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 another²,³
- The hypothalamus is a critical “control center” for maintaining sleep-wake state stability³,⁵

### Pathophysiology of Narcolepsy

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

- In narcolepsy, loss of hypocretin neurons in the hypothalamus leads to⁶:
  - insufficient activation of histamine neurons and wake-promoting neurons outside of the hypothalamus⁵,⁷
  - insufficient inhibition and intermittent activation of non-REM sleep-promoting neurons and REM sleep-promoting neurons⁷,⁹
- Excessive daytime sleepiness (EDS) and symptoms of REM sleep dysregulation (e.g., cataplexy) reflect the underlying sleep-wake state instability of narcolepsy²,⁷

### 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 brain¹⁰
- Histamine neurons:
  - promote wakefulness by activating cortical neurons and wake-promoting neurons outside of the hypothalamus¹⁰
  - inhibit non-REM sleep-promoting neurons directly and indirectly by reinforcing activation of wake-promoting neurons⁵,¹⁰
  - inhibit REM sleep-promoting neurons⁵,¹⁰,¹²

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¹Based 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. 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. This process results in sleep-wake state instability.

Signs and symptoms of narcolepsy are manifestations of the underlying sleep-wake state instability.

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