

The Neurobiology & Pharmacology of Sleep: An Overview

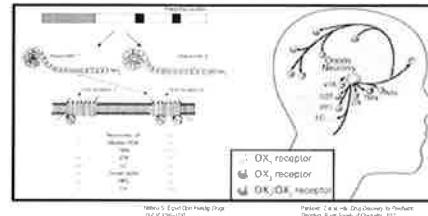
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Emerging Science in Sleep: Discovery of Orexins

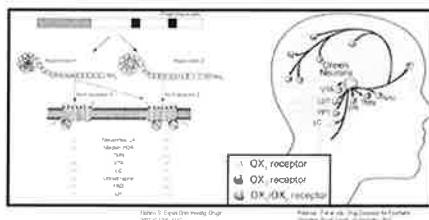


- Orexin (hypocretin) discovered by 2 groups (Yanagisawa et al 1998, de Lecea et al 1998) and linked with canine narcolepsy (Mignot et al 1999)¹
- Orexin peptides bind with different affinities to OX1R and OX2R, which are differentially expressed in the CNS^{2,3}

1. Saper CB et al. *Nature*. 2005;437:1257-1263
2. Reckhow Z et al. eds. *Drug Discovery for Psychiatric Disorders*. Royal Society of Chemistry, 2012
3. Nishida S. *Expert Opin Investig Drugs*. 2007;16:1785-1797

4. Sakurai T. *Nat Rev Neurosci*. 2007;8:171-181
5. Thorek TD et al. *Neuron*. 2000;27:469-474

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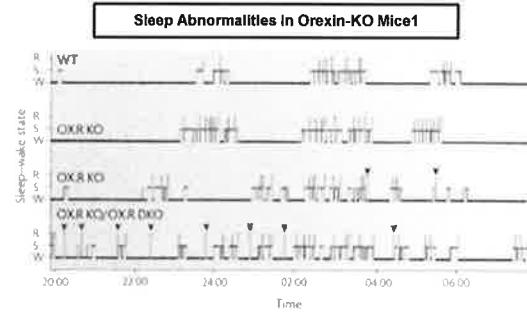


- Orexin signalling plays a key role in increasing arousal across species⁴
- Orexin neurons (<100 thousand) are highly localized to the hypothalamus^{4,5}

1. Saper CB et al. *Nature*. 2005;437:1257-1263
2. Reckhow Z et al. eds. *Drug Discovery for Psychiatric Disorders*. Royal Society of Chemistry, 2012
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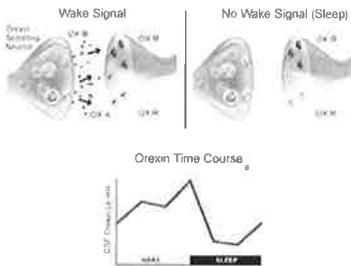
Orexins as a Key Stabilizer of Wakefulness



DKO, double knock-out; KO, knock-out; OX₁R, orexin-1 receptor; OX₂R, orexin-2 receptor

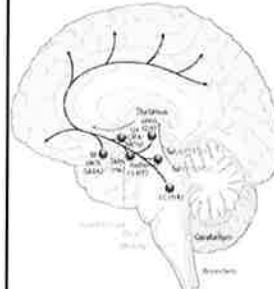
1. Sakurai T. *Nat Rev Neurosci*. 2007;8:171-181.

Orexin Signaling Throughout the Day



*Extrapolated from rat and non-human primate data. Ethical methods of CSF assessment prevent accurate readings in humans.
1. Rankovic Z et al, eds. *Drug Discovery for Psychiatric Disorders*. Royal Society of Chemistry, 2012.

Wake Promotion: Arousal Promoting Regions of the Brain

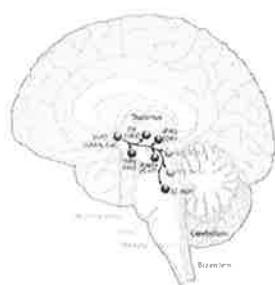


Locus	Neurotransmitter(s)
Pedunculopontine nuclei (PPt)	Acetylcholine (ACh)
Laterodorsal tegmental nucleus (LDT)	ACh
Locus coeruleus (LC)	Norepinephrine (NA)
Raphe nuclei	Serotonin (5-HT)
Ventrolateral periaqueductal gray (vPAG)	Dopamine (DA)
Tuberoventral nucleus (TMN)	Histamine (His)
Lateral hypothalamus (LHA)	Orexin (ORX) or melanin-concentrating hormone (MCH)
Basal forebrain (BF)	γ-aminobutyric acid (GABA) or ACh

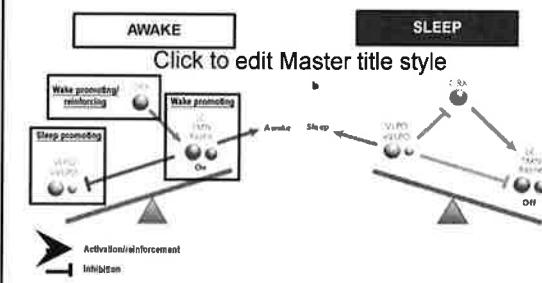
E.Saper CB et al. *Nature* 2005;437:125-126

Sleep Promotion: Ventral lateral preoptic nuclei (VLPO)

Locus	Neurotransmitter(s)
Ventral lateral preoptic nuclei (VLPO)	γ-aminobutyric acid (GABA) and galanin



Saper's Flip-Flop Switch: Describing the Transitions Between Wake and Sleep



E.Saper CB et al. *Nature* 2005;437:125-126