Identification of the neuronal suppressor of cataplexy, sudden weakening of muscle control in narcolepsy

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External stimulus causing excitement such as laughter by a joke augments the amygdala activity. In narcolepsy patient (left) lacking orexin neurons, activities of the amygdala become excessive, causing cataplexy. In healthy person (right), orexin neurons augment the activities of serotonin neurons in the dorsal raphe nucleus, which reduce activities of the amygdala due to increased release of serotonin in the amygdala, which in turn inhibits cataplexy. Credit: Kanazawa University

Narcolepsy is a disorder caused by losing orexin neurons, marked by excessive daytime sleepiness and cataplexy, and sudden weakening of muscle control. Previously, we found two kinds of neurons preventing narcolepsy by receiving orexin from orexin neurons—the first are noradrenaline neurons in the locus coeruleus of the brain suppressing sleepiness. The other type is serotonin neurons in the dorsal raphe nucleus of the brain, which inhibit cataplexy.

In this study, the international research team led by the researchers of Kanazawa University has discovered that serotonin neurons in the dorsal raphe nucleus inhibit cataplexy by reducing activities of the amygdala that controls emotion.

Serotonin neurons in the dorsal raphe nucleus extend projections throughout the brain and send information. In this study, using an optogenetic tool, the team discovered that cataplexy was almost completely inhibited by artificial augmentation of serotonin release induced by selectively stimulating serotonin nerve terminals in the amygdalas of narcolepsy model mice. The same experimental operation in the other brain region that controls REM sleep did not inhibit cataplexy. In addition, the team found that serotonin release reduced amygdala activity. When amygdala activity was artificially reduced in a direct manner, cataplexy was inhibited; when activity in the amygdala was artificially augmented, the frequency of cataplexy attacks increased. Furthermore, the effect of orexin neurons inhibiting cataplexy was found to be abolished when serotonin release was inhibited.
selectively in the amygdala.

Cataplexy is triggered by sudden emotional excitement of positive valence, such as hearty laughter. This study has revealed that serotonin neurons do not directly suppress muscle control, but inhibit cataplexy by reducing and controlling activities of the amygdala, which is involved in communicating emotional excitement. In fact, it is known that the amygdalas of narcolepsy patients without orexin neurons respond excessively when the patients see, for example, interesting photos. The team believes that the current study has made a big step forward to understanding the whole picture of the narcolepsy mechanism. It is also expected that new therapies will be developed for cataplexy.

When serotonin nerve terminals in the amygdala are stimulated to augment serotonin release, cataplexy is inhibited (indicated by arrow in the upper part) while sleepiness is not inhibited (lower part). On the other hand, stimulation of serotonin nerve terminals in the other region controlling REM sleep does not induce any changes. LDTg, laterodorsal tegmental nucleus; SLD, sublaterodorsal nucleus; SNC, substantia nigra compact part; vPAG, ventrolateral periaqueductal gray. Credit: Kanazawa University


Provided by Kanazawa University