

Narcolepsy study finds surprising increase in neurons that produce histamine

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A new study provides surprising evidence that people with narcolepsy have an increased number of neurons that produce histamine, suggesting that histamine signaling may be a novel therapeutic target for this potentially disabling sleep disorder.

"The orexin/hypocretin neuropeptides promote [wakefulness](#), and researchers have known for 13 years that [narcolepsy](#) is caused by loss of the orexin/hypocretin neurons in the hypothalamus," said principal investigator Thomas Scammell, MD, professor of Neurology at Beth Israel Deaconess Medical Center in Boston, Mass. "We found that narcolepsy is also associated with a very large increase in the number of neurons producing histamine, another wake-promoting neurotransmitter."

The study involved counting the number of [hypothalamic neurons](#) producing orexin, melanin-concentrating hormone and histamine in seven narcolepsy patients and 12 patients that served as a control group. The researchers also examined these systems in mouse models of narcolepsy (six orexin/ataxin-3 transgenic mice and five orexin ligand [knockout mice](#), compared to six wild-type mice).

Results show that narcolepsy patients had 94 percent more histaminergic tuberomammillary nucleus (TMN) neurons. This increase was more pronounced in five narcolepsy patients with severe orexin neuron loss compared to two patients with less severe loss. Likewise, the number of histaminergic TMN neurons was increased 53 percent in orexin ligand

knockout mice compared to wild type mice, while orexin/ataxin-3 [transgenic mice](#) showed an intermediate 28 percent increase.

According to the authors, the surprising increase in wake-promoting histaminergic neurons in narcolepsy may be a compensatory response to the loss of orexin/hypocretin neurons. It also may contribute to some of the symptoms of narcolepsy such as preserved consciousness during cataplexy and fragmented nighttime sleep.

"Previous studies have assumed that loss of the orexin neurons was a sufficient explanation for the symptoms of narcolepsy, and this large increase in histamine-producing neurons was unexpected," said Scammell. "This new observation suggests that drugs that reduce histamine signaling at night may improve sleep in narcolepsy, whereas drugs that enhance histamine signals may be a good option for promoting alertness during the day."

Scammell noted that medications that enhance histamine signaling are now under development.

The research abstract was published recently in an online supplement of the journal *SLEEP*, and Philipp Valko, MD a member of the Scammell Lab will present the findings Monday, June 3, in Baltimore, Md., at SLEEP 2013, the 27th annual meeting of the Associated Professional Sleep Societies LLC.

The American Academy of Sleep Medicine reports that narcolepsy is a form of hypersomnia that involves daily periods of irrepressible need to sleep or daytime lapses into sleep. In some cases this sleepiness occurs in unusual situations as sudden, irresistible sleep "attacks." When left untreated, narcolepsy can be socially disabling and isolating.

Provided by American Academy of Sleep Medicine

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