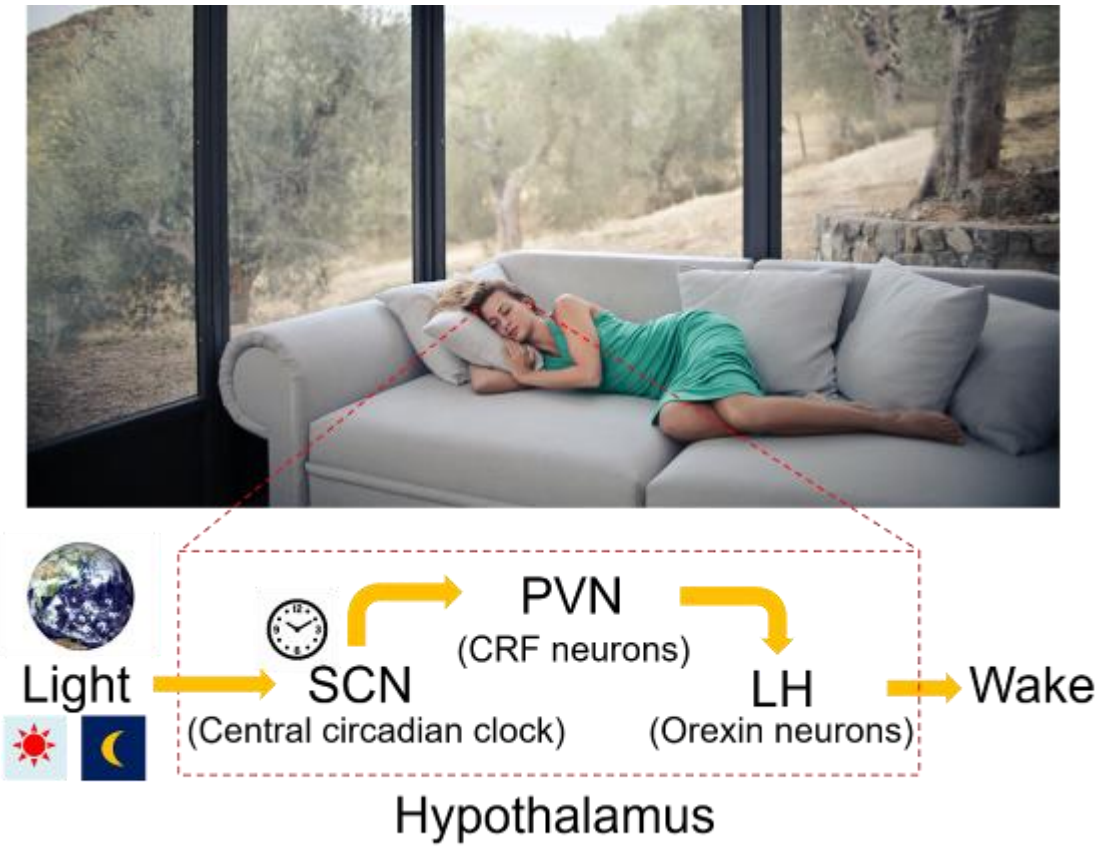
News Release

Title

A neuronal circuit that links stress, sleep, and circadian clock

Key Points

- GABA in the central circadian clock regulates neuronal activity of corticotropin-releasing factor (CRF) neurons
- CRF neurons are active during wakefulness
- Activation of CRF neurons subsequently activates orexin neurons, which involved in regulation of wakefulness



Summary

The research team led by Dr. Daisuke Ono and Prof. Akihiro Yamanaka of Graduate School of Medicine, Nagoya University, collaborating with Takashi Sugiyama of Olympus Corporation found that a neuronal circuit that link stress, sleep, and circadian clock in mammals. These achievements were published online Science Advances on November 6th, 2020 (U.S. Eastern Time).

We wake up in the morning, and go to bed in the night. This sleep/wakefulness cycle is repeated every day, which is regulated by the central circadian clock located in the small brain area named suprachiasmatic nucleus (SCN) in the hypothalamus. Whereas, when we feel

stress, we sometimes have a difficulty to fall asleep in the night. In general, it is known that corticotropin-releasing factor (CRF) modulates the neuroendocrine stress response. Although it has been thought that circadian clock and stress have a significant role for the regulation of sleep/wakefulness, its neuronal mechanisms have not been identified so far. In this research, we identified that the SCN regulates sleep/wakefulness via CRF neurons in the hypothalamic paraventricular nucleus (PVN). Furthermore, CRF neurons subsequently activate orexin neurons which are important for maintaining of wakefulness. This finding would give us new clinical approach to treat stress or circadian clock related insomnia.

Research Background

Physiology and behavior, such as sleep/wakefulness, exhibit 24-hour rhythms called circadian rhythms. In mammals, a daily rhythm of sleep/wakefulness is regulated by the central circadian clock located in the SCN. Whereas, when we encounter severe life-threatening conditions, we need to keep awake to escape from danger even during mid night. Thus, circadian clock and stress response have a significant role for the regulation of sleep and wakefulness. However, neuronal circuits that regulate sleep/wakefulness by circadian clock and stress response have not been identified.

Research Results

Taking advantage of optogenetics and optical imaging, we identified that activation of CRF neurons in the PVN increased time in wakefulness in mice. This wake promoting effect was due to further activation of orexin neurons which are important of maintaining of wakefulness. Furthermore, in vivo Ca^{2+} recording revealed that CRF neurons in the PVN were active during wakefulness. On the other hand, when we suppressed or ablated CRF neurons, time in wakefulness or locomotor activity were reduced. We also found that neuronal activity of CRF neurons in the PVN was regulated by GABAergic neurons located in the SCN.

Research Summary and Future Perspective

We identified for the first time a neuronal mechanism of circadian regulated sleep/wakefulness in nocturnal animals. However, we cannot answer how the nocturnal and diurnal difference is regulated in the brain. Further research is required to answer the question in future.

Publication

The mammalian circadian pacemaker regulates wakefulness via CRF neurons in the paraventricular nucleus of the hypothalamus
Science Advances

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