KNOW narcolepsy®

There's More to Know!

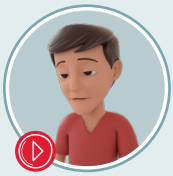
Rethinking Narcolepsy

Learn about sleep-wake state instability, narcolepsy, and the role of histamine. Watch these videos today at **KnowNarcolepsy.com/hcp**.

Neurobiology of Sleep and Wakefulness

There are three distinct states of sleep and wakefulness: wakefulness, non-REM sleep, and REM sleep.[1]

- Coordinated systems in the brain ensure stable boundaries and predictable transitions between states and also ensure that elements of one state do not intrude into another[2,3]
- The hypothalamus is a critical "control center" for maintaining sleep-wake state stability[3-5]



Pathophysiology of Narcolepsy

Narcolepsy is a disorder characterized by sleep-wake state instability.[2]

- In narcolepsy, loss of hypocretin neurons in the hypothalamus leads to*:
  - insufficient activation of histamine neurons and wake-promoting neurons outside of the hypothalamus[6,7]
  - insufficient inhibition and intermittent activation of non-REM sleep–promoting neurons and REM sleep–promoting neurons[7-9]
- Excessive daytime sleepiness (EDS) and symptoms of REM sleep dysregulation (e.g., cataplexy) reflect the underlying sleep-wake state instability of narcolepsy [2,7]

Role of Histamine in Sleep and Wakefulness

Like hypocretin neurons, histamine neurons play an important role in promoting and stabilizing wakefulness.[2,10-12,†]

- The tuberomammillary nucleus, located in the hypothalamus, is the only neuronal source of histamine in the brain[10]
- Histamine neurons:
  - promote wakefulness by activating cortical neurons and wake-promoting neurons outside of the hypothalamus[10]
  - inhibit non-REM sleep–promoting neurons directly and indirectly by reinforcing activation of wake-promoting neurons[5,10]
  - inhibit REM sleep–promoting neurons[5,10,12]

*Based on animal and human studies.
†Based on in vitro and in vivo animal studies.

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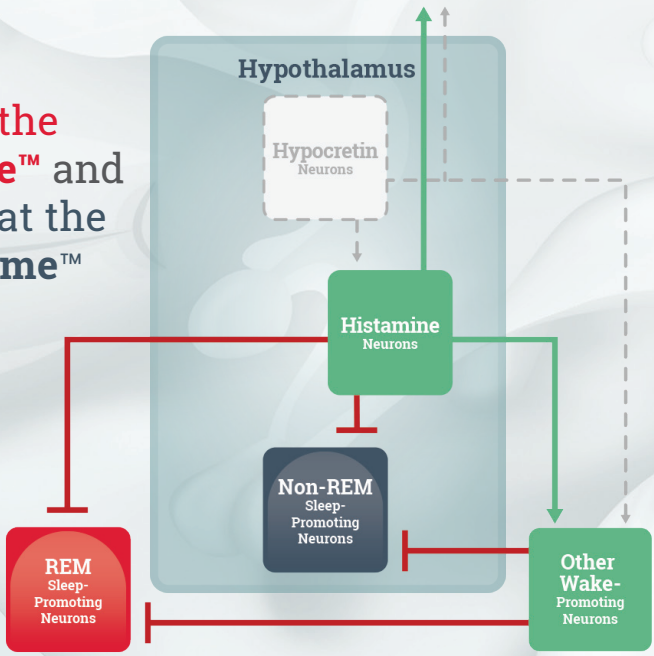
Know the Science of Sleep-Wake State Instability

Hypocretin and histamine neurons play complementary roles in wakefulness.[13]

The loss of hypocretin causes insufficient activation of histamine neurons and wake-promoting neurons during the day, which can lead to insufficient inhibition and intermittent activation of **REM sleep**–promoting neurons and **non-REM sleep**–promoting neurons.[2,5-8,10] This process results in sleep-wake state instability.[2,3]

REM at the **Wrong Time™** and **Non-REM** at the **Wrong Time™**



Signs and symptoms of narcolepsy are manifestations of the underlying sleep-wake state instability.[2,7]

Learn more at **KnowNarcolepsy.com/hcp**

1. Brown RE et al. *Physiol Rev*. 2012;92(3):1087-1187. **2.** España RA, Scammell TE. *Sleep*. 2011;34(7):845-858. **3.** van der Heide A, Lammers GJ. In: Thorpy MJ, Billiard M, eds. *Sleepiness: Causes, Consequences and Treatment*. Cambridge, UK: Cambridge University Press; 2011:111-125. **4.** Shan L et al. *Nat Rev Neurol*. 2015;11(7):401-413. **5.** Scammell TE et al. *Neuron*. 2017;93(4):747-765. **6.** Scammell TE. *N Engl J Med*. 2015; 373(27):2654-2662. **7.** Saper CB et al. *Neuron*. 2010;68(6):1023-1042. **8.** Pillen S et al. *Curr Treat Options Neurol*. 2017;19(6):23. **9.** Saper CB et al. *Nature*. 2005; 437(7063):1257-1263. **10.** Haas HL et al. *Physiol Rev*. 2008;88(3):1183-1241. **11.** Schwartz MD, Kilduff TS. *Psychiatr Clin North Am*. 2015;38(4):615-644. **12.** Scammell TE et al. *Sleep*. 2019;42(1):doi:10.1093/sleep/zsy183. **13.** Anaclet C et al. *J Neurosci*. 2009;29(46):14423-14438.

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