ROLE OF THE OREXIN SYSTEM ON AROUSAL, ATTENTION, FEEDING BEHAVIOUR AND SLEEP DISORDERS

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ABSTRACT

The orexin-A/hypocretin-1 and orexin-B/hypocretin-2 are neuropeptides synthesized by a cluster of neurons in the lateral hypothalamus. Orexins play an significant role in regulating arousal and attention. The term "arousal" refers to a person's general state of alertness or excitation, both physiological and psychological. Arousal levels ranges on a continuum from drowsiness through alertness to excitement. Orexin plays an important role in the regulation of feeding behaviour. The orexin stimulates food intake and reduces the metabolic rate, increasing and maintaining the body's energy reserves. Orexins play also a fundamental role in the regulation of the sleep-wake cycle by increasing arousal levels and maintaining wakefulness. Its deficit can cause narcolepsy. Key to the diagnosis of narcolepsy is the combination of a common symptom, excessive daytime sleepiness, and an uncommon symptom, cataplexy, i.e. a sudden and transient episode of muscle weakness

Keywords*: orexin, hypocretin, arousal, attention, sleep, narcolepsy.*

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Introduction

The orexin-A/hypocretin-1 and orexin-B/hypocretin-2 are neuropeptides synthesized by a cluster of neurons in the lateral hypothalamus. They were discovered almost simultaneously by two independent research groups[1-3]. The "hypocretin" term arises from the fact that the neurons secreting the peptide are localized in the lateral hypothalamus and share significant sequence homology with the incretin family of gut hormones.

The "orexin" term is due to the role played by this peptide in the control of feeding and metabolism[3-6]. Currently, the two terms are used interchangeably in the literature. Orexins selectively act on two G protein-coupled receptors: the orexin/hypocretin 1 receptor (Ox1R/HcrtR1), which is selective for orexin A (OxA)/hypocretin 1, and the orexin 2 receptor (Ox2R/HcrtR2), which binds both OxA/hypocretin 1 and orexin B/hypocretin 2 (OxB) with high affinity. Orexin-producing neurons (orexin neurons) are variable in size (the cell body diameter

ranges from 15-40 μm) and shape (spherical, fusiform or multipolar), and have been assumed to number around 3000 in the rat brain, or 7000 in the human brain[7-12]. From these regions, orexin neurons project widely to the entire neuroaxis, excluding the cerebellum. These neurons receive a variety of signals related to environmental, physiological and emotional stimuli, and innervate brain regions that regulate wakefulness and arousal, motivation and emotions, and motor and autonomic functions. Further, orexins are also involved in various hypothalamic functions such as energy homeostasis and neuroendocrine functions[13-26].

Arousal and Attention

It has been suggested that orexins play an significant role in regulating arousal and attention. The term "arousal" refers to a person's general state of alertness or excitation, both physiological and psychological. Arousal levels ranges on a continuum from drowsiness through alertness to excitement. On the other hand, at any arousal level, attention or selective attention is not a global cerebral state. Rather, selective attention is allocated on relevant inputs, thoughts and actions, while at the same time irrelevant or distracting inputs are ignored[27-35]. Selective attention affects the way in which people encode sensory input and store this information in memory[37-40].

Orexins likely regulate attention and arousal via interactions with a variety of ascending neuromodulatory systems, including dopamine neurons in the ventral midbrain, noradrenergic neurons in the locus coeruleus, cholinergic neurons in the basal forebrain. Orexin fibers and both orexin receptor subtypes are distributed in cholinergic parts of the basal forebrain, where application of orexin peptides increases cell activity and cortical acetylcholine release. It has been suggested that dysfunction in orexin-acetylcholine interactions may play a role in the arousal and attentional deficits that accompany neurodegenerative conditions as diverse as Alzheimer's disease, schizophrenia and drug addiction, and age-related cognitive decline[41-43].

Feeding Behaviour

Orexin plays an important role in the regulation of feeding behaviour. The orexin stimulates food intake and reduces the metabolic rate, increasing and maintaining the body's energy reserves. The injection of orexin into the lateral ventricles or in different brain regions stimulates feeding behaviour. In addition, if the rats are subjected to food deprivation, the production of orexin in the lateral hypothalamus increases. Normal mice which is administered a single meal a day, always at the same time, show an increase in locomotor activity just before mealtimes. The activity of orexin neurons markedly increases during the food-anticipatory period under restricted feeding in wild-type mice. It is likely that orexin neurons convey an efferent signal from putative food-entrainable oscillator or oscillators to increase wakefulness and locomotor activity. The axons of neurons that secrete orexin establish contacts with multiple brain structures known to be involved in the motivational states and in the movement, as the neocortex, periaqueductal gray, reticular formation, thalamus and locus coeruleus[43,44].

Sleep Disorders

Orexins play also a fundamental role in the regulation of the sleep-wake cycle by increasing arousal levels and maintaining wakefulness. Its deficit can cause narcolepsy. Key to the diagnosis of narcolepsy is the combination of a common symptom, excessive daytime sleepiness, and an uncommon symptom, cataplexy, i.e. a sudden and transient episode of muscle weakness. In humans, narcolepsy with cataplexy is a relatively rare disorder with a prevalence that falls between 25 and 50 per 100,000 people. Some combination of genetic and environmental factors is probably involved in the development of human narcolepsy as evidenced by the reported 25 to 31% of monozygotic twins who are concordant for the disorder.

Advances in the pathophysiology of narcolepsy have been made by studying forward (i.e., positional cloning in canine narcolepsy) and reverse (i.e., mouse gene knockout) genetics. The bred dogs with narcolepsy have the disturbance depended on the mutation of the orexin receptor 2 gene (Hcrtr2). Also in the mice whith mutation of the orexin gene there are narcoleptic symptoms. As human patients with narcolepsy, these animals shifted directly from wakefulness into REM sleep, and show periods of cataplexy while they were awake. Other authors administering to rats the hypocretin-2-saporin neurotoxin that destroys orexin neurons. The destruction of the orexinergic system induced symptoms reminiscent of narcolepsy.

In humans, abnormalities of the orexinergic system may produce narcolepsy. Nishino et al. measured hypocretin levels in the cerebrospinal fluid (CSF) of nine people with narcolepsy and 8 controls. All narcoleptic patients were HLA-DR2/DQB1*0602 positive. Hypocretin was detectable in all controls, but undetectable in seven of nine patients, regardless of duration of illness, medication, age, or gender. In the two patients with high levels of orexin, the narcolepsy might be mediated by a deficiency of hypocretin receptors (as opposed to a defect in production). Authors also suggested that an HLA-associated autoimmune-mediated destruction of hypocretin-containing neurons in the lateral hypothalamus might produce narcolepsy in these patients.

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