The hippocampal-prefrontal pathway in modulation of sleep and wakefulness

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Sleep is a natural behavioral state of rest that takes up a third of our lifetime. It is essential for physical and mental health. Insufficient sleep can profoundly impair cognitive performance during wakefulness. In fact, long-term sleep deprivation is linked to many health problems, including depression, obesity, and cardiovascular diseases. Moreover, sleep disorders are one of the most common clinical problems. Yet, mechanisms regulating sleep are poorly understood. Nevertheless, several brain regions including the brainstem, preoptic and lateral hypothalamus, and basal forebrain have been implicated in sleep. Intriguingly, recent studies identified high level of activity in prefrontal cortex (PFC) and hippocampus (HPC) in patients with insomnia, suggesting that cortical activity might promote arousal and suppress sleep. Furthermore, increased cortical drive has been implicated in deep, long rebound sleep after sleep deprivation, suggesting that reduced cortical activity during wakefulness might facilitate the transition from wake to sleep. However, mechanisms of how neuronal activity in the HPC and PFC control sleep remain unclear.

The HPC and PFC are known to control cognitive and mnemonic functions. The HPC is involved in learning and memory whereas the PFC has been implicated in working memory and executive functions. In particular, the monosynaptic projection from the HPC (ventral HPC, or vHPC in rodents) to PFC is involved in cognition and emotional regulation in healthy subjects; and its impairment may contribute to cognitive dysfunction in schizophrenia. Recently, we found that the vHPC-PFC connectivity is critical to top-down attention, a thought-driven process to selectively concentrating on a discrete aspect of information. In light that attention and arousal interact closely and attention levels correlate with those of arousal and wakefulness, we hypothesize that the vHPC-PFC connectivity may be necessary to maintain the wakefulness and sleep states and thus regulate sleep-wake transition. Preliminary experiments found that the vHPC-PFC synchrony during sleep is reduced in theta and gamma oscillations but increased in delta oscillation, compared with wakefulness. Moreover, the vHPC-PFC connectivity was reduced at delta and theta frequencies in the wake-sleep transition. In sleep-wake transition the vHPC-PFC connectivity was increased at delta, theta and low gamma frequencies. These results suggest for the first time that the vHPC-PFC connectivity may be involved in regulating wakefulness and sleep. To further prove this conclusion, we used optogenetics to specifically activate or inhibit vHPC-PFC pathway. The result turned out that specifically activate vHPC-PFC pathway promote sleep to wake transition and prolong wakefulness duration, whereas specifically inhibit vHPC-PFC pathway promote wake to sleep transition and prolong sleep

duration. These results revealed novel mechanisms of sleep regulation and provided potential targets for therapeutic intervention of sleep disorders.