Reversible gene expression control of serotonin receptor 1A in orexin neurons reveals physiological significance of serotonergic inhibitory inputs to orexin neurons
オレキシン神経特異的なセロトニン受容体 1A の可逆的発現制御を用いたセロトニン神経からオレキシン神経への抑制性入力の生理的役割の解明

The neurons producing neuropeptide orexin (orexin neurons) have an important role in the maintenance of arousal. It is reported that serotonergic neurons in the raphe nucleus are densely innervated by orexin neurons. These serotonergic neurons express both orexin receptors, OX1R and OX2R, and are activated by orexin. On the other hand, orexin neurons are innervated by serotonergic neurons in the raphe nucleus, and are inhibited by serotonin through the serotonin 1A receptor (Htr1a). Although these results suggest that serotonergic input forms a negative feedback circuit, its physiological role has not been completely understood.

To reveal this, we generated transgenic mice in which orexin neurons specifically express tetracycline transactivator *orexin/tTA*. tTA enable to induce gene expression to bind tetracycline responsive element in the absence of doxycycline (DOX). In *orexin/tTA; Tet-O Htr1a* (Htr1a over expression) mice, in situ hybridization revealed that Htr1a mRNA was reversibly regulated in the orexin neurons by applying or removing DOX from chew. Electrophysiological analysis of orexin neurons revealed that inhibitory effect by serotonin application was approximately 2-hold prolonged using *Htr1a* over expression mice compare with control mice. EEG and EMG recording from *Htr1a* over expression mice revealed that these mice showed fragmentation of wakefulness in active period, the early dark period. DOX application for 5 days consolidated wakefulness in the early dark period. It was fragmented again by removing DOX for 14 days. Although stage transition frequency was significantly increased in Htr1a over expression mice in the early dark period, sleep/wakefulness pattern in the light period was not significantly different from control mice. These results suggest that inhibitory inputs from serotonergic neurons to orexin neurons function as negative feedback circuitry to preserve the activity of orexin neurons in moderate range in the early dark period.

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