**News Release**

**Title**

Transgenic Archaerhodopsin-3 Expression in Hypocretin/Orexin Neurons Engenders Cellular Dysfunction and Features of Type 2 Narcolepsy

**Key Points**

- **We created new transgenic mice, orexin-Arch mice, that can apply optogenetics inhibition to orexin neurons**
- **Long-term suppression of orexin neurons induced sleep.**
- **These transgenic mice line proved to be useful as a model mouse of type 2 narcolepsy.**

**Summary**

A research group led by Professor Akihiro Yamanaka at the Nagoya University in Japan conducted joint research with a group led by Professor Thomas S. Kilduff at the SRI in US, and succeeded in creating the first mouse model for type 2 narcolepsy.

Narcolepsy, a sleep disorder, is a sudden onset of sleep with excessive daytime sleepiness. It is said that 1 in 2000 Japanese have narcolepsy. The main symptoms of narcolepsy are a sudden onset of sleep, a sudden loss of muscle tone (cataplexy), and the hallucinations of sleep paralysis. There are types 1 and 2 of narcolepsy, and patients with type 2 narcolepsy do not have symptoms of cataplexy.

Here, we created a new transgenic mouse line, orexin-Arch to control the activity of orexin neurons, which play an important role in maintaining wakefulness. Recently, a research technique called optogenetics has been introduced into neuroscience research. We created mice that express a green light-sensitive proton pump, archarhodopsin-3, exclusively in orexin neurons. Archarhodopsin-3 enables inhibit neural activity by sensing green light. When green light was applied into the hypothalamus, it was actually able to suppress the activity of orexin neurons, and as a result, mice started sleep.

In addition, transgenic mice that express a large amount of the archarhodopsin-3 protein in orexin neurons, homozygous transgenic mice, showed abnormality in circadian rhythm, metabolic and sleep disturbances without illumination of green light into the hypothalamus. The mice showed an increase in REM sleep seen in patients with narcolepsy, but no cataplexy-like behavioral arrest which is characteristic of narcolepsy type 1. Since there is no loss of orexin neurons, it can be said that it succeeded in making a model mouse of type 2 narcolepsy.

To understand the mechanisms by which type 2 narcolepsy, it is important to have model animals that exhibit similar symptoms. In the case of type 1 narcolepsy, the mouse in which the orexin neurons were ablated were a model mouse for type 1 narcolepsy, but there was no model mouse of type 2 narcolepsy. This study may help to understand mechanisms, and better treatments for type 2 narcolepsy.

**Research Background**

Narcolepsy, a sleep disorder, is a sudden onset of sleep with excessive daytime sleepiness. It is said that around 1 in 100 Japanese have narcolepsy. The main symptoms of narcolepsy are a sudden onset of sleep, a sudden loss of muscle tone (cataplexy), and hallucinations of sleep paralysis and falling asleep. There are types 1 and 2 of narcolepsy, and people with type 2 narcolepsy do not have symptoms of cataplexy. To understand the mechanisms by which disease occurs, it is important to have model mice that exhibit similar symptoms. In the case of type 1 narcolepsy, the mouse in which the orexin neurons were ablated were a model mouse, but there was no model mouse of type 2 narcolepsy. This study may help understand mechanisms, causes, and better treatments for type 2 narcolepsy.

**Research Results**

Here, we created a new transgenic mice line to control the activity of the orexin neurons in the hypothalamus. Recently, a technique called optogenetics has been developed in the neuroscience research field. We created mice that express a light-sensitive proton pump called archarhodopsin-3 exclusively in orexin neurons. archarhodopsin-3 enables block neural activity by sensing green light. When green light was applied into the hypothalamus, it was actually able to suppress the activity of orexin neurons, and as a result, mice started sleep.

In addition, transgenic mice that express a large amount of the archarhodopsin-3 protein in orexin neurons, homozugous transgenic mice, showed abnormality of circadian rhythm, metabolic and sleep disturbances without illumination of green light onto the hypothalamus. The mice showed an increase in REM sleep seen in patients with narcolepsy, but no cataplexy-like symptoms characteristic of narcolepsy type 1. Since no loss of orexin neurons was observed, we succeeded in creating a model mouse of type 2 narcolepsy.

**Research Summary and Future Perspective**

We would like to contribute to the development of drugs that improve the symptoms of type 2 narcolepsy by screening various drugs using these new model mice for type 2 narcolepsy.

**Publication**

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