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Review

Sleep disorders, obesity, and aging: The role of orexin

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ABSTRACT

The hypothalamic neuropeptides orexin A and B (hypocretin 1 and 2) are important homeostatic mediators of central control of energy metabolism and maintenance of sleep/wake states. Dysregulation or loss of orexin signaling has been linked to narcolepsy, obesity, and age-related disorders. In this review, we present an overview of our current understanding of orexin function, focusing on sleep disorders, energy balance, and aging, in both rodents and humans. We first discuss animal models used in studies of obesity and sleep, including loss of function using transgenic or viral-mediated approaches, gain of function models using exogenous delivery of orexin receptor agonist, and naturally-occurring models in which orexin responsiveness varies by individual. We next explore rodent models of orexin in aging, presenting evidence that orexin loss contributes to age-related changes in sleep and energy balance. In the next section, we focus on clinical importance of orexin in human obesity, sleep, and aging. We include discussion of orexin loss in narcolepsy and potential importance of orexin in insomnia, correlations between animal and human studies of age-related decline, and evidence for orexin involvement in age-related changes in cognitive performance. Finally, we present a summary of recent studies of orexin in neurodegenerative disease. We conclude that orexin acts as an integrative homeostatic signal influencing numerous brain regions, and that this pivotal role results in potential dysregulation of multiple physiological processes when orexin signaling is disrupted or lost.

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1. Introduction

Identified by two independent groups, the endogenous neuropeptides, orexin A and B (also known as hypocretin 1 and 2), and their associated G-protein coupled orexin type 1 and 2 receptors (OX1R and OX2R, respectively, also known as hypocretin receptor type 1 and 2), constitute the multi-functional central orexin system (de Lecea et al., 1998; Sakurai et al., 1998). Orexin synthesis is relatively confined to neurons in the lateral–posterior–perifornical hypothalamus, while orexin receptors are widely distributed in a brain site-specific manner (Marcus et al., 2001; Trivedi et al., 1998). Unlike orexin synthesizing neurons, orexin fibers are ubiquitous, extensively innervating peripheral and central targets (Date et al., 1999; España et al., 2005; Nixon and Smale, 2007; Peyron et al., 1998). Due to the extensive terminal field, central orexin signaling is well positioned to integrate and orchestrate multiple physiological processes such as arousal, whole-body energy metabolism, reward seeking, autonomic function, and ventilatory control (Burdakov et al., 2013; de Lecea and Huerta, 2014; Karnani and Burdakov, 2011; Kotz et al., 2012; Mahler et al., 2012). Aberrant orexin function has been associated with several pathophysiologies, such as obesity, narcolepsy and other sleep disorders, as well as the occurrence and severity of age-related disorders (Fadel et al., 2013). Here we briefly review the literature documenting the role of orexin in sleep disorders, energy balance, and aging. We discuss animal models and clinical studies, highlighting how alterations in central orexin signaling affects body weight, food intake, sleep patterns, and progression of age-related pathologies. We conclude that central orexin signaling is a promising target for pharmacological therapies to alleviate a myriad of disorders.

2. Animal models

2.1. Rodent models for studying the role of orexin in obesity

Initial behavioral studies suggested that orexin was important in mediating central control of ingestive behavior and energy metabolism (Bray, 2000; Lubkin and Stricker-Krongrad, 1998; Sakurai et al., 1998). These studies showed orexin A had opposite effects on energy balance since exogenous orexin A stimulated hyperphagia and energy expenditure. This is unusual in that most peptides known to stimulate ingestion also inhibit sympathetic activity and thermogenesis, reducing energy expenditure (reviewed in Bray, 2000). Subsequent studies have indicated orexin influences individual propensity for weight gain, and have shown that orexin receptor stimulation results in a net negative energy balance. Rodent models for studying the role of orexin in obesity have been developed and tested, and include genetic gain and loss-of-function models, as well as pharmacologic and outbred models of individual variability.

2.1.1. Loss-of-function

Mice lacking orexin function either through genetic knockout (KO) of the gene encoding orexin or through postnatal ablation using an ataxin toxin develop late onset obesity (Chemelli et al., 1999; Hara et al., 2001, 2005). In both models, food intake and energy expenditure are affected by the absence of orexin function. These animals are hypophagic (eat less), and have substantially reduced energy expenditure, which appears to be primarily due to reductions in physical activity (Hara et al., 2001). Hara et al. (2005) showed important phenotypic differences in deleting orexin function by these two methods: losing the orexin *gene vs.* losing the entire orexin *neuron*. With the latter approach, co-localized neurotransmitters, including dynorphin, cocaine and amphetamine-related transcript, glutamate, neuronal activity-regulated pentraxin, and others are lost, and thus the impact that these neurotransmitters and their projections have on energy balance are also affected. Studies have shown that in the orexin/ataxin-3 model and in orexin gene KO mice, the obesity phenotype depends upon the mouse genetic background, level of knockdown and environment (Fujiki et al., 2006; Hara et al., 2005). While both the KO mice with a mixed or C57Bl/6J genetic background and the orexin/ataxin-3 mice with a C57Bl/6J background are heavier than wild type mice, body weight is similar between mixed background orexin/ataxin-3 mice and wild type mice. Body weights of orexin/ataxin-3 mice are greater than orexin KO mice and the body weight of heterozygote mice on a mixed background is intermediate between that of homozygous knockouts and wild type mice. The latter suggests that severity of obesity increases as orexin function declines. Female mice exhibit a higher level of obesity, potentially indicating greater sensitivity to orexin loss in females (Fujiki et al., 2006). Together, these data suggest that orexin (*e.g. vs.* other co-localized factors) and genetic background are critical for the obese phenotype on orexin-manipulated animal models (Fujiki et al., 2006; Hara et al., 2005). Injection studies demonstrate that a single intraperitoneal administration of a selective orexin 1 receptor antagonist (SB-334867-A) reduces food intake in both male and female rats (Haynes et al., 2000). Further, the same antagonist delivered chronically into cerebral ventricles of leptin deficient (ob/ob) mice over 14 days reduced body weight gain by reducing food intake (Haynes et al., 2002), although leptin deficient mice have baseline differences in energy regulation, limiting interpretation.

2.1.2. Gain of function

Studies by Yanagisawa and colleagues have demonstrated that orexin overexpression promotes energy expenditure while also reducing food intake and that central administration of an orexin receptor 2 agonist reduced diet-induced obesity (Funato et al., 2009). Reduction in energy expenditure is in agreement with other studies, but reduction in food intake by an orexin agonist is surprising. It is unclear why this discrepancy exists. Nonetheless, transgenic overexpression of orexin and the orexin receptor 2 affords protection from obesity when mice are placed on a high fat diet. Novak and Levine (2009) have shown that daily injection of orexin A into the hypothalamic paraventricular nucleus results in weight loss in rats, and recently, Perez-Leighton et al. (2012) showed that daily orexin A injections into the rostral lateral hypothalamus reduces fat mass gain in rats on a high fat diet. These

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