

Positive regulation between orexin/hypocretin neurons

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Orexin is a neuropeptide which is produced in few number of neurons (orexin neurons) located in the lateral hypothalamic area. Orexin is a natural ligand for two types of G-protein coupled receptors termed OX1R and OX2R. Prepro-orexin or OX2R null animals showed a fragmentation of sleep/wakefulness and cataplexy-like behavioral arrest. These are similar to symptoms observed in narcolepsy. These suggest that orexin and OX2R have an important role in the maintenance of arousal. However, it is not clear that which neurons expressing the OX2R are involved.

Electrophysiological analysis of orexin neurons revealed that orexin activates orexin neurons. Orexin-induced depolarization was observed in the presence of TTX suggested direct effect. Additionally, orexin A and B induced equal level of depolarization suggested involvement of the OX2R. To identify the receptor subtype, we used OX1R and OX2R null mice. Although orexin neurons in the OX1R null mice showed comparable depolarization with orexin neurons in wild type mice, orexin neurons in the OX2R null mice did not show any significant depolarization by applying orexin. These results suggest that orexin activates orexin neurons via the OX2R. Next, we analyzed indirect regulation via glutamatergic neurons. sEPSC frequency in orexin neurons was increased by orexin application in the wild type and OX1R null mice, but not in the OX2R null mice. On the other hand, immuno-electron microscopic analyses revealed synapse-like structures between orexin neurons, suggesting direct synaptic connection. In conclusion, orexin activates orexin neurons directly and indirectly via the OX2R. An activation of orexin neurons by other orexin neurons via the OX2R might be involved in the maintenance of arousal.