OX2R-selective orexin agonism is sufficient to ameliorate narcoleptic symptoms, cataplexy and sleep/wakefulness fragmentation in mouse models

Yamamoto Hikari, Yoko Irukayama, Yukiko Ishikawa, Yukiko Namekawa, Tsuyoshi Nemoto, Hiromu Tanaka, Genki Takahashi, Masashi Yanagisawa

International Institute for Integrative Sleep Medicine (WPI-IIIS), Tsukuba Univ.

Loss of orexin-producing neurons in the lateral hypothalamus causes the chronic sleep disorder narcolepsy-cataplexy. Narcoleptic humans suffer from two major symptoms, excessive sleepiness and cataplexy in the active phase, and these symptoms in mouse models are manifested as sleep/wakefulness fragmentation and SOREMs (direct transitions from wakefulness to REM sleep), respectively. The neuropeptides orexin-A (OXA) and orexin-B (OXB) act on two receptors orexin type-1 receptor (OX1R) and orexin type-2 receptor (OX2R). Orexin receptor agonists are expected to be of potential value for treating human narcolepsy. Here, to confirm the fundamental strategy aimed at improving narcoleptic symptoms, we examined the association between orexin receptor subtypes and these symptoms by intracerebroventricular (ICV) administration of the OX2R-selective agonist [Ala^{11}, $_{D\text{-}}Leu^{15}$]-OXB in orexin knockout mice. OXA and [Ala^{11}, $_{D\text{-}}Leu^{15}$]-OXB similarly decreased the number of SOREMs. Further, transition frequencies between NREM sleep and wake states in narcoleptic model mice were similarly decreased. We confirmed in vivo that [Ala^{11}, $_{D\text{-}}Leu^{15}$]-OXB did not activate OX1R-expressing LC noradrenergic neurons by Fos staining. Therefore, OX2R-selective agonism is sufficient to ameliorate narcoleptic symptoms, both cataplexy and fragmentation of wakefulness in model mice. Activation of LC noradrenaline neurons expressing OX1R are not essential for suppression of these symptoms.