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Orexins: looking forward to sleep, back at addiction

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The Roman god Janus displays two faces, one looking back and the other toward what lies ahead. Like Janus, we can look back over the last several years and appreciate how much we have learned about the roles of the orexin neuropeptides in the regulation of wakefulness and sleep, the control of body weight and metabolism, and the regulation of motivation and addiction¹. Looking ahead, we may soon see the application of these discoveries to clinical practice.

In this issue, Brisbare-Roch *et al.* describe a novel, orally administered drug that produces sleepiness through selective blockade of orexin signaling². Quite possibly, this drug may be clinically useful for promoting sleep, and, by modulating reward circuits, it may become a novel treatment for drug addiction.

Orexin-A and orexin-B (also known as hypocretin-1 and hypocretin-2) are produced by a cluster of neurons in the posterior lateral hypothalamus (Fig. 1). The orexin neurons help promote and sustain wakefulness by providing excitatory drive to a variety of brain regions that govern arousal and alertness. In addition, orexins are essential regulators of REM sleep, the sleep stage characterized by vivid dreams and paralysis of nearly all muscles.

The importance of orexin is especially clear in people with narcolepsy. These individuals have an acquired loss of the orexin-producing neurons, which results in chronic sleepiness and intrusions into wakefulness of REM sleep-like phenomena, including dream-like hallucinations and cataplexy (emotionally triggered episodes of muscle weakness similar to the paralysis of REM sleep^{3–5}).

Brisbare-Roch *et al.* found that a new orexin antagonist (ACT-078573) selectively blocked both orexin receptors (OX₁ and OX₂) at nanomolar concentrations, but it had little affinity for other G protein-coupled receptors². The drug was orally active and rapidly entered the brain. When given to rats during their active period, it increased REM and non-REM sleep for at least 12 hours, and dogs treated with it spent more time in a sleeping posture as shown by video analysis. In a small number of people treated with the drug during the day, many felt sleepy, and, when permitted to nap, they fell asleep quickly. Many sedatives can produce sensations of drunkenness or unsteadiness, but these and other side effects were uncommon with this orexin antagonist.

The sleepiness produced by this drug affirms that orexins promote wakefulness in people, just as suggested by much animal research. More importantly, this drug may have several useful clinical applications.

At first glance one might think that an orexin antagonist could be a useful addition to the current selection of drugs for insomnia. Many of the medications now used to promote sleep, such as benzodiazepines and the newer agents such as zolpidem, enhance signaling through GABA_A receptors. Other choices include GABA_B agonists, antihistamines and

melatonin agonists, yet patients sometimes find the current drugs ineffective or the side effects intolerable.

The early findings with this orexin antagonist show that it can promote sleep, but not everyone with sleep problems is likely to find it effective. The authors show this compound was moderately effective at promoting sleep when given to rats and dogs during the active period, but, in striking contrast to traditional sedatives, it had no effect when given during their rest periods. Orexins are released during active wakefulness but not during the sleep period^{6–8}, so this drug may not benefit most people with insomnia. On the other hand, it may be very effective in shift workers or people with jet lag trying to sleep when their biological clock is signaling wakefulness.

In mice, rats, dogs and people, disrupted orexin signaling causes narcolepsy with cataplexy^{3–5,9–11}. Although the new orexin antagonist thoroughly blocks orexin signaling and produces sleepiness, surprisingly it does not appear to produce cataplexy. In part, this may be a consequence of the authors' definition of cataplexy that differs from prior studies in narcoleptic rodents (in which the EEG pattern during cataplexy resembles that seen in REM sleep; see refs. ^{10,12}). But even when this drug was given to people, no obvious cataplexy occurred.

This lack of cataplexy could be due to the experimental conditions: cataplexy in people is often triggered by laughter, and heartfelt mirth is very difficult to elicit in the lab. It is also possible that cataplexy only develops with chronic loss of orexin signaling, so it will be important to assess carefully whether cataplexy develops after weeks of treatment with the antagonist.

Another possible use of this orexin antagonist is suggested by new work indicating that orexin neurons play an essential role in modulating reward pathways¹³. Rewarding stimuli such as cocaine, morphine and food trigger release of dopamine from the mesolimbic dopamine projections, and excessive activity in this pathway can cause addiction. Orexins enhance signaling in this reward network, and mice lacking orexins not only eat less but also show much less addictive behavior with morphine or amphetamines^{14,15}. Thus, by reducing activity in reward pathways, an orexin antagonist might be useful in the treatment of obesity or drug addiction by reducing food or drug craving and the risk of relapse. Still, this may not be as simple as it appears: rats and dogs treated with the orexin antagonist were sluggish and moved less around their cages. It is unclear whether they moved less because they were sleepy or because their reward pathways were inactivated (reducing their motivation to move).

Hence, an orexin antagonist may help people troubled by substance abuse only if it can be given at a dose that dampens activity in reward pathways without producing too much sedation or a general lack of motivation.

A wealth of animal research has demonstrated the importance of orexins in promoting arousal, regulating reward and driving appetite, and this new antagonist provides an opportunity to better understand the functions of orexins in human behavior. The early findings with this drug are encouraging, yet much more needs to be done before it can be brought to the clinic. First, it will be essential to define which patients are most likely to benefit from the sedating actions of this drug; then, sleep recordings will need to be examined in detail to ensure that acute and chronic use of the antagonist produces good quality sleep without triggering cataplexy when the patients are awake. It may also be worthwhile to test this antagonist as a novel therapy for the treatment of substance abuse.

However, like the two faces of Janus, it will be important when evaluating orexin antagonists to be wary of the implications of their other face: reducing the motivation that is the zest of life.

References

1. Siegel JM. *Annu Rev Psychol.* 2004; 55:125148.
2. Brisbare-Roch C, et al. *Nat Med.* 2007; 13:150–155. [PubMed: 17259994]
3. Peyron C, et al. *Nat Med.* 2000; 6:991–997. [PubMed: 10973318]
4. Thannickal TC, et al. *Neuron.* 2000; 27:469–474. [PubMed: 11055430]
5. Crocker A, et al. *Neurology.* 2005; 65:1184–1188. [PubMed: 16247044]
6. Lee MG, Hassani OK, Jones BE. *J Neurosci.* 2005; 25:6716–6720. [PubMed: 16014733]
7. Mileykovskiy BY, Kiyashchenko LI, Siegel JM. *Neuron.* 2005; 46:787–798. [PubMed: 15924864]
8. Estabrooke IV, et al. *J Neurosci.* 2001; 21:1656–1662. [PubMed: 11222656]
9. Chemelli RM, et al. *Cell.* 1999; 98:437–451. [PubMed: 10481909]
10. Beuckmann CT, et al. *J Neurosci.* 2004; 24:4469–4477. [PubMed: 15128861]
11. Lin L, et al. *Cell.* 1999; 98:365–376. [PubMed: 10458611]
12. Mochizuki T, et al. *J Neurosci.* 2004; 24:6291–6300. [PubMed: 15254084]
13. Harris GC, Wimmer M, Aston-Jones G. *Nature.* 2005; 437:556–559. [PubMed: 16100511]
14. Hara J, Yanagisawa M, Sakurai T. *Neurosci Lett.* 2005; 380:239–242. [PubMed: 15862893]
15. Narita M, et al. *J Neurosci.* 2006; 26:398–405. [PubMed: 16407535]

Figure 1.

Among their many functions, the orexin neurons promote wakefulness and modulate reward pathways. The orexin neurons innervate and excite many brain regions that drive arousal and attention, including the locus coeruleus and the dorsal raphe. Rewarding stimuli trigger release of dopamine from the mesolimbic projections between the ventral tegmental area and the nucleus accumbens, and orexins enhance signaling in this pathway. As Brisbare-Roch *et al.* have found, an orexin antagonist that blocks these signals can promote sleep (by reducing arousal) and possibly aid in the treatment of drug addiction (by dampening reward signals).