News Release

Title

Dissociating orexin-dependent and -independent functions of orexin neurons using novel Orexin-Flp knock-in mice

Key Points

○Sleep disorder "Narcolepsy" is caused by specific degeneration of orexin neurons.

○Orexin neurons release not only orexin but also other neurotransmitters. However, little is known about the role of other neurotransmitters in the regulation of sleep/wakefulness.

○Newly developed knock-in mice, in which orexin neurons exclusively expressed DNA recombinase called Flippase (Orexin-Flippase mice), were used to isolate orexin-dependent and -independent functions of orexin neurons. Neural manipulation to orexin neurons using Orexin-flippase mice revealed that orexin is indispensable to maintain sustained wakefulness and to prevent from cataplexy, a sudden muscle weakness triggered by emotion.

Summary 1 In a study done at the Nagoya University, Japan, Chowdhury and colleagues isolated orexin-dependent and -independent functions of orexin neurons. They generated a novel mouse line, which they named Orexin-flippase, that express Flippase recombinase exclusively in the orexin neurons. Using such mice, authors could control gene expression regulation in orexin neurons. Flippase recombinase recognize and help recombination of DNA sequences different from another recombinase called Cre, which enabled dual manipulation. Moreover, homozygous Orexin-Flippase mice do not express orexin peptide. These mice showed narcolepsy phenotype, fragmentation of sleep/wakefulness. Manipulation of the activity of orexin neurons without orexin using chemogenetics enabled the researchers to dissociate orexin-dependent and -independent functions in the regulation of sleep/wakefulness. Slice patch clamp recording showed that orexin neurons has decreased activity and cell body was slight swelling in the absence of orexin.

Summary 2 Homozygous Orexin-Flippase mice are orexin-knockout mice which show narcolepsy symptoms such as fragmentation of sleep/wakefulness and cataplexy, sudden muscle weakness triggered by emotion. Chemogenetic activation of orexin neurons without orexin restored most of the symptoms of narcolepsy. However, cataplexy was not restored but rather deteriorated. From this study authors concluded that neurotransmitters other than orexin have a role in the regulation of sleep/wakefulness, however, orexin was indispensable to prevent cataplexy.

Research Background

Sleep disorder "Narcolepsy" is caused by specific degeneration of orexin neurons. Narcolepsy patients showed excessive daytime sleepiness, fragmentation of sleep/wakefulness

and cataplexy. This fact suggests that orexin is involved in the maintenance of wakefulness. Orexin neurons release not only orexin but also other neurotransmitters, such as glutamate and dynorphin. However, little is known about the role of other neurotransmitters in the regulation of sleep/wakefulness. To reveal this, authors based in Nagoya University generated orexin-Flippase knock-in mice and applied chemogenetic manipulation to orexin neurons.

Research Results

Homozygous Orexin-Flippase mice are orexin-knockout mice. These mice showed narcolepsy phenotypes such as fragmentation of sleep/wakefulness and sudden muscle weakness, cataplexy. Manipulation of the activity of orexin neurons without orexin using chemogenetics enabled to dissociate orexin-dependent and -independent functions in the regulation of sleep/wakefulness. Slice patch clamp recording from orexin neurons without orexin showed that orexin neuron without orexin has decreased activity and cell body was slight swelling. Chemogenetic activation of orexin neurons without orexin restored fragmentation of sleep/wakefulness. However, cataplexy was not restored but rather deteriorated. Taken together, these results suggest that neurotransmitters other than orexin have a role in the regulation of sleep/wakefulness. However, orexin was indispensable to prevent cataplexy.

Research Summary and Future Perspective

By generating bigenic mice by crossing orexin-Flippase with Cre-expressing mice, it will be possible to analyze functional interactions between orexin neurons and other neurons to understand the neural regulatory mechanism of sleep/wakefulness.

Publication

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