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Partial ablation of the orexin field induces a sub-narcoleptic phenotype in a conditional mouse model of orexin neurodegeneration

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Abstract

Narcolepsy type 1 (Na-1) and 2 (Na-2) are characterized by an inability to sustain wakefulness and are likely caused by degeneration of orexin neurons. Near complete orexin neurodegeneration depletes orexin-A from the cerebrospinal fluid and produces Na-1. The pathophysiology of Na-2 is less understood but has been hypothesized to be due to less extensive loss of orexin neurotransmission. The orexin-tTA; TetO diphtheria toxin A mouse allows conditional control over the extent and timing of orexin neurodegeneration. To evaluate partial ablation of the orexin field as a model of Na-2, orexin-A positive cell counts and sleep/wake phenotypes (determined by piezoelectric monitoring) were correlated within individual mice after different protocols of diet-controlled neurodegeneration. Partial ablations that began during the first 8 days of study were 14% larger than partial ablations induced during the last 8 days of study, 6 weeks later and prior to sacrifice of all mice, suggesting orexin-A positive cell death continued despite the resumption of conditions intended to keep orexin neurons intact. Sleep/wake of mice with 71.0% orexin-A positive cell loss, initiated at the beginning of study, resembled that of orexin-intact controls more than mice with near complete neurodegeneration. Conversely, mice with 56.6% orexin-A positive cell loss, created at the end of study, had sleep/wake phenotypes that were similar to those of mice with near complete orexin-A positive cell loss. Collectively, these results suggest that compensatory wake-promotion develops in mice that have some critical portion of their orexinergic system remaining after partial ablation.

hypocretin, mouse, narcolepsy, neurodegeneration, orexin, piezoelectric sleep monitoring, sleep

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