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Review

Orexin: A potential role in the process of obstructive sleep apnea

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ABSTRACT

Obstructive sleep apnea (OSA) is a complicated disease with an unrecognized mechanism. Obesity, sex, age, and smoking have been found to be independent correlates of OSA. Orexin (also named hypocretin) mainly secreted by lateral hypothalamus neurons has a wide array of biological functions like regulating sleep, energy levels and breathing. Several clinical studies found ties between orexin and OSA. Because of the close correlation between orexin and obesity, sex, age and smoking (which are the key risk factors for OSA patients), we hypothesize that orexin may play a key role in the pathogenesis of OSA.

Contents

Obstructive sleep apnea is a common but still underrecognized disorder. It is patho-physiologically characterized by repetitive collapse of the upper airway which could cause reduction in ventilation (hypopneas) or total cessation of ventilation (sleep apnea) during sleep, followed by intermittent hypoxemia, and hypercapnia. Moreover, repetitive episodes of obstructive respiratory events cause sleep fragmentation, which predisposes OSA patients to work-related or driving accidents and poor work and social functions. Although it is clear that upper airway collapse most often results from a combination of anatomic factors that predispose the airway to collapse during respiration plus neuromuscular compensation that is insufficient during sleep to maintain airway potency [135], the mechanism in the process of OSA is not clear.

Orexin (orexin-A and orexin-B), as endogenous peptide ligands for two orphan G-protein-coupled receptors (OX1 and OX2 receptor) [19,106], functions in a wide array of biological regulation of sleep, energy and breathing. Results from previous studies have suggested that the orexin neurons were mainly located in the lateral hypothalamic area of the brain [19,106], while it was also found in the peripheral tissues [39]. In addition, although the number of the orexin neurons in the brain was limited, the nerve fibers containing orexin-A and/or orexin-B have been showed to project widely from the hypothalamus to various brain regions [18,96,129].

Due to the close relationship between orexin and obesity, sex, age and smoking, which are the key risk factors for OSA, we focus to clarify the function of orexin in the process of OSA and hypothesize that orexin may play a key role in the pathogenesis of OSA.

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1. Narcolepsy, orexin, and OSA

Narcolepsy is a chronic sleep disorder characterized by excessive daytime sleepiness (EDS), cataplexy, and rapid eye movement (REM) sleep-related symptoms (such as sleep paralysis and hypnagogic hallucinations) [85]. Several studies showed that a large number of human narcolepsy-cataplexy was associated with central orexin deficiency [86,95,128]. In addition, orexin or a deficiency in its receptors caused narcolepsy and has been found in other species such as dogs [25] and mice [31].

Accordingly, there may be a connection between narcolepsy, orexin and OSA since coexisting OSA was a common phenomenon in patients with narcolepsy [92,107]. A recent study showed that in 132 narcolepsy patients, 33 patients (24.8%) had OSA [107]. It is interesting that 10 of them were initially diagnosed only with OSA and the diagnosis of narcolepsy was delayed by 6–8 years [107]. It seems that long term OSA may cause narcolepsy. Since it was reported that orexin system deficiency caused narcolepsy in clinical studies, it was possible that OSA may cause narcolepsy through long term damage of orexin systems.

2. Age, orexin, and OSA

It was found that the number of orexin immuno-reactive cells decreased with age in rodents [15,57,110]. In addition, a reduction of the orexin fibers was also reported in a few species of older animals' brains [22,138,139]. Furthermore, decreased expression of genes including the prepro-orexin, orexin-A, orexin-B and their receptors was also showed in several studies [98,127]. As a result, it is not strange that the waking [77] or feeding [3,124] promoting effects and sympathetic regulation [41] induced by intracerebroventricular (ICV) of orexin was attenuated or abolished in old rats since the orexin signaling including orexin receptors or fibers decreased with age.

Interestingly, the prevalence of OSA increased with age while the orexin system degenerating in old people. It is plausible that the prevalence of OSA in old people is due to decreased orexin system activity. Whereas, the cerebrospinal fluid (CSF) orexin-A levels did not change with age [50] and the plasma orexin-A levels even increased in old people [72]. However, in their studies [50,72], too many confounding factors such as obesity, smoking and various other conditions were not excluded, which made the result unreliable. Furthermore, in Matsumura's report [72], venous blood was obtained from fasting subjects at 9:00 a.m, while fasting would cause immediate alternation of orexin levels [59] which also made the results inaccurate. On the other hand, genioglossus activity was increased by ICV injection of orexin [94], thus reductions in orexin could contribute to the suppression of upper airway dilator activity which may facilitate OSA. Therefore, whether the degeneration of orexin and high prevalence of OSA in old people was closely correlated needed to be investigated since lower plasma orexin-A levels were found in OSA patients in several clinical studies as well [4,16,84].

OSA prevalence appears to increase steadily with age during midlife, but age trends in older aged people do not indicate a simple positive correlation of OSA with age [135]. In addition, in this report, although the prevalence of sleep apnea increased monotonically with age, the severity of sleep apnea, as indicated by both number of events and minimum oxygen saturation, decreased with age [13]. Therefore, the question of whether OSA in older adults represents a distinct clinical entity that is seen only in middle aged adults remains a controversial issue [100]. Orexin has been documented to be contributed to suppressed center sleep apnea [61,62,80]. Accordingly, prevalence of sleep apnea increasing with age may be due to the increased center type but not obstructive type of sleep apnea because of degeneration of the orexin system. The hypothesis will be partly agreed on in this report which found central apnea appeared to account for a monotonically increased relationship with age [13].

3. Sex, orexin, and OSA

In most population-based studies, gender is always as a risk factor for OSA. About a 2–3 fold greater risk for men compared with women has been reported [122] but the reasons for the risk difference are not clear. Since abnormal sex hormones were found in OSA patients [29,69,90,108] and hormone replacement therapy was effective for reducing the incidence and severity of OSA symptoms [12,44], most hypotheses to account for the gender disparity focus on a role of sex hormones in OSA pathogenesis.

In normal condition, the production of testosterone/estrogen was regulated by hypothalamic–pituitary–gonadal (HPG) axis. Orexin have been suggested to be involved in the regulation of the HPG axis [88,102,116]. Orexin receptors were detected in hypothalamus such as the medial preoptic nucleus, the anterior hypothalamic nucleus, and the ventromedial nucleus [70] and also detected in pituitary gland [81], testis [47,53] and ovary [47,117]. In addition, orexinergic nerve fibers were also present in the median eminence and pituitary gland [18,47]. Therefore, orexin may directly or indirectly influence the synthesis and/or liberation of releasing pituitary hormones and the sex hormones in plasma. Indeed, orexins were found to stimulate GnRH release from the hypothalamus of male [101,102] and proestrous female rats [102]. Besides, pretreated with 17β-estradiol and progesterone, plasma LH levels of ovariectomized rats were increased after intracerebroventricular injection of orexin, whereas in untreated ovariectomized rats, intracerebroventricularly injected orexins decreased plasma LH levels [46,99,125]. Furthermore, orexin appears to have a dual effect on LH release in ovariectomized rats, being stimulatory in the rostral preoptic area but inhibitory in the medial preoptic area and arcuate/median eminence [118]. The relationship between orexin system and LH in female gender seems more complicated since the expression of orexin receptors in rat ovaries also fluctuate with the estrous cycle [117].

On the other hand, the orexin system was regulated by sex hormone levels. In the hypothalamus of adult male Long–Evans rats (325 g), orexin neurons immunoreactivity and orexin protein were decreased by castration, while restored by estradiol [78]. But in male Wistar rats (8 weeks old)[49] or Sprague–Dawley rats (200∼250 g) [115], orchidectomy could not cause any change of the mRNA levels of prepro-orexin in the hypothalamus [49] but was able to result in an increasing OX1 receptor levels in pituitary, while this effect would be reversed by testosterone [49,115]. The different results may be due to the different species. However, age seems to play a more important role on orexin and more likely to be affected by a decreased reproductive ability. In female rats, the pituitary OX1 receptor mRNA levels were increased 12-fold after ovariectomy compared with shamoperated rats, which was inhibited by treatment with 17β-estradiol [49].

Although the data from these studies were controversial, the relation between orexin and sex hormones seems unique and exhibits a difference in gender. The regulation between orexin system and the sex hormones are well explained in Fig. 1 [88] and Fig. 2. Orexin was able to increase the plasma levels of LH, however, inhibited by higher levels of LH or sex hormones in plasma. There is a balance between sex hormones and orexin. The hypothesis was also supported by these reports: the testosterone levels rise during sleep, but fall on waking [68,111], while the orexin levels and the activity of orexin neurons increase during the active phase but decrease during the resting phase [24,133,136].