【Grant-in-Aid for Specially Promoted Research】

Creating a molecular biology of sleep through forward genetics

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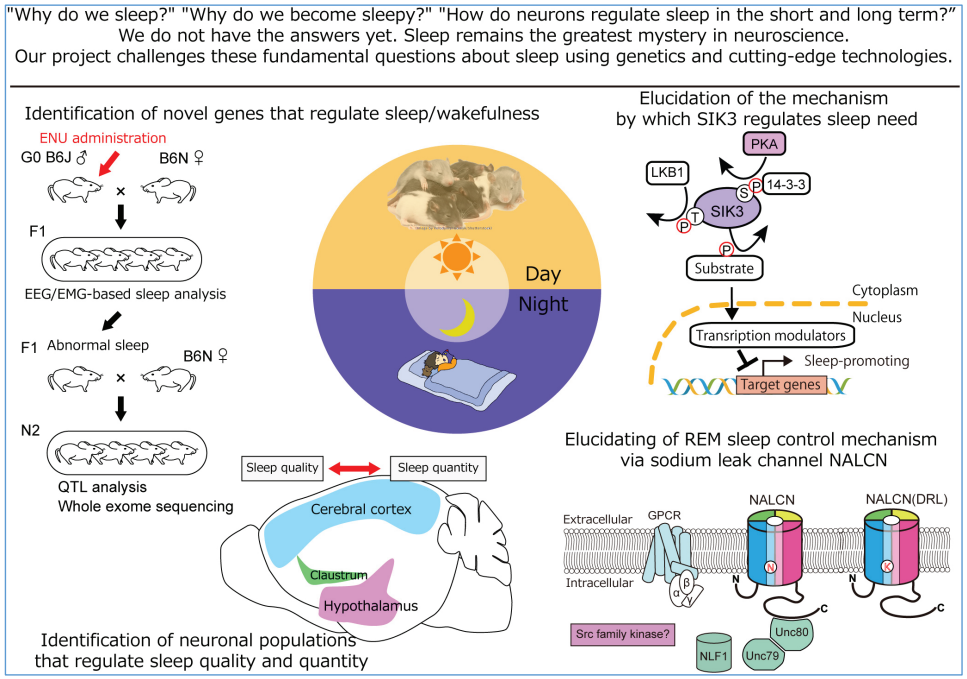
Purpose and Background of the Research

●Outline of the Research

Even with all advances in science and technology, we still cannot answer simple questions such as "Why do we sleep?", "Why do we become sleepy?", and "Why do we dream?" Sleep remains the greatest mystery in neuroscience. We have found key molecules to solve this mystery of sleep using forward genetic approach with randomly mutagenized mice.

In this project, we will identify new sleep regulatory molecules by EEG/EMG-based screening for sleep abnormalities in mice, and have also focused on kinases, ion channels, and transcriptional regulators that we have been discovered so far, using state-of-the-art technologies such as in vivo imaging, optogenetics, and multi-omics to elucidate the mechanisms that regulate NREM and REM sleep. Elucidation of sleep mechanisms will lead to the development of new sleep medications and the development of therapeutic interventions for psychiatric, dementia, and metabolic diseases that often accompany insomnia.



●Identification of novel genes that regulate sleep/wakefulness

In the biomedical field, genetics has contributed greatly to the elucidation of phenomena whose mechanisms are unknown. By applying genetics to sleep research, we will discover novel sleep-regulating genes through dominant screening and suppressor screening of hypersomnia model mice.

●Elucidation of the mechanism by which SIK3 regulates sleep need

Gain-of-function mutant form of SIK3 in neurons increases sleep in terms of quality and quantity. In general, kinases sever as a substrate for another kinases, and multiple kinases are connected as a cascade to conduct signal transduction. The output of this signaling is usually a change in the expressions of a particular set of genes. In addition, it may result in functional and structural changes in synapses via the modification of cytoskeleton and related proteins. In this study, we will identify a group of molecules that comprise SIK3 signaling pathway for sleep regulation to clarify the molecular mechanism that regulates sleep-wake.

●Elucidating the mechanisms how different neuronal populations regulate sleep quality and quantity

The brain is a complex circuit composed of neurons with different properties. Sleep and wakefulness are transitions between states of the brain itself, and it is thought that specific populations of neurons are responsible for the induction and homeostatic regulation of sleep. However, responsible neuronal groups remain to be identified. Using cell-type and circuit-specific modulation of SIK3 pathway using gene-modified mice and viral vectors, we will identify and characterize neurons that determine the quantity and quality of sleep.

●Elucidating of REM sleep control mechanism via sodium leak channel NALCN

REM sleep is different from NREM sleep in terms of eye movements, dreaming and muscle atonia. During REM sleep, the cerebral cortex exhibits brain waves similar to those of wakefulness, with hippocampal theta waves (6-9 Hz). When switching from NREM sleep to REM sleep, EEG exhibits abrupt changes. Although the switching mechanism is currently unknown, we plan to utilize NALCN(DRL)-mutants that are abnormal in this respect to elucidate the neuronal populations and molecular mechanisms involved in the switching and maintenance of NREM and REM sleep.

Expected Research Achievements

1) Identification of molecules that comprise the SIK3 pathway to uncover a signaling pathway in neurons that regulates sleep need.
2) Identification of target genes of the SIK3 pathway regulating sleep need.
3) Identification of brain regions and neuronal groups that determine sleep quality and quantity.
4) Identification of brain regions and neural groups that are required for REM sleep characteristics such as abrupt changes in EEG waves.
5) Discovery of novel sleep-regulating genes through forward genetic approach.

We will uncover as many mysteries of sleep as possible. Understanding of sleep will lead to the development of new intervention sleep-related mental and physical disorders and will contribute to the improvement of the health of the people.

Homepage Address, etc.	https://wpi-iiis.tsukuba.ac.jp/ https://sleepymouse.jp/