

## Physiological significance of serotonergic inhibitory inputs to orexin neurons

The neurons producing neuropeptide orexin/hypocretin (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, expression of Htr1a mRNA is reversibly regulated in the orexin neurons by applying or removing doxycycline (DOX) from chow. Electrophysiological analysis of orexin neurons revealed that inhibitory effect of serotonin was approximately 2-fold prolonged in *Htr1a* over expression mice compared with control mice. EEG and EMG recording from *Htr1a* over expression mice revealed that these mice showed fragmentation of wakefulness in the early dark period. DOX application for 5 days cancelled Htr1a mRNA over expression in the orexin neurons and consolidated wakefulness in the early dark period. DOX removing for 14 days over expressed Htr1a mRNA, and wakefulness was fragmented again. However, 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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