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REVIEW

Roles of orexins in the regulation of body weight homeostasis

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Summary Lateral hypothalamic neuropeptides, orexins, have been recognized as one of the most important regulators of sleep/wakefulness states. Besides, these peptides are also regarded as an important factor that regulates feeding behavior, owing to their localization within the lateral hypothalamic area, the classic ''feeding center'', pharmacological activities, and the fact that prepro-orexin mRNA is upregulated when animals are fasted. This review summarizes the role of orexins in the regulation of feeding behavior and body weight homeostasis in relation to other systems that involve orexinergic neurotransmission.
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Introduction

Orexins are hypothalamic neuropeptides identified in 1998 [1]. Several studies showed that orexin deficiency causes narcolepsy in humans and animals, implicating these hypothalamic neuropeptides in play a critical role in the regulation of sleep/wakefulness states [2—6]. However, orexins were initially recognized as regulators of feeding behavior, firstly because of their exclusive production in the lateral hypothalamic area (LHA), a region known as the ''feeding center'', and secondly because of their pharmacological activity; intracerebroventricular (ICV) injection of orexins induced feeding behavior in rats and mice [1,7—9]. Recent studies further suggested that orexins play roles in the coordination of emotion, energy homeostasis, reward system, drug addiction, and arousal [10—17]. This review focuses especially on the role of orexins in the regulation of feeding, body weight and energy homeostasis in relation to other systems in which orexins are shown to be involved (Fig. 1).

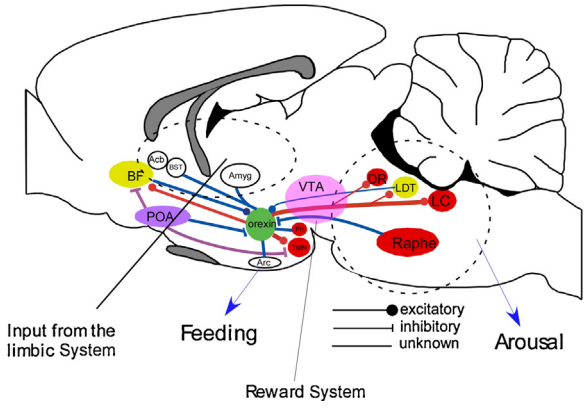

Figure 1 Input and output of orexin neurons. Orexin neurons receive input from the limbic system, including the amygdala and bed nucleus of stria terminalis. These neurons also receive inhibitory projections from the preoptic area, a region which is thought to play an important role in sleep regulation. Orexin neurons are also sensing peripheral metabolic signals to monitor animal's energy balance. Orexin neurons send excitatory projections to the arousal center in the brain stem. BF: basal forebrain; Acb: nucleus accumbens; BST: bed nucleus of the stria terminalis; Amyg: amygdala; POA: preoptic area; Arc: arcuate nucleus; VTA: ventral tegmental area; DR: dorsal raphe; LDT: laterodorsal tegmental nucleus; LC: locus coeruleus; Raphe: raphe nuclei; TMN: tuberomammillary nucleus.

Overview of the orexin system

Orexins and their structures

In 1998, we identified novel neuropeptides, orexin A and orexin B, from rat brain extracts as two endogenous ligands for two orphan G-protein-coupled receptors by a method so-called ''reverse pharmacology'', which utilized receptor-expressing cell lines as the assay system [1]. Molecular cloning studies showed that both orexin A and orexin B are derived from a common precursor peptide, *prepro-orexin*. An mRNA encoding the same precursor peptide was independently identified by de Lecea et al. as a hypothalamus-specific transcript [18]. de Lecea et al. predicted that the transcript encoded a polypeptide precursor that is proteolytically cleaved to produce two isopeptides, and named them as hypocretin-1 and hypocretin-2 (corresponding to orexin A and orexin B, respectively).

Orexin A and orexin B constitute a novel distinct peptide family, showing no significant homology with any other peptides [19]. Structural analysis of purified peptide showed that orexin A is a 33-amino-acid peptide with an N-terminal pyroglutamyl residue, two intra-chain disulfide bonds, and C-terminal amidation. This structure is completely conserved among mammalian species (human, rat, mouse, cow, sheep, dog and pig). Orexin B is a 28-amino-acid, C-terminally amidated linear peptide. Amino acid sequences of various species of orexin B show that there are several inter-species differences, although highly conserved. The C-terminal half of orexin B is very similar to that of orexin A, whereas the N-terminal half is more variable.

Transcriptional regulation of orexin

Prepro-orexin mRNA is highly specifically expressed by a population of neurons which are located in and around the LHA [1,20]. The expression of orexin has been shown to be upregulated by fasting [1], suggesting that the transcriptional regulatory system of orexin gene should include the mechanisms that restrict the expression of orexin mRNA in a selective population of neurons in the LHA, and that increase its expression during fasting. However, very limited information has been available to elucidate these mechanisms so far.

The 3.2-kb 5′-flanking region of the human *prepro-orexin* gene is sufficient for the specific expression in orexin neurons [20,21], and thus has been used as a promoter to drive specific

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