News Release

Title

REM sleep-active MCH neurons are involved in forgetting hippocampus-dependent memories

Key Points

- **It was not well understood that the mechanism of how memory is fixed and erased during sleep.**
- **Using mice, we discovered that a small number of melanin-concentrating hormone-producing nerves (MCH nerves) located in the hypothalamus are active during REM sleep and have a role in erasing memory.**
- **To reveal the role of the MCH nerve in memory will contribute to the development of a treatment for post-traumatic stress disorder (PTSD) in which the memories of experiences with strong fear remain as trauma.**

Summary

The neural mechanisms underlying memory regulation during sleep are not yet fully understood. We found that rapid eye movement (REM) sleep-active melanin-concentrating hormone (MCH)-producing neurons in the hypothalamus actively contribute to forgetting. Hypothalamic MCH neurons densely innervated the dorsal hippocampus. Activation or inhibition of MCH neurons impaired or improved hippocampus-dependent memory, respectively. Activation of MCH nerve terminals in vitro reduced firing of hippocampal pyramidal neurons by increasing inhibitory inputs. Wake- and REM sleep-active MCH neurons were distinct populations that were randomly distributed in the hypothalamus. REM sleep state-dependent inhibition of MCH neurons impaired hippocampus-dependent memory without affecting sleep architecture or quality. REM sleep-active MCH neurons in the hypothalamus are thus involved in active forgetting in the hippocampus.

Research Background

Our memory is thought to be consolidated or erased during sleep, but the mechanism is not clear. In particular, it was not well understood how “REM sleep”, which appears only after “non-REM sleep”, which is a deep sleep state, is related to memory. During REM sleep we have dreams, but usually dreams cannot be memorized and are forgotten soon after waking up. This suggests the existence of neurons that inhibit to remember dreams during REM sleep, but it has not been found so far.

This research group has been studying the role of MCH neurons in the regulation of sleep and wakefulness, focusing on the localization of melanin-concentrating hormone neurons (MCH nerves) in the hypothalamus that regulates endocrine and autonomous functions. From previous studies, the MCH neurons were implicated in appetite since MCH injection into the

ventricle in the brain induced feeding behavior. However, functions in sleep/wakefulness are elucidated using new experimental techniques, optogenetics and chemogenetics that enable manipulate the activities of specific type of neurons. This study group used these techniques to manipulate the activities of MCH neurons. Activation of MCH neurons is converted Non-REM sleep to REM sleep, and total REM sleep time was increased. This result suggested that MCH neurons are involved in the regulation of REM sleep.

Research Results

Using cutting edge technologies to manipulate activity of specific type of neurons, optogenetics and chemogenetics, this research group found that memory was impaired when MCH neurons were activated, and memory was improved when MCH neurons were suppressed. In particular, MCH neurons projecting to the hippocampus, which is the central area of memory, inhibited the activity of pyramidal neurons to impaire memory during REM sleep.

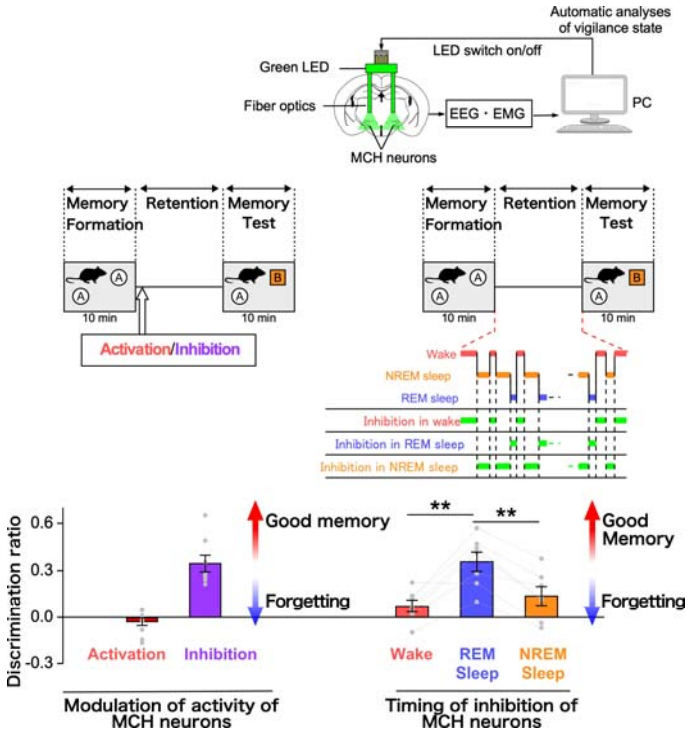

Figure 1: Sleep and wakefulness dependent inhibition of MCH neurons. Inhibition of MCH neurons during REM sleep in retention period improved memory suggesting activity of MCH neurons in REM sleep impairs memory.

Next, this group investigated that how the activity of the MCH neurons changes across sleep and wakefulness state change. Fiber photometry, which enables measure neural activity freely behaving animal, was applied. It found that MCH neuron activity increased during REM sleep and wakefulness in mice. Then, this group applied calcium imaging of MCH neurons at the single cell resolution using micro endoscope which is 2 g weight microscope enables mount on mouse head. They found that there are three types of MCH neurons in the brain, that is 1) wake active MCH neurons, 2) REM sleep active MCH neurons and 3) wake and REM sleep active MCH neurons.

Further to investigate the relationship between sleep and MCH neurons activity during the memory retention period, novel object recognition test and sleep and wakefulness state dependent inhibition of MCH neurons were performed. In novel object recognition test, after formation of memory the object, MCH neural activity was inhibited in retention period with sleep and wakefulness state dependent manner, that is 1) only during REM sleep, 2) only during

non-REM sleep or 3) only during awakening. As a result, memory improvement was observed only when MCH neural activity was suppressed during REM sleep. However, suppressing MCH activity activity during non-REM sleep and awakening did not affect memory (Figure 1).

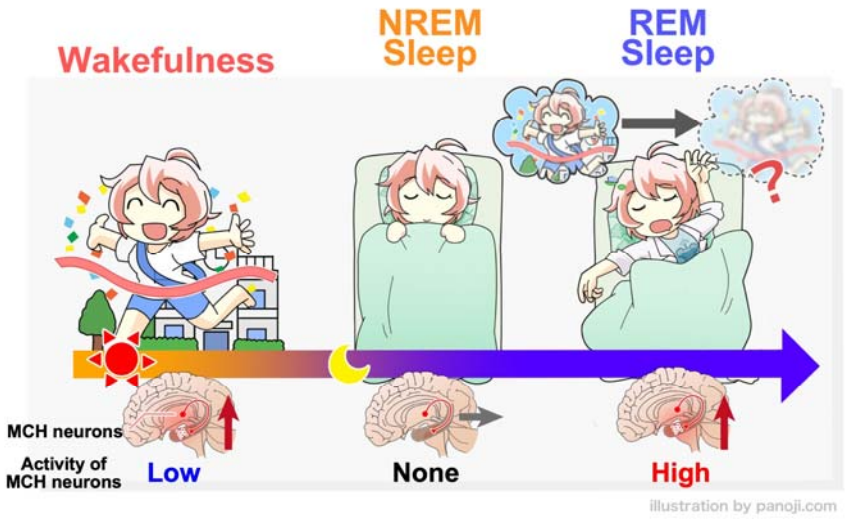

Figure 2: Activity of MCH neurons are low in wakefulness and high in REM sleep. Activity of MCH neurons in REM sleep inhibited neurons in the hippocampus to forget memory during REM sleep.

From these results, it became clear that MCH neurons that are active during REM sleep are involved in memory forgetting through suppression of hippocampal neurons (Figure 2).

Research Summary and Future Perspective

Although many researches have been done on memory consolidation during sleep, little has been done on memory erasure or forgetting. Newly discovered mechanism that MCH neurons erase memory will contribute to understand memory control during sleep.

In addition, activation of MCH neurons also erased the memory of the contextual fear conditioning. Therefore, if MCH neurons can be selectively activated, this can be applied to treat post-traumatic stress disorder (PTSD) which is strong fear remains as a trauma, by erasing memory.

Publication

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