

【Grant-in-Aid for Scientific Research (S)】

Integrated Disciplines (Complex Systems)



Title of Project : Elucidation of Sleep/Wakefulness Regulation through Novel Sleep-regulating Genes Identified by a Forward Genetic Approach

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Research Project Number : 26220207 Researcher Number : 20202369

Research Area : Brain sciences

Keyword : Sleep

【Purpose and Background of the Research】

Although sleep is ubiquitously observed in mammalian species, the regulatory mechanism of sleep/wakefulness remains unknown. Through a large-scale forward genetic screen of randomly mutagenized mice, we have recently established 10 pedigrees showing heritable sleep abnormalities. We then have succeeded in identifying genetic

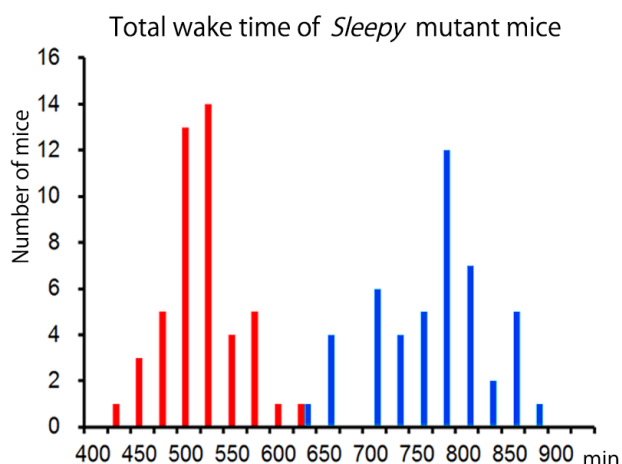


Figure 1 Histogram of total wake time of *Sleepy* mutant mice (red) and wild-type littermates (blue). *Sleepy* mutant mice show robust sleep phenotype.

mutations in two pedigrees termed *Sleepy* and *Dreamless*. In the present project, we are aiming to elucidate the neural networks regulating sleep/wakefulness behaviors through *Sleepy* gene- or *Dreamless* gene-modified mice. By examining the function of wild-type and mutant forms of the *Sleepy* and *Dreamless* proteins, we will dissect the intracellular mechanism regulating sleep. These efforts will enable us to make a paradigm-shifting breakthrough in the field of sleep research.

【Research Methods】

To identify the brain regions or neuronal populations responsible to sleep/wakefulness abnormalities caused by the mutations in the *Sleepy* and *Dreamless* genes, we will produce gene-modified mice in which the mutant forms of genes can be activated in a Cre-dependent way. By crossing these mice with Cre driver mice or by stereotaxically injecting Cre viral vectors, we will identify neural circuits regulating sleep. Through

quantitative mass spectrometry of proteins from mutant brains and electrophysiological assessment of mutant neurons, we will elucidate the intracellular signal pathway regulating sleep.

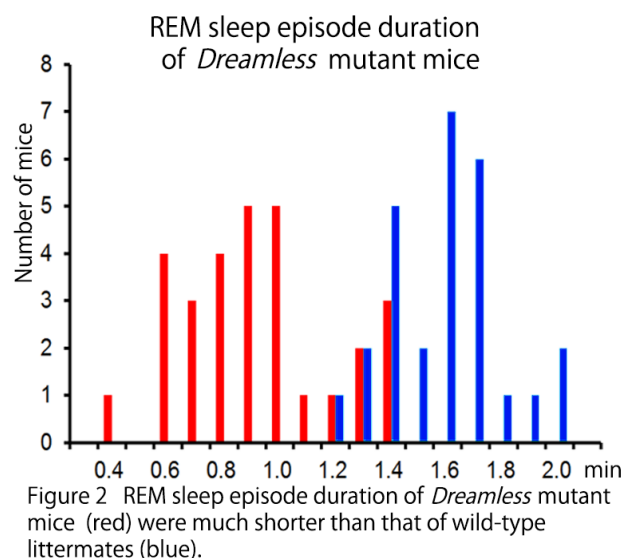


Figure 2 REM sleep episode duration of *Dreamless* mutant mice (red) were much shorter than that of wild-type littermates (blue).

【Expected Research Achievements and Scientific Significance】

By focusing on novel sleep-regulating genes, this project will elucidate the fundamental mechanism confining sleep amounts and the switching mechanism between NREM sleep and REM sleep. The project may also prove that the *Sleepy* and *Dreamless* proteins are attractive drug targets for sleep disorders.

【Publications Relevant to the Project】

- Chemelli, Yanagisawa et al. Narcolepsy in orexin knockout mice: molecular genetics of sleep regulation. *Cell* 98, 437-451, 1999.
- Takahashi JS, Shimomura K, Kumar V. Searching for genes underlying behavior: lessons from circadian rhythms. *Science* 322, 909-912, 2008.

【Term of Project】 FY2014-2018

【Budget Allocation】 150,100 Thousand Yen

【Homepage Address and Other Contact

Information】 <http://sleepymouse.tsukuba.ac.jp>