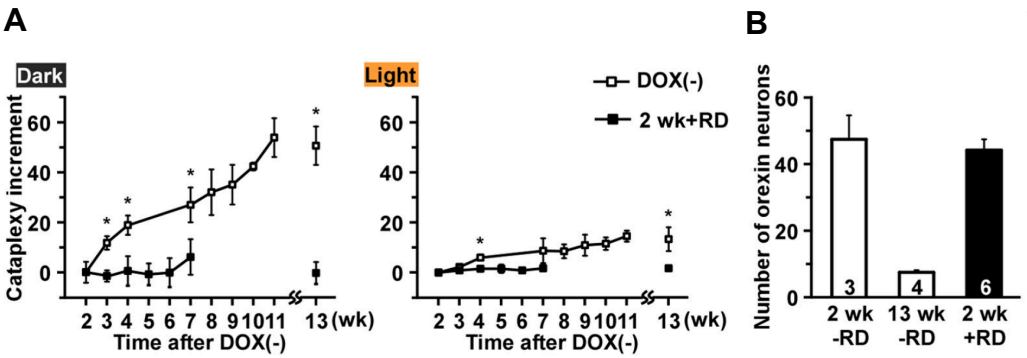
A Novel mouse model for the study of narcolepsy and orexin system function

Background

Narcolepsy is a chronic sleep disorder characterized by excessive daytime sleepiness, fragmentation of sleep/wakefulness, hypnagogic hallucinations, sleep paralysis, and cataplexy. In humans, the onset of narcolepsy is typically in adolescence or early adulthood. Because definitive diagnosis may take as long as a decade, it is difficult to study the development of symptomatology after initial onset of the disorder. Narcolepsy is a chronic neurodegenerative disease caused by a deficiency of orexin/hypocretin-producing neurons in the lateral hypothalamus. Animal models have helped elucidate the role of orexin neurons in sleep/wakefulness regulation, metabolism, and addiction. However, current animal models congenitally lack the orexin peptides, receptors, or neurons and thus do not replicate the typical post-pubertal onset of this disorder in humans. Furthermore, current mouse models have limited utility in the development of novel pharmacological treatments for narcolepsy because cataplexy events are relatively infrequent.

Technology Overview

To create a model with closer fidelity to human narcolepsy, researchers used the Tet-off system in which expression of diphtheria toxin A (DTA) in orexin neurons is controlled by the presence or absence of doxycycline (DOX). By changing DOX-containing diet to normal diet, all narcolepsy symptoms were reproduced in this model mice, that is robust cataplexy as well as disrupted sleep architecture and weight gain.



DOX was removed from diet at 12 weeks of age for 2 weeks followed by DOX replacement for 10 weeks. **A**, Increment in the number of cataplexy bouts during the dark (left) and light (right) periods relative to the number of bouts at 2 weeks of DOX(-). **B**, The number of orexin-immunoreactive (orexin-ir) cell bodies at the end of the DOX(-) 2 weeks + RD trial, with DOX(-) for 2 weeks and 13 weeks plotted as a comparison.

Benefits

The symptoms of narcolepsy vary from patients who only show intense daytime drowsiness to those who have numbing attacks. This transgenic mice are able to control orexin neural elimination at any time, making it possible to generate mice that are similar to the symptoms of each patient. The development of therapeutic drugs by generating mice with various symptoms with this mouse model will greatly contribute to the treatment of human narcolepsy, which varies in symptoms among individuals.

Applications

Because the orexin/hypocretin system has been implicated in the control of metabolism and addiction as well as sleep/wake regulation, this model mice are a novel model in which to study these functions, for pharmacological studies of sleep/wake fragmentation or cataplexy, and to understand the process of network reorganization as orexin input is lost.

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