

Orexin Receptors

Key References

Chemtani, R.M., et al., Narcolepsy in orexin knockout mice: Molecular genetics of sleep regulation., *Cell*, **98**, 437-451 (1999).

DeLecea, L., et al., The hypocretins: Hypothalamic-specific peptides with neuroexcitatory activity., *Proc. Natl. Acad. Sci. USA*, **95**, 322-327 (1998).

Lin, L., et al., The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene., *Cell*, **98**, 365-376 (1999).

Marcus, J.N., et al., Differential expression of orexin receptors 1 and 2 in the rat brain., *J. Comp. Neurol.*, **435**, 6-25 (2001).

Mieda, M., et al., Orexin peptides prevent cataplexy and improve wakefulness in an orexin neuron-ablated model of narcolepsy in mice., *Proc. Natl. Acad. Sci. USA*, **101**, 4649-4654 (2004).

Peyron, C., et al., A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains., *Nature Med.*, **6**, 991-997 (2000).

Sakurai, T., et al., Orexins and orexin receptors: A family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior., *Cell*, **92**, 573-585 (1998).

Siegel, J.M., Hypocretin (orexin) role in normal behavior and neuropathology., *Annu. Rev. Psychol.*, **55**, 125-148 (2004).

Smart, D., et al., Characterization of recombinant human orexin receptor pharmacology in a Chinese hamster ovary cell-line using FLIPR., *Br. J. Pharmacol.*, **128**, 1-3 (1999).

Taheri, S., et al., The role of hypocretins (orexins) in sleep regulation and narcolepsy., *Annu. Rev. Neurosci.*, **25**, 283-313 (2002).

Trivedi, P., et al., Distribution of orexin receptor mRNA in the rat brain., *FEBS Lett.*, **438**, 71-75 (1998).

Willie, J.T., et al., Distinct narcolepsy syndromes in orexin receptor-2 and orexin null mice molecular genetic dissection of non-rem and rem sleep regulatory processes., *Neuron*, **38**, 715-730 (2003).

Overview

Orexin-A and orexin-B are 33- and 28-residue peptides, respectively, that were originally isolated from the rat hypothalamus. Orexin-A contains an amidated carboxy terminus, a cyclized pyroglutamyl residue at the amino terminus and two intramolecular disulfide bridges between Cys⁶-Cys¹² and Cys⁷-Cys¹⁴. Orexin-B is amidated at its carboxy terminus and shares 46% amino acid identity with orexin-A. Both peptides are derived by proteolytic cleavage from a 130 amino acid precursor, prepro-orexin, which is encoded by a gene localized to chromosome 17q21 in humans. Orexin-A is fully conserved across mammalian species, while rat and human orexin-B differ by two amino acids. Both peptides bind to two G protein-coupled receptors, termed OX₁ and OX₂, and mediate increases in intra-cellular calcium concentrations. The receptors display 64% homology, are most closely related (26%) to the Y₂ neuropeptide Y receptor and are highly conserved across species, with a 94% homology between the rat and human receptors. Orexin-A is equipotent at OX₁ and OX₂ receptors, while orexin-B displays moderate (~10 fold) selectivity for OX₂ receptors.

Independent of the isolation of the orexins, another group identified a hypothalamic-specific mRNA encoding a precursor protein they termed prepro-hypocretin and predicted that proteolytic processing would yield two peptides, hypocretin-1 (residues 28-66) and hypocretin-2 (residues 69-97). These researchers also predicted both peptides would be amidated and added the caveat that the N-terminus of hypocretin-1 was not defined. Subsequent comparisons showed that prepro-orexin and prepro-hypocretin were the same peptide, and that orexin-B and amidated hypocretin-2 were identical. Moreover, orexin-A and

hypocretin-1 corresponded, allowing for the overestimation of the N-terminus of hypocretin-1.

Prepro-orexin mRNA is found in the hypothalamus, and to a markedly lesser extent, the testes, adrenals and myenteric plexus. Orexin-A and orexin-B are predominantly located in the hypothalamus, but due to extrahypothalamic projections are also found elsewhere in the brain, most notably the locus coeruleus and spinal cord, as well as in the adrenals and small intestine. OX₁ receptors are expressed mainly in the hypothalamus and locus coeruleus, as well as in the hippocampus, dorsal raphe and, to a lesser extent, other brain areas and the spinal cord. OX₂ receptors are also expressed in the hypothalamus, as well as the cortex and the spinal cord, and a few discrete brain nuclei. Both receptors are also expressed in the pituitary and the gut.

Recently, several compounds have been developed to help characterize the orexin system. These include two peptides, [Ala²⁷]orexin-B(6-28) and [Pro¹¹]orexin-B(6-28), both of which show at least 1000-fold selectivity for OX₂ versus OX₁ receptors. A number of small molecule antagonists for orexin receptors have been reported, notably the OX₁ receptor antagonist, SB-334867-A, which displays affinities of 40 and 2000 nM at OX₁ and OX₂ receptors, respectively. In rats, this compound has been shown to inhibit feeding, to accelerate the transition between feeding and resting, and to have effects on analgesia, hypertension and the central release of nor-epinephrine. Another non-peptide orexin receptor antagonist, SB-674042, displays a >100 fold selectivity for inhibiting calcium mobilization induced by OX₁ versus OX₂ receptor activation.

The orexin system has been implicated in the control of feeding behavior, especially the behavioral satiety sequence and energy homeostasis, as well as neurocrine and cardiovascular effects, including modulation of blood pressure. The orexins are also involved in the regulation of the sleep-wake cycle, with orexin-A stimulating the locus coeruleus and so increasing arousal. Several studies have shown that a mutation in the OX₂ receptor in some breeds of dog leads to narcolepsy. In addition, disruption of the prepro-peptide in mice or rats gives rise to narcoleptic symptoms, while disruption of OX₁ or OX₂ receptors in mice also leads to sleep abnormalities. Furthermore, patients with narcolepsy appear to have a disrupted orexin system, with most cases seeming to occur as a result of a lack of orexin.

Orexin Receptors

CURRENTLY ACCEPTED NAME	OX ₁	OX ₂
ALTERNATE NAME	Hcrtr1 Orexin-A receptor	Hcrtr2
STRUCTURAL INFORMATION	425 aa (human)	445 aa (human)
SUBTYPE SELECTIVE AGONISTS	Orexin-A (O6012) > Orexin-B (O6137 (h), O6262 (r,m))	Orexin-A (O6012) = Orexin-B (O6137 (h), O6262 (r,m)) [Ala ²⁷]-orexin-B(6-28), [Pro ¹¹]-orexin-B(6-28)
SUBTYPE SELECTIVE ANTAGONISTS	SB-334867-A, SB-674042	Not known
SIGNAL TRANSDUCTION MECHANISMS	Gq ₁₁ (increase IP ₃ /DAG)	Gq ₁₁ (increase IP ₃ /DAG)
RADIOLIGANDS OF CHOICE	[¹²⁵ I]-Orexin-A, [³ H]-SB-674042	[¹²⁵ I]-Orexin-A
TISSUE EXPRESSION	Prefrontal cortex (r), infralimbic cortex (r), hippocampus (r), paraventricular thalamic nucleus (r), ventromedial hypothalamic nucleus (r), dorsal raphe nucleus (r), locus coeruleus (r), adrenal zona fasciculate-reticularis (h), adrenal medulla (h)	Cerebral cortex (r), basal forebrain cholinergic nuclei (r), hippocampus (r), paraventricular premammillary nuclei (r), midline and intralaminar thalamus (r), raphe nuclei (r), hypothalamic nuclei (r)
PHYSIOLOGICAL FUNCTION	Sleep-wakefulness, energy homeostasis	Sleep-wakefulness
DISEASE RELEVANCE	Not known	Narcolepsy (canine)

Abbreviations

SB-334867-A: 1-(2-Methylbenzoxazol-6-yl)-3-[1,5]naphthyridin-4-yl-urea hydrochloride

SB-674042: (5-(2-Fluoro-phenyl)-2-methyl-thiazol-4-yl)-1-((S)-2(5-phenyl-(1,3,4)oxadiazol-2-ylmethyl)-pyrrolidin-1-yl)-methanone

h: human

m: mouse

r: rat

FOOTNOTES