News Release

Title

GABA neurons in the ventral tegmental area regulate non-rapid eye movement sleep in mice

Key Points

○Little is known about the regulatory mechanism of sleep/wakefulness

○Dopaminergic neurons are located in the Ventral tegmental area (VTA). VTA is known to regulate reward response. Although GABAergic neurons are also located in the VTA, its function has not been elucidated so far.

○This study revealed that GABAergic neurons in the VTA regulate non-REM sleep.

Summary 1 Ventral tegmental area (VTA) is known to be involved in reward response since dopaminergic neurons are located in the VTA. However, VTA contains GABAergic and glutamatergic neurons alongside dopamine neurons. In a study done at the Nagoya University, Japan, Chowdhury and colleagues focused on GABAergic neurons in the VTA (VTA-GABA neurons) to reveal its physiological role in the regulation of sleep/wakefulness. Authors manipulated VTA-GABA neurons by using recently developed optogenetics or chemogenetics techniques which allow manipulation of the activity of targeted neurons. To target GABAergic neurons in the VTA authors used GAD67-Cre mice, in which GABAergic neurons exclusively express Cre recombinase. Adeno-associated virus-mediated gene delivery was performed to deliver the Cre-dependent genes in VTA-GABA neurons. Activation of VTA-GABA neurons using chemogenetics increased time in non-REM sleep. On the other hand, inhibition of VTA-GABA neurons using optogenetics immediately induced wakefulness. To reveal the role of VTA-GABA neurons in physiological sleep/wakefulness regulation, the activity of VTA-GABA neurons across sleep/wakefulness state change was measured by using fiberphotometry. The activity of VTA-GABA neurons was high in non-REM sleep and was low in wakefulness and REM sleep. These VTA-GABA neurons were also found to densely innervate the hypothalamus. Orexin neurons, which are located exclusively in the hypothalamus, were implicated in the maintenance of wakefulness. Using in vitro optogenetics and electrophysiological analysis, the authors found that VTA-GABA neurons directly innervate and inhibit orexin neurons to promote non-REM sleep. Taken together, this study revealed that VTA-GABA neurons regulate non-REM sleep by inhibiting orexin neurons in the hypothalamus.

Summary 2 Neural manipulation techniques, such as optogenetics or chemogenetics, were applied to GABAergic neurons in the ventral tegmental area (VTA) to reveal the physiological role of these neurons. Authors found that VTA-GABA neurons regulate non-REM sleep by

directly inhibiting orexin neurons in the hypothalamus which are implicated in the maintenance of wakefulness.

Research Background

Sleep/wakefulness cycle, which includes wakefulness, non-rapid eye movement (Non-REM) sleep and REM sleep are the familiar physiological phenomenon. However, the neural regulatory mechanism of sleep/wakefulness has not been elucidated so far. Dopaminergic neurons were distributed in the ventral tegmental area (VTA). VTA is known to be involved in reward response and motivation. Although GABAergic neurons were also located in the VTA, little is known about the physiological function of these neurons.

Research Results

To reveal the physiological function of GABAergic neurons in the ventral tegmental area (VTA), optogenetics or chemicogenetics was applied to VTA-GABA neurons to manipulate the activity of the targeted neurons. Activation of VTA-GABA neurons using chemogenetics increased time in non-REM sleep. On the other hand, inhibition of VTA-GABA neurons using optogenetics immediately induced wakefulness. Fiberphotometry recording revealed the activity of VTA-GABA neurons across sleep/wakefulness state. The activity of VTA-GABA neurons was high in non-REM sleep and low in wakefulness and REM sleep. VTA-GABA neurons were found to densely innervate the hypothalamus. Orexin neurons were implicated in the maintenance of wakefulness and exclusively located in the hypothalamus. In vitro optogenetics and electrophysiological analysis revealed that VTA-GABA neurons directly innervated and inhibited orexin neurons to promote non-REM sleep. Taken together, authors found that VTA-GABA neurons were important neurons to regulate non-REM sleep by inhibiting orexin neurons in the hypothalamus.

Research Summary and Future Perspective

GABAergic neurons in the ventral tegmental area (VTA) regulate non-REM sleep. Results published in this study showed that GABAergic neurons in the VTA could be a fruitful target for drug development to treat sleep disorders. It is well known that most of the sleep-inducing drugs cause drug dependence with the chronic application. GABAergic neurons in the VTA could have a functional relationship with dopaminergic neurons in the VTA which are implicated in the dependence and reward. This result might also lead to a conceptual and systematic framework to study the association between sleep and psychiatric disorders and which may generate opportunities to study VTA-related dysregulation in mental disorders.

Publication

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