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学位論文題目	Genetic analyses of molecules and neural circuits regulating REM sleep （レム睡眠の制御を担う分子や神経回路の同定と解析）

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論文の内容の要旨
Abstract of thesis

In this doctoral dissertation, Mr. Chih-Yao Liu describes the Genetic analyses of molecules and neural circuits regulating REM sleep. The summary is as follows:

（目的 Purpose）

Rapid-eye-movement (REM) sleep is a distinct physiological state observed in certain mammalian or avian animal species and is featured by desynchronized neocortical activity, sympathetic activation, and muscle atonia. While REM sleep is well known as a major source of dreaming, the physiologic roles of REM sleep and the neural substrates that contribute to generating REM sleep remain poorly understood. The sublaterodorsal nucleus (SLD), located in the mesopontine tegmental area, has been shown to have a crucial role in REM sleep regulation. However, the precise identity of the neurons critically involved remain unsolved. In this doctoral dissertation, the author aimed to identify the molecular markers for neurons that regulate REM sleep and generate genetic tools that allow manipulation of REM sleep, which should enable analyses of the physiologic roles of REM sleep from a totally novel approach.

（対象と方法　Materials and Methods）

The author used Cpne7 and Chrm3 as potential markers of SLD neurons that regulate REM sleep. These two genes were previously identified as candidate genes selectively expressed in the SLD. The author generated Cpne7 and Chrm3-Cre KI mice to drive the expression of Cre recombinase in these neurons. By using these Cre-KI mouse strains, either Cpne7+ or Chrm3+ neurons in the SLD were genetically labeled by Cre expression.

（結果　Results）

Analyses of these two mouse strains suggested that Cpne7+ and Chrm3+ neurons negatively or positively regulate REM sleep, respectively. When the SLD-Cpne7 neurons were activated using the designer receptor exclusively activated by designer drugs (DREADD) system, the amount of REM sleep was drastically reduced. By contrast, when the SLD-Chrm3 neurons were genetically ablated via Cre dependent DT-A expression, the amount of REM sleep was strikingly diminished. Furthermore, SLD-Chrm3 Neuron ablated mice exhibited significantly reduced anxiety like behaviors and depression like behaviors, perhaps implicating a role for REM sleep in regulating emotion. Moreover, homozygous Cpne7-Cre KI mice, in which the Copine7 was not detected, showed higher amount of REM sleep after cage changing, suggesting that the protein product of Cpne7 per se is involved the regulation of REM sleep under environmental stimuli.

（考察　Discussion）

From these results, it is suggested that two distinct populations of neurons, Cpne7+ and Chrm3+ neurons in the SLD contribute to the bi-directional regulation of REM sleep. In addition, Cpne7, a gene whose in vivo function was totally unknown, is involved in the regulation of REM sleep.

審査の結果の要旨
Abstract of assessment result

（批評　General Comments）

In this doctoral dissertation, the author generated Cpne7 and Chrm3-Cre KI mice to genetically label Cpne7+ or Chrm3+ neurons in the SLD by Cre expression. These two KI mice are very unique and powerful tools for analysis of molecular mechanism of REM sleep. In addition, the author clearly demonstrated that Cpne7+ and Chrm3+ neurons negatively or positively regulate REM sleep. This finding is basic information to understand molecular mechanism of REM sleep.

（最終試験の結果　Assessment）

The final examination committee conducted a meeting as a final examination on May 14, 2020. The applicant provided an overview of dissertation, addressed questions and comments raised during Q&A session. All of the committee members reached a final decision that the applicant has passed the final examination.

（結論　Conclusion）

The final examination committee approved that the applicant is qualified to be awarded Doctor of Philosophy in Human Biology.