News Release

Title

The role of GABA neurons in the central circadian clock has been discovered

Key Points

- ○GABA in the central circadian clock refines spontaneous firing and cytosolic Ca^{2+} rhythms.
- ○Deletion of GABA in the central circadian clock does not affect molecular circadian rhythms.
- ○The central circadian clock specific GABA deletion deteriorates behavioral activity rhythms.

Summary

The research team led by Dr. Daisuke Ono and Prof. Akihiro Yamanaka of Graduate School of Medicine, Nagoya University, collaborating with Prof. Ken-ichi Honma and Prof. Sato Honma of Hokkaido University Graduate School of medicine, and Prof. Yuchio Yanagawa of Gunma University Graduate School of medicine revealed that inhibitory neurons (GABAergic neurons) in the central circadian clock, suprachiasmatic nucleus (SCN), refined circadian output rhythms.

Physiology and behavior, such as sleep/wakefulness, body temperature, endocrine functions, exhibit 24 hour oscillation called circadian rhythms. Temporal order of physiology and behavior is regulated by the central circadian clock located in the SCN. Our finding can be developed to understand how the SCN regulate physiological phenomena. Furthermore, it would give us new clinical approaches to variety of diseases related with circadian clock in future. These achievements were published online *Communications Biology* on June 21th, 2019 (10 a.m. GMT).

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Research Background

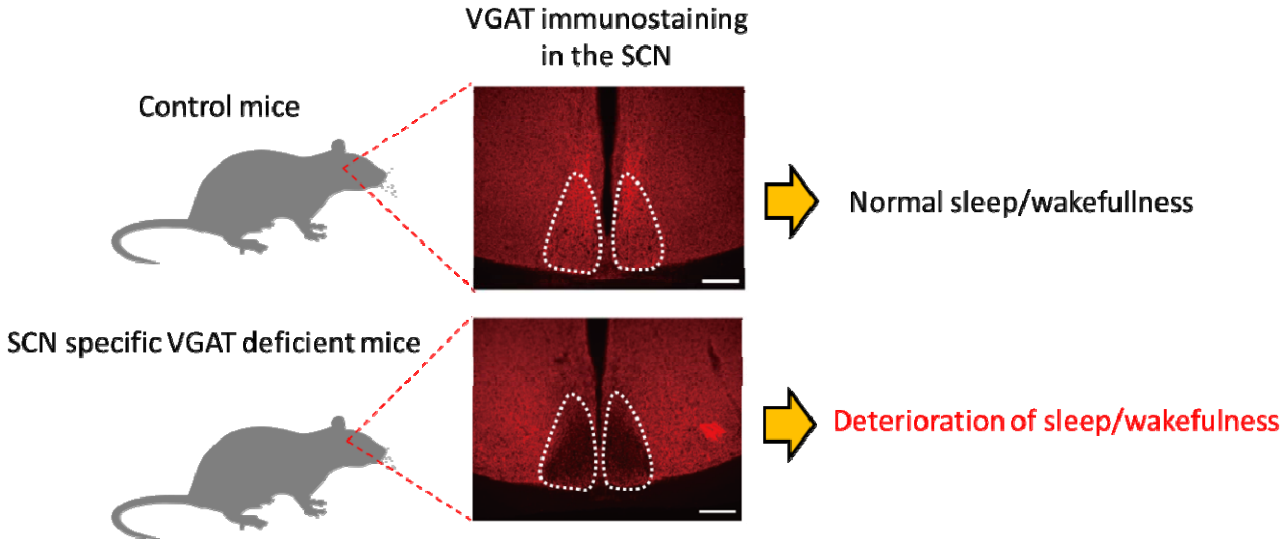
The temporal order of physiology and behavior in mammals is controlled by the master circadian clock located in the SCN. The SCN generates the endogenous circadian oscillation which entrains to a day-night alternation. The SCN is composed of heterogeneous neurons with various neurotransmitters. Among them an inhibitory neurotransmitter, γ-Amino-Butyric-Acid (GABA) is expressed in almost all SCN neurons, however, its role in the circadian physiology is still unclear.

Research Results

In the present study, we examined GABA signaling in the SCN using mice lacking vesicular GABA transporter (VGAT$^{-/-}$) or GABA synthesizing enzyme, glutamate decarboxylase (GAD65$^{-/-}$/67$^{-/-}$). We simultaneously measured the circadian rhythms with a bioluminescence reporter for the clock gene product PER2 (PER2::LUC), spontaneous firing and intracellular calcium (Ca^{2+}) level for several circadian cycles in the cultured SCN slices of perinatal mice. The SCN lacking GABA exhibits burst firings throughout 24 hours. A burst firing was associated with an abrupt increase in intracellular Ca^{2+}, which was synchronous throughout the entire SCN slice. By contrast, the circadian PER2 rhythm was essentially kept intact. We also found that SCN-specific VGAT depletion in the adult mice showed deteriorated circadian behavioral rhythms.

Research Summary and Future Perspective

In conclusion, GABA is necessary for suppressing the burst firing of neuronal activity and abrupt increases of intracellular Ca^{2+} levels but not for the generation and stability of molecular circadian oscillation in the SCN. The GABA network may refine the circadian firing rhythm to ensure noiseless communications with the neurons outside the SCN.



Publication

"GABA in the suprachiasmatic nucleus refines circadian output rhythms in mice"

Daisuke Ono[1, 2], Ken-ichi Honma[3], Yuchio Yanagawa[4], Akihiro Yamanaka[1, 2], and Sato Honma[3]

[1]Department of Neuroscience II, Research Institute of Environmental Medicine, Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-8601, Japan

[2]Department of Neural Regulation, Nagoya University Graduate School of Medicine, Nagoya 466-8550, Japan

[3]Research and Education Center for Brain Science, Hokkaido University Graduate School of

Medicine, Sapporo, 060-8638, Japan
[4]Department of Genetic and Behavioral Neuroscience, Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan

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