

Press Release

2017.11.20 | International Institute for Integrative Sleep Medicine (WPI-IIIS)

A neuropeptide that regulates behavior: a key to ease excessive fear

Orexin, a neuropeptide in the brain, is known to play an important role in sleep/wake regulation. Recent study conducted in a sleep institute in Japan found a novel function of orexin – it also plays a critical role in regulation of the level of behavioral responses against fear. This discovery may shed light on the treatment of fear-related disorders.

Fear is an adaptive behavioral response that allows animals to predict potential threats based on memory of past aversive experiences, which is stored in the amygdala and hippocampus. Excessive or inappropriate fear, however, can lead to psychiatric conditions such as phobia, anxiety, panic disorder, and post-traumatic stress disorder (PTSD). Fear is sometimes evoked with association of aversive experiences previously paired with a similar, but distinct stimulus or context to related cues or similar situations, a process known as “fear generalization.” While there are behavioral advantages of this ability to adapt flexibly to various circumstances, this must be appropriately controlled to be beneficial for an organism. The neuronal mechanisms as to how fear learning is generalized or modulated to adapt other stimuli that contain similar, but distinct elements of a learned threat had remained to be a mystery. A research led by Shingo Soya and Takeshi Sakurai of International Institute of Integrative Sleep Medicine (WPI-IIIS), University of Tsukuba, found that a hypothalamic neuropeptide, orexin, plays a critical role in regulation of the level of fear-related responses in situations that resemble past aversive experiences.

Along with its important function in maintaining wakefulness, orexin is a key molecule in the shift to a ‘vigilant’ state in emotionally arousing situations, with the function of sustaining arousal via recruitment of downstream monoaminergic neurons. One of the downstream signaling pathways of orexin is noradrenergic neurons in the locus coeruleus (NA neurons), which promote wakefulness and increase attention. Orexin integrates appropriate behavioral responses and external emotional stimuli to deal with stressful and/or emotionally-salient situations.

The researchers demonstrated that orexin neurons are strongly activated by fear conditioned cues or contexts, and lead to the activation of downstream pathways, including NA neurons. When the

orexin→NA→amygdala circuit was artificially and specifically activated with light (a method called ‘optogenetics’), fear-related behavior increased in a similar but distinct from the training context. Increased activation of these circuits enhanced the fear response in otherwise neutral situation, revealing the ability of this circuit to open the “gate of fear.” In other words, the increase of the activity of these circuits might be required for shifting anxiety to the actual fear. Activation of this circuit gates fear against trace elements, which are normally ignored as indicators of danger. Conditions that naturally activate orexin neurons, such as fasting, could result in an orexin-dependent shift to a ‘vigilance’ state and alter the selection of a behavioral response to avoid and handle environmental threats in real-world situation.

“Our study proposes the orexin→NA→amygdala circuit is involved in the mechanism of fear expression and generalization. The inhibition of orexin receptor (OX1R) may provide a promising avenue for treating psychiatric conditions that are characterized by exaggerated and/or inappropriate fear-related responses triggered by external cues, such as panic disorder and PTSD,” Sakurai concludes. ■

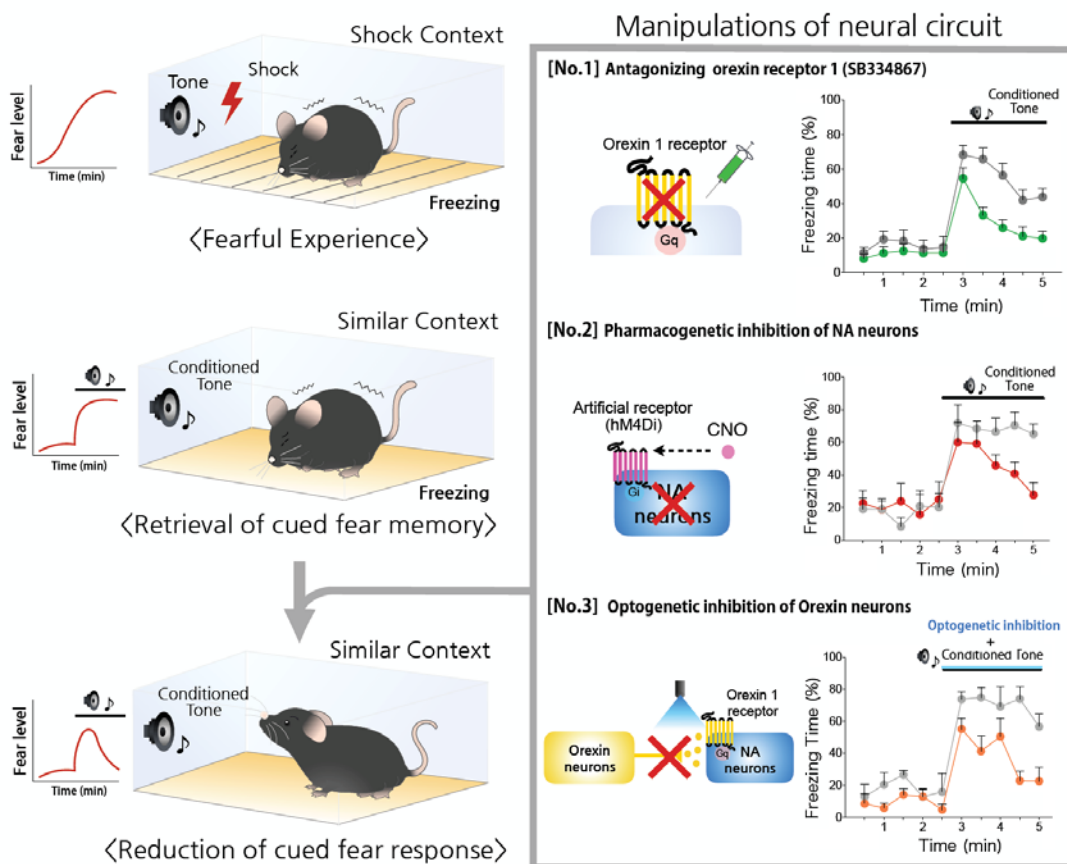


Figure 1. Reduced fear response by manipulating the neural circuit

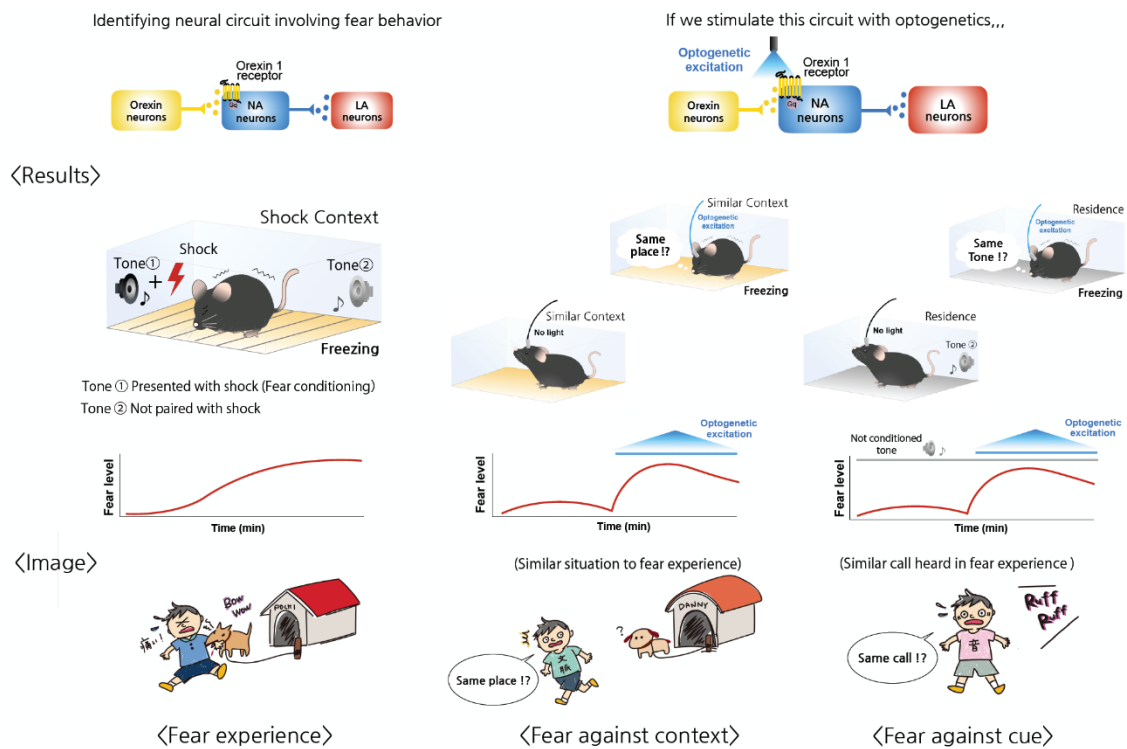


Figure 2. Outline of the optogenetic experiments and presumption in real life

Bibliographic information

Soya S, Takahashi TM, McHugh TJ, Maejima T, Herlitze S, Abe M, Sakimura K, Sakurai T. (2017) Orexin modulates behavioral fear expression through the locus coeruleus. *Nat. Comm.* doi: 10.1038/s41467-017-01782-z

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