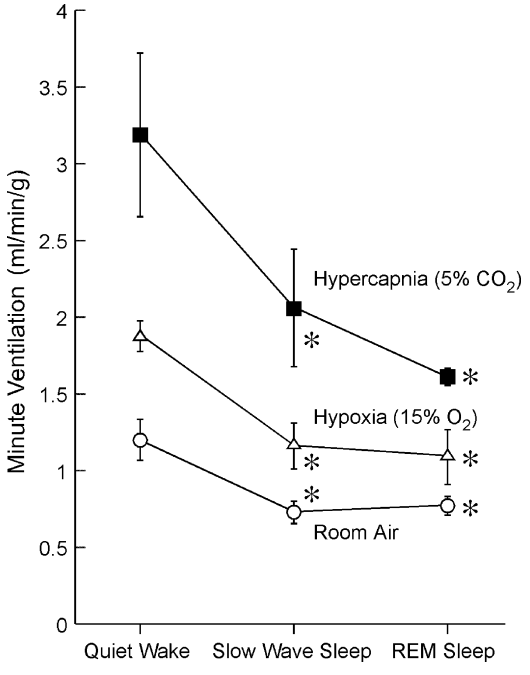

Fig. 2. Relationship between vigilance states and minute ventilation under various gas conditions. Note that vigilance state-dependent changes in minute ventilation (QW > SWS ≥ REM) is well preserved under hypoxic and hypercapnic conditions. In the reported experiment (Nakamura et al., 2003), data are expressed means ± S.E.M. of five wild-type mice. *$P < 0.05$ compared with QW.

anatomic feature establishes the basis for the contributions by orexin to the control of multiple physiological functions, including respiration.

In this review, I will summarize our recent discovery of the possible contribution of orexin to the state-dependent adjustment of central respiratory regulation. Reviews regarding the other functions of orexin, including those with regard to feeding behavior, energy homeostasis, sleep/wake cycle, motivation, stress, and regulation of the cardiovascular and neuroendocrine systems, can be found elsewhere (Willie et al., 2001; Kukkonen et al., 2002; Shirasaka et al., 2003; Saper et al., 2005; Harris and Aston-Jones, 2006; Zhang et al., 2006b; Sakurai, 2007).

2. Possible participation of orexin in respiratory control during the sleep/wake cycle

We have focused on the possible role of orexin in respiratory regulation in the context of vigilance state dependence for the following reasons. First, the axons of orexin-containing neurons project to some respiration-related sites such as the nucleus tractus solitarius; Pre-Bötzinger complex; retrotrapezoid, hypoglossal, raphe, and phrenic nuclei (Fig. 4) (Peyron et al., 1998; Fung et al., 2001; Berthoud et al., 2005; Young et al., 2005; Rosin et al., 2006). Second, the intracerebroventricular administration of orexin promoted both wakefulness (Espana et al., 2001) and ventilation (Zhang et al., 2005). Because basal respiration and respiratory reflex regulations are significantly different between the awake and sleep states (Section 1.1), orexin may represent missing connection between the vigilance state and vigilance state-dependent respiratory control. Third, orexin-deficient mice exposed to a stressor presented an attenuated fight-or-flight response, including