News Release

Title

Dual Orexin and MCH neuron-ablated mice display severe sleep attacks and cataplexy

Key Points

・Orexin and MCH-neurons ablated mice showed frequent sleep attacks with elevated spectral power in the delta and theta range, a unique state that we named “delta-theta sleep”.

・DT sleep is a novel brain state, in which the EEG spectra is distinguished from the NREM, REM or cataplexy.

・MCH neurons have a role to suppress cataplexy.

Summary

Narcolepsy is one of the sleep disorders, which the patients have symptoms that is day-time sleepiness, hallucination and cataplexy and so. The cause of narcolepsy had been unclear for a long while. In the last decade, researches revealed that narcolepsy is resulted from the loss of orexin peptide-producing neurons (orexin neurons) by auto-immunoreaction. However, the mechanism of day-time sleepiness or cataplexy caused by absence of orexin neurons is still uncertain. On the other hand, melanin-concentrating hormone-producing neurons (MCH neurons) are existed next to orexin neurons in the lateral hypothalamus. We previously showed that MCH neurons have higher activity in REM sleep (Izawa et al., Science 2019) and plays a role in regulation of REM sleep (Tsunematsu et al., J Neurosci 2014). It is still unknown how the interaction between orexin and MCH neurons regulates sleep/wakefulness and cataplexy. Previously, we generated narcolepsy model mice in which orexin neurons were exclusively ablated with timing-control manner. These mice almost re-produced symptoms observed in narcolepsy patients (Tabuchi et al., J Neurosci 2014). In this research, we used the same method to generate both orexin and MCH neurons-ablated mice. We analyzed the alteration of sleep/wakefulness pattern or progression of cataplexy during ablation. The orexin and MCH neurons-ablated mice showed frequent short sleep attacks during wakefulness. In this sleep attack, EEG contained dominant delta (1-5Hz) and theta (6-10Hz) wave band. This EEG is different from all other known sleep stages, such as NREM or REM sleep. Therefore, we named this state as DT sleep, delta theta sleep. Furthermore, the significant increment of duration in cataplexy designated that MCH neurons play a suppressive role in duration of cataplexy.

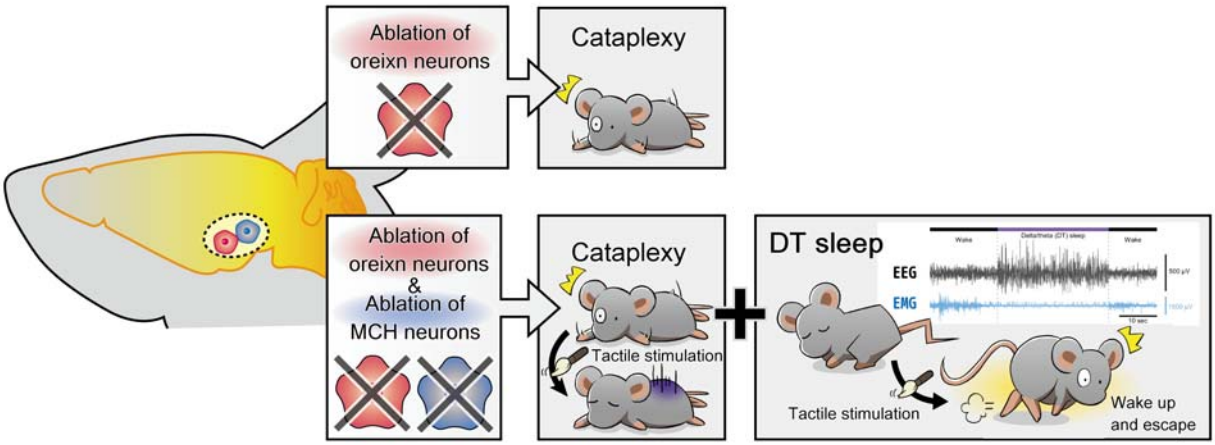
Research Background

The neuronal mechanism of regulating sleep/wakefulness is unknown. Within a decade, it is well-known that orexin neurons play a crucial role in maintaining wakefulness. Specific loss of orexin neurons cause narcolepsy, which patients are hard to maintain wakefulness and fall asleep in inappropriate condition. Cataplexy, a sudden muscle weakness triggered by strong emotion, such as laughing, is one of the symptom of narcolepsy. However, the neuronal

mechanism underling these symptoms is still unclear. On the other hands, how the MCH neurons, which is located next to orexin neurons in the lateral hypothalamus, regulate sleep/wakefulness functionally interact with orexin neurons. This research use both orexin and MCH neurons ablated mice to identify the alteration of sleep/wakefulness and cataplexy compare with orexin neurons ablated mice.

Research Results

Ablation of orexin and MCH neurons induced frequent short sleep attacks. This sleep attack has dominant delta and theta wave band in EEG. This feather is distinguished from other sleep stages, NREM and REM sleep. Therefore, we named it "DT sleep" (see Figure). The average time of DT sleep persist about 15 sec, and DT sleep was observed up to 180 times per day. The drugs to treat cataplexy had no effect on DT sleep indicated that cataplexy and DT sleep have different neuronal mechanism. Moreover, the significant increasing duration of cataplexy in orexin and MCH-ablated mice indicated that MCH neurons play a suppressive role in duration of cataplexy.



Research Summary and Future Perspective

In clinical case, it has been reported that the hypersomnia is observed in the patient having low orexin and MCH peptide concentration in the CSF. Combining with our results, it indicates that the clarify the neuronal circuit of MCH neurons with orexin neurons help to understand symptom of narcolepsy such as sleep abnormality and cataplexy.

Publication

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