SLEEP

Counting orexins

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The sleep–wake cycle in mammals is tightly regulated by the levels of orexins, a family of two hypothalamic peptides. During awake periods, orexin levels are high and contribute to maintain alertness. In a paper published in *Nature Medicine*, Jenck and colleagues now describe the use of an orexin receptor antagonist that elicits somnolence without cataplexy at single doses administered orally during the active period of the circadian cycle.

Orexins are produced by a discrete number of neurons in the hypothalamus, which connect to various brain regions involved in the regulation of wakefulness. Orexins and their receptors have been in the limelight since their connection with narcolepsy — a debilitating disorder in which patients spontaneously fall asleep and which is often accompanied by cataplexy — was discovered. The authors have now identified and optimized a potent, selective and competitive orexin receptor antagonist, ACT-078573, and have investigated its physiological effects after oral administration in healthy rats, dogs and humans.

Studies in rats demonstrated that the antagonist can cross the blood–brain barrier and is well tolerated even at very high doses. The effect of different doses of ACT-078573 on alertness was measured by telemetric electroencephalography and the drug was compared to the hypnotic sleep medication zolpidem, a GABA (γ-aminobutyric acid)-A receptor modulator, which is available on the market. The amount of time that animals spent in their active waking state was measured over 12 hours after administration of the drug. At doses of 30 mg kg^{-1} or higher, the antagonist significantly reduced the active time of the animals with a level of effect that was comparable to zolpidem. Similar observations were made in dogs, and the authors noted no drug-related loss of muscle tone and therefore no indication that the antagonist induced cataplexy. In humans, also tested at the beginning of the active part of their circadian cycle, doses of up to 1000 mg kg^{-1} of the antagonist were well tolerated and no severe or adverse effects were reported apart from diminished alertness and decreased latency to sleep stage 2.

Doses of 30 mg kg^{-1} or higher of the antagonist resulted in increased duration of REM (rapid eye movement) and non-REM sleep in rats, unlike GABA-A receptor modulators that decrease REM-sleep. Therefore, the antagonist induces a state that more closely resembles physiological sleep.

This study has shown that a specific antagonist of orexin receptors can induce sleep without cataplexy or other side effects when administered at single doses to healthy rodent, canine or human subjects. If safety is maintained after long-term treatment, orexin receptor antagonists could provide a new way to treat sleep disorders that result from disturbed circadian orexin release.

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ORIGINAL RESEARCH PAPER Brisbare-Roch, C. *et al.* Promotion of sleep by targeting the orexin system in rats, dogs and humans. *Nature Med.* **13**, 150–155 (2007)
FURTHER READING Sakurai, T. The neural circuit of orexin (hypocretin): maintaining sleep and wakefulness. *Nature Rev. Neurosci.* **8**, 171–181 (2007)