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Orexin links emotional stress to autonomic functions

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ABSTRACT

We studied autonomic functions in orexin-deficient mice and found abnormalities in the emotional state-dependent adjustment of the central autonomic regulation on circulation and respiration. These are summarized as follows. 1) Orexin-deficient mice exposed to a stressor exhibited an attenuated fight-or-flight response, including increases in respiration and blood pressure and stress-induced analgesia. 2) Stimulation to the amygdala (AMG) or the bed nucleus of the stria terminalis (BNST), both of which are implicated in the stress-induced autonomic responses, induced long-lasting cardiorespiratory excitation in wild-type mice but not in the orexin neuron-ablated mice. Hence, it is likely that the orexin system is one of the essential modulators required for orchestrating the neural circuits controlling autonomic functions and emotional behaviors.

1. Introduction

1.1. Orexin (hypocretin)

Orexins (orexin-A and orexin-B), also known as hypocretins (hypocretin 1 and hypocretin 2, respectively), are hypothalamic neuropeptides (de Lecea et al., 1998; Sakurai et al., 1998). They are cleaved from a common precursor molecule, prepro-orexin (130 residues), forming orexin-A (33 amino acids) and orexin-B (28 amino acids) (Sakurai et al., 1998; Willie et al., 2001). Orexin-A binds with equal affinity to the orexin receptors-1 and -2 whereas orexin-B selectively binds to the orexin receptor-2 (Sakurai et al., 1998; Willie et al., 2001).

Although orexins were first described as hypothalamic neuropeptides facilitating appetite (Sakurai et al., 1998) and arousal (Chemelli et al., 1999), later studies showed that orexins also modulate motivation (Harris and Aston-Jones, 2006), analgesia (Watanabe et al., 2005; Yamamoto et al., 2002), and autonomic regulation of the cardiovascular (Dun et al., 2000; Shirasaka et al., 1999; Zhang et al., 2006b), respiratory (Young et al., 2005; Zhang et al., 2005), and neuroendocrine (Jászberényi et al., 2000) systems.

1.2. Orexin-deficient mice—an animal model of human narcolepsy

Narcolepsy is a sleep disorder characterized by excessive daytime sleepiness in which a patient experiences extreme fatigue and suddenly falls asleep at inappropriate times. Although the cause of narcolepsy was not determined for many years after its discovery, a strong link between narcolepsy and orexin was discovered just a year after the discovery of orexin. The cause of narcolepsy in hereditary narcoleptic Doberman was a mutation in the orexin receptor-2 gene (Lin et al., 1999) and prepro-orexin knockout (ORX-KO) mouse showed a narcoleptic phenotype (Chemelli et al., 1999). Indeed, the number of orexin neurons is reduced in human narcolepsy (Thannickal et al., 2000).

At present, there are two genetically engineered mice models of orexin deficiency to study possible roles of intrinsic orexin in physiological functions including sleep/wake regulation. One is the ORX-KO mouse that was developed by a conventional knockout technique (Chemelli et al., 1999) and another is the orexin neuron-ablated mouse (Hara et al., 2001). The latter was developed using a transgenic technique by introducing a truncated Machado–Joseph disease gene product (ataxin-3) with an expanded polyglutamine stretch under the control of the orexin promoter. In these orexin/ataxin-3 transgenic (ORX/ATX-Tg) mice, orexin-containing neurons are selectively and postnatally degenerated, and reach >99% loss at the age of 4 months (Hara et al., 2001). Orexinergic neurons contain not only orexin but also other neuropeptides or modulatory factors such as dynorphin (Chou et al., 2001), galanin (Hakansson et al., 1999), glutamate (Abrahamson et al., 2001; Rosin et al., 2003), and nitric oxide (Cheng et al., 2003). In addition to orexin, these substances also disappear in “orexin neurons” of the ORX/ATX-Tg mice.

Although the cause of orexin deficiency in both mice models is not the same as that in human's (presumably autoimmune) (Hallmayer et al., 2009), both mice expressed a narcoleptic phenotype demonstrating the importance of orexin in sleep/wake regulation.

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1.3. Autonomic malfunction in human narcolepsy

There are only a few reports describing autonomic regulation in narcoleptic patients. Sachs and Kaijser (1982) reported that unmedicated narcoleptic patients showed attenuated autonomic reflexes (changes in blood pressure and heart rate) in a handgrip test and Valsalva maneuver, but not in face immersion or orthostatic tests. Because some but not all reflexes had been disturbed, they proposed intact peripheral nerves and a localization of the defect to the central nervous system. Reports on basal blood pressure in narcoleptic patients are rather controversial. The same authors reported normal blood pressure and heart rate at rest before the autonomic testing (Sachs and Kaijser, 1982). However, Guilleminault (1993) reported that withdrawal of medication with amphetamine for four weeks significantly decreased blood pressure in narcoleptic patients, indicating low blood pressure when not taking a central stimulant. Both of the sympathetic and parasympathetic basal activities seemed to be decreased since heart rate and blood pressure variabilities were significantly decreased in untreated narcoleptic patients (Fronczek et al., 2008). As to regulation of breathing, narcoleptic patients had more frequent sleep apneas compared to healthy controls (Chokroverty, 1986) or patients with idiopathic CNS hypersomnia (Baker et al., 1986).

1.4. Anatomical evidence supporting orexinergic modulation of autonomic homeostasis

The location of orexin-containing cell bodies is restricted to the lateral hypothalamic area (LHA), 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, brainstem, cerebellum, and spinal cord, suggesting that orexin-containing neurons have widespread connections throughout the CNS (Elias et al., 1998; Nambu et al., 1999). Specifically, cardiorespiratory-related sites that receive an orexin-containing innervation are the nucleus tractus solitarius; pre-Bötzinger complex; periaqueductal gray; rostral ventrolateral medulla; intermediolateral cell column of the spinal cord; retrotrapezoid, hypoglossal, raphe, and phrenic nuclei (Fig. 1) (Antunes et al., 2001; Berthoud et al., 2005; Dergacheva et al., 2005; Dun et al., 2000; Fung et al., 2001; Geerling et al., 2003; Peyron et al., 1998; Rosin et al., 2006; Smith et al., 2002; Volgin et al., 2002; Young et al., 2005). Approximately 50% of hypothalamic neurons that innervate both the sympathetic efferent and motor cortex or medial prefrontal cortex which is implicated in mental stress showed orexin-like immunoreactivity (Krout et al., 2005, 2003).

Moreover, orexin-containing neurons receive inputs from the regulatory centers for sleep/wakefulness and emotional stress coping; e.g., ventrolateral preoptic area, locus coeruleus, dorsal raphe, amygdala, bed nucleus of stria terminalis (BNST), suprachiasmatic and tuberomammillary nuclei (Sakurai et al., 2005; Yoshida et al., 2006; Zhang et al., 2009). Numerous neurons in the amygdala, a putative center for biological value judgment (Pitkanen et al., 1997), are retrogradely labeled by cholera toxin B subunit injected into the PFA (Yoshida et al., 2006) and by the trans-synaptic transport of tetanus toxin expressed by the orexin promoter (Sakurai et al., 2005).

These anatomic features are consistent with orexin-containing neurons coupling regulatory networks of consciousness (sleep/wakefulness and emotional stress) and unconscious homeostatic networks (Fig. 1).

2. Autonomic malfunctions in orexin-deficient mice

2.1. Cardiorespiratory regulation during stress

Research on neural mechanisms of state-dependent adjustments of central autonomic regulation has been sparse, despite its importance from the perspective of quality of life. Our daily life does not only involve calm, resting states. Life is full of perturbations that include active conditions, such as movements, eating, and communicating. During such active periods, cardiorespiratory regulation must be adjusted for bodily demands, which differ from those during resting states, by modulating or resetting homeostatic points (Kumada et al., 1990). Localization of orexin-containing neuron cell bodies in PFA and DMH prompted us to examine a possible role of orexin in the defense response against stressors because stimulation of these areas elicited behavioral “rage” along with the specific autonomic response that was termed the “defense response” (Fig. 2) (DiMicco et al., 2002; Hess, 1954; Jordan, 1990).

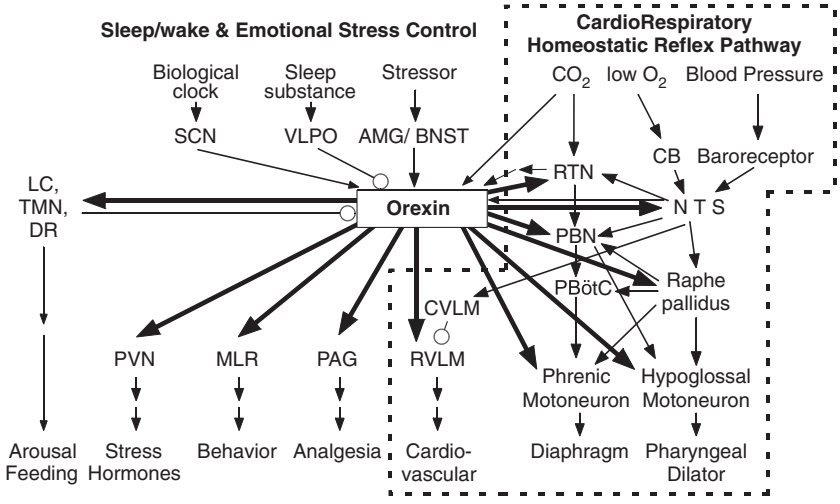

Fig. 1. Proposed pathways for the modulation of autonomic homeostasis by orexin. Many nuclei in the homeostatic reflex pathway against the changes in CO_2, O_2, and blood pressure receive projections from orexin-containing neurons in the hypothalamus (thick line). Simultaneously, orexin-containing connections are engaged in sleep/wake regulation and emotional stress-induced autonomic and behavioral changes. Arrows indicate a probable excitatory connection and circles indicate an inhibitory connection. Nuclei without direct connection to/from orexin-containing neurons are omitted for simplicity. Abbreviations: AMG, amygdala; BNST, bed nucleus of stria terminalis; CB, carotid body; CVLM, caudal ventrolateral medulla; DR, dorsal raphe; LC, locus coeruleus; MLR, medullary locomotor region; NTS, nucleus tractus solitarius; PAG, periaqueductal gray; PBN, parabrachial nucleus; PBötC, pre-Bötzinger complex; PVN, paraventricular nucleus; RTN, retrotrapezoid nucleus; RVLM, rostral ventrolateral medulla; SCN, suprachiasmatic nucleus; TMN, tuberomammillary nucleus; VLPO, ventrolateral preoptic nucleus.