Orexin

From Wikipedia, the free encyclopedia

Orexin, also called hypocretin, is a neurotransmitter that regulates arousal, wakefulness, and appetite.[1] The most common form of narcolepsy, in which the sufferer briefly loses muscle tone (cataplexy), is caused by a lack of orexin in the brain due to destruction of the cells that produce it.[2]

The brain contains very few cells that produce orexin; in a human brain, about 10,000 to 20,000 neurons[2] in the hypothalamus.[1] However, the axons from these neurons extend throughout the entire brain and spinal cord,[3] where there are also receptors for orexin.

Orexin was discovered in 1998 almost simultaneously by two independent groups of rat-brain researchers.[4][5] One group named it orexin, from orexis, meaning "appetite" in Greek; the other group named it hypocretin, because it is produced in the hypothalamus and bears a weak resemblance to secretin, a hormone found in the gut.[2] The scientific community has not yet settled on a consensus for which word to use.

Contents

1. Isoforms
2. Function
   2.1 Brown fat activation
   2.2 Wakefulness
   2.3 Food Intake
   2.4 Pharmacologic potential
   2.5 Lipid metabolism
   2.6 Mood

Identifiers

<table>
<thead>
<tr>
<th>Symbol</th>
<th>PF02072 (<a href="http://pfam.xfam.org/family?acc=PF02072">http://pfam.xfam.org/family?acc=PF02072</a>)</th>
</tr>
</thead>
<tbody>
<tr>
<td>InterPro</td>
<td>IPR001704 (<a href="http://www.ebi.ac.uk/interpro/entry/IPR001704">http://www.ebi.ac.uk/interpro/entry/IPR001704</a>)</td>
</tr>
<tr>
<td>SCOP</td>
<td>1cq0 (<a href="http://scop.mrc-lmb.cam.ac.uk/scop/search.cgi?tlev=fa;&amp;pdb=1cq0">http://scop.mrc-lmb.cam.ac.uk/scop/search.cgi?tlev=fa;&amp;pdb=1cq0</a>)</td>
</tr>
<tr>
<td>SUPERFAMILY</td>
<td>1cq0 (<a href="http://supfam.org/SUPERFAMILY/cgi-bin/search.cgi?search_field=1cq0">http://supfam.org/SUPERFAMILY/cgi-bin/search.cgi?search_field=1cq0</a>)</td>
</tr>
<tr>
<td>OPM superfamily</td>
<td>154 (<a href="http://opm.phar.umich.edu/families.php?superfamily=154">http://opm.phar.umich.edu/families.php?superfamily=154</a>)</td>
</tr>
<tr>
<td>OPM protein</td>
<td>1wso (<a href="http://opm.phar.umich.edu">http://opm.phar.umich.edu</a>)</td>
</tr>
</tbody>
</table>
Isoforms

There are two types of orexin: orexin-A and -B (hypocretin-1 and -2). They are excitatory neuropeptide hormones with approximately 50% sequence identity, produced by cleavage of a single precursor protein. Orexin-A is 33 amino acid residues long and has two intrachain disulfide bonds; orexin-B is a linear 28 amino acid residue peptide. Studies suggest that orexin-A may be of greater biological importance than orexin-B. Although these peptides are produced by a very small population of cells in the lateral and posterior hypothalamus, they send projections throughout the brain. The orexin peptides bind to the two G-protein coupled orexin receptors, OX₁ and OX₂, with orexin-A binding to both OX₁ and OX₂ with approximately equal affinity while orexin-B binds mainly to OX₂ and is 5 times less potent as OX₁.[6]

The orexins are strongly conserved peptides, found in all major classes of vertebrates.

Function

The orexin system was initially suggested to be primarily involved in the stimulation of food intake, based on the finding that central administration of orexin-A and -B increased food intake. In addition, it stimulates wakefulness and energy expenditure.

Brown fat activation

Obesity in orexin knockout mice is a result of inability of brown preadipocytes to differentiate

<table>
<thead>
<tr>
<th>available protein structures:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfam structures (<a href="http://pfam.sanger.ac.uk/family/PP02072?tab=pdbBlock">http://pfam.sanger.ac.uk/family/PP02072?tab=pdbBlock</a>)</td>
</tr>
<tr>
<td>PDB RCSB PDB (<a href="http://www.rcsb.org/pdb/search/smartSubquery.do?smartSearchSubtype=PfamIdQuery&amp;pfamID=PF02072">http://www.rcsb.org/pdb/search/smartSubquery.do?smartSearchSubtype=PfamIdQuery&amp;pfamID=PF02072</a>); PDBe (<a href="http://www.ebi.ac.uk/pdbe-srv/PDBExpore?pfam?pfamID=PF02072">http://www.ebi.ac.uk/pdbe-srv/PDBExpore?pfam?pfamID=PF02072</a>); PDBj (<a href="http://pdbj.org/searchFor?query=PF02072">http://pdbj.org/searchFor?query=PF02072</a>)</td>
</tr>
<tr>
<td>PDBsum structure summary (<a href="http://www.ebi.ac.uk/thornton-srv/databases/cgi-bin/pdbsum/GetPfamStr.pl?pfam_id=PF02072">http://www.ebi.ac.uk/thornton-srv/databases/cgi-bin/pdbsum/GetPfamStr.pl?pfam_id=PF02072</a>)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>orexin (hypocretin) neuropeptide precursor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solution phase NMR structure of orexin B based on the PDB coordinates 1CQ0 (<a href="http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=1CQ0">http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=1CQ0</a>).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Identifiers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symbol</td>
</tr>
<tr>
<td>Alt. symbols</td>
</tr>
</tbody>
</table>
into brown adipose tissue (BAT), which in turn reduces BAT thermogenesis. BAT differentiation can be restored in these knockout mice through injections of orexin. Deficiency in orexin has also been linked to narcolepsy, a sleep disorder. Furthermore narcoleptic people are more likely to be obese. Hence obesity in narcoleptic patients may be due to orexin deficiency leading to impaired thermogenesis and energy expenditure.[7]

Wakefulness

Orexin seems to promote wakefulness. Recent studies indicate that a major role of the orexin system is to integrate metabolic, circadian and sleep debt influences to determine whether an animal should be asleep or awake and active. Orexin neurons strongly excite various brain nuclei with important roles in wakefulness including the dopamine, norepinephrine, histamine and acetylcholine systems[8][9] and appear to play an important role in stabilizing wakefulness and sleep.

The discovery that an orexin receptor mutation causes the sleep disorder canine narcolepsy[10] in Doberman Pinschers subsequently indicated a major role for this system in sleep regulation. Genetic knockout mice lacking the gene for orexin were also reported to exhibit narcolepsy.[11] Transitioning frequently and rapidly between sleep and wakefulness, these mice display many of the symptoms of narcolepsy. Researchers are using this animal model of narcolepsy to study the disease.[12] Narcolepsy results in excessive daytime sleepiness, inability to consolidate wakefulness in the day (and sleep at night), and cataplexy, which is the loss of muscle tone in response to strong, usually positive, emotions. Dogs that lack a functional receptor for orexin have narcolepsy, while animals and people lacking the orexin neuropeptide itself also have narcolepsy.

Central administration of orexin-A strongly promotes wakefulness, increases body temperature, locomotion and elicits a strong increase in energy expenditure. Sleep deprivation also increases orexin-A transmission. The orexin system may thus be more important in the regulation of energy expenditure than food intake. In fact, orexin-deficient narcoleptic patients have increased obesity rather than decreased BMI, as would be expected if orexin were primarily an appetite stimulating peptide. Another indication that deficits of orexin cause narcolepsy is that depriving monkeys of sleep for 30–36 hours and then injecting them with the neurochemical alleviates the cognitive deficiencies normally seen with such amount of sleep loss.[13][14]

In humans, narcolepsy is associated with a specific variant of the human leukocyte antigen (HLA) complex.[15] Furthermore, genome-wide analysis shows that, in addition to the HLA variant, narcoleptic humans also exhibit a specific genetic mutation in the T-cell receptor alpha locus.[16] In conjunction, these genetic anomalies cause the immune system to attack and kill the critical orexin neurons. Hence the absence of orexin-producing neurons in narcoleptic humans may be the result of an autoimmune disorder.[17]
**Food Intake**

Orexin increases the craving for food, and correlates with the function of the substances that promote its production.

Leptin is a hormone produced by fat cells and acts as a long-term internal measure of energy state. Ghrelin is a short-term factor secreted by the stomach just before an expected meal, and strongly promotes food intake.

Orexin-producing cells have recently been shown to be inhibited by leptin (through the leptin receptor pathway), but are activated by ghrelin and hypoglycemia (glucose inhibits orexin production). Orexin, as of 2007, is claimed to be a very important link between metabolism and sleep regulation. Such a relationship has been long suspected, based on the observation that long-term sleep deprivation in rodents dramatically increases food intake and energy metabolism, i.e., catabolism, with lethal consequences on a long-term basis. Sleep deprivation then leads to a lack of energy. In order to make up for this lack of energy, many people use high-carbohydrate and high-fat foods that ultimately can lead to poor health and weight gain. Other dietary nutrients, amino acids, also can activate orexin neurons, and they can suppress the glucose response of orexin neurons at physiological concentration, causing the energy balance that orexin maintains to be thrown off its normal cycle.\(^{[18]}\)

**Pharmacologic potential**

The research on orexin mimics is still in an early phase, although many scientists believe that orexin-based drugs could help narcoleptics and increase alertness in the brain without the side effects of amphetamines.

Merck reported at the Sleep 2012 conference that insomniacs taking an orexin blocker, suvorexant, fell asleep faster and slept an hour longer. Suvorexant was tested for three months on over a thousand patients in a phase III trial. Survorexant has undergone three phase III trials and will be available in late 2014 or early 2015 as "Belsomra".

Preliminary research has been conducted that shows potential for orexin blockers in the treatment of alcoholism. Lab rats given drugs which targeted the orexin system lost interest in alcohol despite being given free access in experiments.\(^{[19]}\)[\(^{[20]}\]

A study has reported that transplantation of orexin neurons into the pontine reticular formation in rats is feasible, indicating the development of alternative therapeutic strategies in addition to pharmacological interventions to treat narcolepsy.\(^{[21]}\)

Because orexin-A receptors have been shown to regulate relapse to cocaine seeking, a new study investigated its relation to nicotine by studying rats. By blocking the orexin-A receptor with low doses of the selective antagonist SB-334,867, nicotine self-administration decreased and also the motivation to seek and obtain the drug. The study showed that blocking of receptors in the insula decreased self-administration, but not blocking of receptors in the adjacent somatosensory cortex. The greatest decrease in self-administration was found when blocking all orexin-A receptors in the brain as a whole. A rationale for this study was the fact that the insula has been implicated in regulating feelings of craving. The insula contains orexin-A receptors. It has been reported that smokers who sustained damage to the insula lost the desire to smoke.\(^{[22]}\)
Lipid metabolism

Orexin-A (OXA) has been recently demonstrated to have a direct effect on an aspect of lipid metabolism. OXA stimulates glucose uptake in 3T3-L1 adipocytes and that increased energy uptake is stored as lipids (triacylglycerol). OXA thus increases lipogenesis. It also inhibits lipolysis and stimulates the secretion of adiponectin. These effects are thought to be mostly conferred via the PI3K pathway because this pathway inhibitor (LY294002) completely blocks OXA effects in adipocytes.[23] The link between OXA and the lipid metabolism is new and currently under more research.

Obesity in orexin-knockout mice is associated with impaired brown adipose tissue thermogenesis.[7]

Mood

High levels of orexin-A have been associated with happiness in human subjects, while low levels have been associated with sadness.[24] The finding suggests that boosting levels of orexin-A could elevate mood in humans, being thus a possible future treatment for disorders like depression. Likewise, it helps explain the incidence of depression associated with narcolepsy.

History and nomenclature

In 1996, Gautvik, de Lecea, and colleagues reported the discovery of several genes in the rat brain, including one they dubbed "clone 35." Their work showed that clone 35 expression was limited to the lateral hypothalamus.[25]

Masashi Yanagisawa and colleagues at the University of Texas Southwestern Medical Center at Dallas, coined the term orexin to reflect the orexigenic (appetite-stimulating) activity of these hormones. In their 1998 paper (with authorship attributed to Sakurai and colleagues) describing these neuropeptides, they also reported discovery of two orexin receptors, dubbed OX₁R and OX₂R.[4]

In 1998, Luis de Lecea, Thomas Kilduff, and colleagues also reported discovery of these same peptides, dubbing them hypocretins to indicate that they are synthesized in the hypothalamus and to reflect their structural similarity to the hormone secretin (i.e., hypothalamic secretin). This is the same group that first identified clone 35 two years earlier.[5][25] De Lecea and colleagues were originally in search of novel genes expressed in the hypothalamus. To do this, they extracted selective DNA found in the lateral hypothalamus. They cloned this DNA and studied it under electron microscopy. Neurotransmitters found in this area were oddly similar to the gut hormone, secretin, so de Lecea decided to name the two forms of peptides hypocretin-1 and hypocretin-2.[26] These cells were first thought to reside and work only within the lateral hypothalamus area, but immunocytochemistry tactics revealed the various projections this area truly had to other parts of the brain. A majority of these projections reached the limbic system and structures associated with it (including the amygdala, septum, and basal forebrain area).

The name of this family of peptides is currently an unsettled issue. The name "orexin" has been rejected by some due to evidence that the
orexigenic effects of these peptides may be incidental or trivial (i.e., orexin induced subjects eat more because they are awake more), though this issue is also unsettled, while other groups maintain that the name "hypocretin" is awkward, pointing out that many neuropeptides have names that are unrelated to their most important functions, and that waking is one of the important factors that supports feeding behavior. Both "orexin" and "hypocretin" will likely continue to appear in published works until a preferred name has been accepted by the scientific community.

**Selective ligands**

Several drugs[27] acting on the orexin system are under development, either orexin agonists for the treatment of conditions such as narcolepsy, or orexin antagonists for insomnia. No non-peptide agonists are yet available, although synthetic Orexin-A polypeptide has been made available as a nasal spray and tested on monkeys. Several non-peptide antagonists are in development however; SB-649,868 is under development by GlaxoSmithKline for sleep disorders and is a non-selective orexin receptor antagonist. Another OX₁ and OX₂ receptor antagonist, almorexant (ACT-078573), is a similar compound under development for primary insomnia by Actelion. A third entry is Merck's suvorexant (Belsomra),[28] which has recently been approved for use.

Most ligands acting on the orexin system so far are polypeptides modified from the endogenous agonists Orexin-A and Orexin-B, however there are some subtype-selective non-peptide antagonists available for research purposes.

- SB-334,867 – selective OX₁ antagonist
- SB-408,124 – selective OX₁ antagonist
- TCS-OX2-29 – selective OX₂ antagonist
- EMPA(drug) (N-Ethyl-2-[(6-methoxy-pyridin-3-yl)-(toluene-2-sulfonyl)-amino]-N-pyridin-3-ylmethyl-acetamide) – selective OX₂ antagonist

**Signal transduction**

Orexinergic neurons have been shown to be sensitive to inputs from Group III metabotropic glutamate receptors,[29] adenosine A₁ receptors,[30] muscarinic M₃ receptors,[31] serotonin 5-HT₁A receptors,[32] neuropeptide Y receptors,[33] cholecystokinin A receptors,[34] and catecholamines,[35][36] as well as to ghrelin, leptin, and glucose.[37] Orexinergic neurons themselves regulate release of acetylcholine,[38][39] serotonin and noradrenaline,[40] so despite the relatively small number of orexinergic neurons compared to other neurotransmitter systems in the brain, this system plays a key regulatory role and extensive research will be required to unravel the details. Orexins act on Gq-protein-coupled receptors signaling through phospholipase C (PLC) and calcium-dependent as well as calcium-independent transduction pathways. These include activation of electrogenic sodium-calcium exchangers (NCX) and a non-specific cationic conductance, likely channels of the transient receptor
potential canonical-(TRPC) type activation of L-type voltage-dependent calcium channels, closure of G-protein-activated inward rectifier potassium channels (GIRK), and activation of protein kinases, including protein kinase C (PKC), protein kinase A (PKA), and mitogen-associated protein kinase, also called mitogen-activated protein kinase (MAPK). Postsynaptic actions of orexins on their numerous neuronal targets throughout the CNS are almost entirely excitatory.[41]

See also

- Leptin

References


25. Gautvik KM, de Lecea L, et al. (1996). "Overview of the most prevalent hypothalamus-specific mRNAs, as identified by directional tag PCR subtraction". 
PMID 8710940.


28. Acuna-Goycolea C, Li Y, Van Den Pol AN (March 2004). "Group III metabotropic glutamate receptors maintain tonic inhibition of excitatory synaptic input to hypocretin/orexin neurons". 
PMID 15044540.

PMID 17093123.

30. Ohno K, Hondo M, Sakurai T (March 2008). "Cholinergic regulation of orexin/hypocretin neurons through M(3) muscarinic receptor in mice". 
PMID 18344611.

PMID 15306649.

32. Fu LY, Acuna-Goycolea C, van den Pol AN (October 2004). "Neuropeptide Y inhibits hypocretin/orexin neurons by multiple presynaptic and postsynaptic mechanisms: tonic depression of the hypothalamic arousal system". 
PMID 15470140.


**External links**

- http://www.sleepfoundation.org/article/compare-different-sleep-aids
http://www.sleepfoundation.org/alert/drug-may-offer-new-approach-treating-insomnia
http://www.sleepfoundation.org/article/orexin-receptor-antagonists-new-class-sleeping-pill


Categories: Genes on chromosome 17 | Endocrinology | Peptide hormones | Neuropeptides | Orexin antagonists

- This page was last modified on 23 October 2014 at 02:17.
- Text is available under the Creative Commons Attribution-ShareAlike License; additional terms may apply. By using this site, you agree to the Terms of Use and Privacy Policy. Wikipedia® is a registered trademark of the Wikimedia Foundation, Inc., a non-profit organization.