OREXIN SYSTEM: NETWORK MULTI-TASKING

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ABSTRACT

Orexin system regulates sleep/wake states and its deficiency result in narcolepsy thus indicating the crucial role of orexins in maintaining wakefulness. There are two types of orexin peptides: the orexin-A (OXA or hypocretin 1) and orexin-B (OXB or hypocretin 2). The Majority of the central nervous system orexin peptides are synthesized in neurons located in the lateral and back hypothalamus and send projections throughout the brain regions Orexin neurons are “multi-tasking” hence regulating also energy homeostasis, reward systems and feeding behaviour through connection with hypothalamic nuclei and through responsiveness to leptine and glucose. It has recently been found a connection with lymbic system suggesting a further possible role of orexins in regulating emotions. All the studies conducted confirm that orexin system regulates vigilance states, energy homeostasis, reward system, and emotions. These crucial role might be the target to develope treatments of narcolepsy, obesity, emotional stress, and drug addiction.

Keywords: Orexin, Obesity, emotional stress, narcolepsy.

DOI: 10.19193/0393-6384_2018_2_55

Received November 30, 2017; Accepted January 20, 2018

Introduction

Orexin A and B are excitatory hypothalamic neuropeptides, which play a key role in various physiologic functions such as sleep and wakefulness regulation, thermoregulation, control of energy metabolism, cardiovascular responses, feeding, and SPA (spontaneous physical activity).

Described by Sakurai et al.10 at the end of the last century (referred to as Hypocretins 1 and 2) they were firstly recognized as regulators of feeding behaviour because of their production in a hypothalamic region known as the feeding centre12,13; further research showed a clear association between hypocretins system and a sleep disorder named narcolepsy hence indicating a regulation of sleep and wakefulness14,15. More recent studies focused the attention on the role of the orexins in the coordination of emotion, energy homeostasis, reward, drug addiction and arousal16-14. These findings suggest that orexin/hypocretin system is involved in regulation of many different physiologic functions and that its implications in metabolism pathways are far to be definately determined.
The orexin/hypocretin system

Orexins are two neuropeptides synthesized, in humans as in mammals, in neurons of lateral hypothalamic and perifornical area\(^{15-17}\). The two subtypes of orexin (A and B) are produced from a common polypeptide precursor (prepro-orexin), through proteolytic processing.

Orexin A is a neuropeptide composed of 33 amino acid with an amino (N)-terminal pyroglutamyl residue, two intra-chain disulphide bonds and carboxy (C)-terminal amidation. Orexin B is a linear neuropeptide sized 28 amino acid, C-terminally amidated. The N-terminal portion has more variability whilst the C-terminal portion is very similar between the two subtypes. The actions of orexins is modulated by their receptors, orexin 1- and orexin 2-receptor (OX1R, OX2R). Orexin 1 receptor has greater affinity for orexin A than B and transmits signals throughout a G-protein class, which activates a cascade leading to an increase in intracellular calcium. By contrast orexin 2 receptor binds the two subtypes of orexin with similar affinities, and is thought to be associated also to a G inhibitory protein class.

These differences indicate that the two types of receptors have different physiological roles\(^{1,18-20}\). Furthermore mRNAs receptors show complementary distribution patterns:

- OX1R distributes in prefrontal and infralimbic cortex (IL), hippocampus (CA2), amygdala, bed nucleus of the stria terminalis (BST), PVT, anterior hypothalamus, dorsal raphe (DR), ventral tegmental area (VTA), LC, and laterodorsal tegmental nucleus (LDT)/pedunculopontine nucleus (PPT);
- OX2R distributes in the amygdala, TMN, Arc, dorsomedial hypothalamic nucleus (DMH), paraventricular nucleus (PVN), LHA, BST, PV.T, DR, VTA, LDT/PPT, CA3 in the hippocampus, and medial septal nucleus.

This support the hypothesis that different receptor subtypes play distinct physiological roles. Orexin neurons project to multiple brain region and the wide distribution of its receptors suggests that orexin system is involved in multiple physiological processes such as arousal and sleep, reward, stress, and energy homeostasis.

Modulation of orexin neurons

Electrophysiological studies on transgenic mice identified several neurotransmitters and neuromodulators influencing the activation or inhibition of orexin neurons activity. For example noradrenaline and serotonin (5HT) inhibit the activity of orexin neurons by sending inhibitory feedback projections. Through its activity on \(\alpha_2\)-adrenoceptors also dopamine can inhibit orexin neurons, whilst histamine has no effect over them. Furthermore agonists of ionotropic glutamate receptors excite orexin neurons, while glutamate antagonists inhibit their activity, thus indicating that glutamatergic neurons tonically activate orexin neurons. Inhibitory stimulation above orexin neurons comes from GABAergic input\(^{21-30}\).

Further studies where conducted in order to perform a screening for factors affecting the activity of orexin neurons. Thanks to the help of transgenic mice it has been possible identifying several factors influencing the activity of orexin neurons:

- activators such as cholecystokinin, neuropeptensin, oxytocin and vasopressin, - inhibitors such as GABA, glucose, 5-HT, noradrenaline, and leptine. Orexine neurons activity should also be modulated by adenosine and concentration in acid and CO\(_2\)\(^{12, 31-33}\). In fact acidification increases neural excitability, whereas alkalization depresses it.

Sleep/wake states regulation

Orexin system is important for maintenance of wakefulness, as demonstrated by the fact that narcolepsy is caused by orexin deficiency in human and animals\(^{34-39}\). Narcolepsy is a neurological disease affecting ~1 in 2000 individuals in the United State.

Narcolepsy is the results of the loss of orexin-A and orexin-B which have excitatory effects once bound with their receptors. These neuropeptides increase their activity during wakefulness through activation of many aminergic nuclei such as locus coeruleus, raphe nuclei, and tuberomammillary nucleus. The final results of orexins action is a stabilization of wake state and prevention of inappropriate transitions into rapid eye movement (REM) or non-REM sleep, and inhibition of REM sleep\(^{40-48}\).

In general, orexin sleep/wake regulation may be considered as relevant and essential for cognition because of its specific action in modulation sleep macroarchitecture and NREM sleep instability (Esposito et al., 2013) Moreover, probably due to the same role in sleep modulation, orexin seems to be involved also in migraine pathogenesis.
Moreover, the relationship between good quality of sleep and cognitive performance has been supported by the evidence of a link between the role of non-rapid eye movement sleep and instability in the child’s cognitive performance and by mechanisms explaining how learning and cognitive performance depend on a good night’s sleep\textsuperscript{(49-55)}.

**The role of orexin system among obesity**

Obesity is a clinical condition characterized by an excess of body fat which can lead to negative effects above health such as metabolic syndrome, type 2 diabetes mellitus, coronary heart disease, and finally a reduced life expectancy. In the last decades incidence of obesity has continuing increased in children and adults all over the world causing alert and attention from public health. Environmental and genetic factors cause large variations among humans susceptibility to obesity. Physical activity, and specifically a component named “non-exercise induced thermogenesis” (NEAT), is a factor determining variability. NEAT includes all forms of energy expenditure not associated with formal exercise, such as standing and fidgeting. A complementary concept to that of NEAT is SPA (spontaneous physical activity), used to describe any type of physical activity that does not qualify as voluntary exercise. NEAT and SPA are hereditable not interchangeable, complementary concepts: NEAT refers to energy expenditure while SPA describes the types of physical activity that result in NEAT.

However the regulation of body weight seems to be more complex according to the lack of orexin neurons. Some Authors found body weight loss and protection against obesity in brain mice submitted to repeated orexin A (OXA) injections; OXA has also been discovered to promote SPA and NEAT following injection of orexin into the rostral LH, hypothalamic paraventricular nucleus, nucleus accumbens, locus coeruleus, dorsal raphe nucleus, tuberomammillary nucleus, and substantia nigra\textsuperscript{(52-60)}.

**Energy Homeostasis**

Some authors pointed out another regulation of orexin system above muscle glucose metabolism through activation of \(\beta_2\)-adrenergic signaling indicating a further regulation of orexin above peripheral energy expenditure and not only feeding. A solid state of awake mediated by orexin could also be important in relation to food intake motivation; when facing reduced food availability animals adapt with a longer awake period, revolutionizing their normal pattern of activity. During starvation the activation of orexin neurons mediated by low leptin and glucose levels, might modulate their activity according to energy expenditure and stores, in order to maintain wakefullness, whilst orexin neuron-ablated mice fail to respond to fasting with increased wakefulness and activity. This is the confirm that orexin neurons mediate energy balance and arousal, maintaining a consolidated state of wakefulness in hungry animals in order to promote alertness\textsuperscript{(65-72)}.

**Reward System**

Recent studies focused their attention on reward system modulation by orexins. Treating narcoleptic patients with amphetamine-like drugs did not lead to addiction to these drugs. Wild-type mice are more susceptible to developing morphine dependence in comparison with orexin knockout mice. Furthermore reward brain circuits in humans affected by narcolepsy were abnormal. In the regulatory mechanisms seem to be clear that orexin neurons modulate reward system and play a predominant role in the mechanism of drug addiction.
Many reports suggest a critical role of orexin signaling in neural plastic effects at glutamatergic synapses in the ventral tegmental area (VTA)\(^{36-79}\).

**Links with brain**

The distribution of orexin neurons in the perifornical area and hypothalamic lateral and posterior area in the rat has been confirmed in humans brain. Orexin-producing neurons are diffusely distributed in multiple brain areas thus modulating the activity of such areas. Orexin neurons projections has been described in the tuberomammillary nucleus (TMN), paraventricular thalamic nuclei (PVT), arcuate nucleus and moreover in the locus ceruleus (LC) as monoaminergic nuclei. It has been confirmed that many orexin-producing neurons are glutamatergic and release glutamate on TMN nucleus. In order to study innervations to orexin neurons, genetically traced mice and rats were used; these studies lead to observe that orexin neurons are linked to several brain areas and nuclei such as lateral parabrachial nucleus (LPB), ventrolateral preoptic nucleus (VLPO), medial and lateral preoptic areas, basal forebrain (BF), posterior/dorsomedial hypothalamus, VTA, DR nucleus, and MnR.

Were furthermore identified associations to areas implied in emotion such as amygdala, nucleus accumbens, and lateral septum; another association was found to areas involved in energy homeostasis system originating in the arcuate nucleus. The findings of all these studies confirm that orexin neurons project to brain areas involved in the maintenance of wake/sleep states; orexin neurons are also linked to hypothalamic nuclei regulating feeding and energy homeostasis. This anatomical structure suggests that the activity of orexin neurons influences multiple brain areas\(^{1-39}\).

In conclusion orexin neurons are multi-tasking neurons and regulate several physiological function such as sleep/wake, feeding, and spontaneous physical activity. SPA and NEAT are key concept in understanding obesity resistance and could become new therapeutic application targets in the near future. Orexin receptors stimulation might be an attractive target of body weight gain correction. Further studies are needed in order to confirm these almost known mechanisms and explore how orexin system regulates emotions, energy homeostasis, feeding behaviour and reward system.

**References**


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