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GUEST EDITORIAL

REM sleep: A biological and psychological paradox

Introduction

Sleep and rest can be satisfactorily explained as adaptive states[1,2] whose core function is energy conservation and behavioral regulation. In addition to these functions, certain recuperative processes may be accomplished within sleep. However, the adaptive role of rapid eye movement (REM) sleep remains a complete mystery. The high levels of brain metabolic demand and attenuation of homeostatic regulation make it difficult to understand how animals benefit from this state. Adding to the mystery, it is well known that drug induced suppression of REM sleep is without any striking effect on behavior. Humans taking selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, monoamine oxidase inhibitors and antidepressants have a massive suppression of REM sleep[3] yet they do not go insane and do not have any apparent impairment of memory – indeed may have some small improvements of memory.[4] Even long term usage of these drugs, with concomitant reduction or elimination of REM sleep does not generally have deleterious effects on health. Indeed they are often given to regulate blood pressure or improve mood. Similarly, no cognitive or health impairment has been identified in the few humans who have lost REM sleep because of brain injury.[5] So, REM sleep truly has earned the name "paradoxical sleep," first given to it by the French researcher Michel Jouvet because of its waking electroencephalogram (EEG) during behavioral sleep. It should be noted that in contrast to the findings in humans, deprivation of rats of REM or non REM sleep by the disk over water method can be lethal.[6] However, this may well be due to stress involved in repeated arousals rather than sleep loss itself. Lethal effects of sleep loss have not been reported in mice, cats or other animal sleep subjects.

So we are left with a profound question; why do all land mammals (but not necessarily marine mammals[1,7]) and many, perhaps all birds have REM sleep[8] if it uses so much energy and can apparently be dispensed with without obvious negative consequences? Several recent papers in this journal address aspects of this paradox.[9–14]

REM sleep and dreaming

The history of dreaming long predates its scientific investigation. Aserinsky and Kleitman[15] showed for the first time that dreaming was associated with a state of low voltage EEG and eye movements during sleep that they called REM sleep. This discovery was followed by the surprising discovery that the physiological state that had been linked to dreams in humans could be identified in most mammals, suggesting that animals dream. The state also recurred in a regular rhythm, with a cycle duration that was positively correlated with body and brain mass.[16]

The assumption that animals have dream-like experience as we do, has to be tempered by more recent findings that human dreaming can be abolished by relatively small cortical lesions that do not interfere with other aspects of REM sleep.[17] Furthermore, it has been established that some humans do not report dreaming. This finding has typically been dismissed as being due to the rapid forgetting of dreams that most of us experience. If a person awakens a few minutes after the end of a REM sleep period they will not report dreaming. But in an impressive test of this hypothesis, non-dream reporters were awakened from REM sleep at all times of the night and many still reported no dreams.[18] Furthermore, human infants have huge amounts of REM sleep, yet it is inconceivable that they could have dream experiences that are similar to adult dreams. Children under the age of 5–6 have dream recall from only 20–30% of REM awakenings, the reported dreams are brief, fragmentary and static. Recall is still below 30% at 8 years of age, not reaching the adult level of 80% until ages 9–11.[19] Furthermore, the primitive mammal platypus, the animal with the greatest amount of REM sleep, does not have cortical activation during most of this state,[20] again casting doubt on the often assumed linkage between REM and higher cognitive processes including dreaming.

Palagini and Rosenlicht[12] review the early art and literature linking dreaming to divine and prophetic messages. The Greek Artemidorus Daldianus cataloged over 30,000 different types of dreams emphasizing their prophetic meaning. In Greek mythology, Hypnos, the god of sleep, Oneiros the god of dreams and Morpheus, the dream shaper, worked together to reduce human suffering. Plato proposed that repressed bestial desires can be expressed in dreams, presaging Freudian 19th and 20th century speculations. Aristotle rejected the idea that dreams are prophetic, indicating that they were the result of sensations occurring in the absence of perception. Medieval concepts applied the Hippocratic theory of humors (blood, black bile, yellow bile and phlegm) to explain dreams, with each fluid causing "vapors" that produced particular types of dreams. Freud, Jung and others used dreams to understand and treat emotional problems on the assumption that dreaming is a meaningful reflection of unconscious mental functioning.

Controversies over dream meaning continue into the modern era. The idea that the movements of the eyes scan the dream images have been disputed,[21] but receives support in studies of REM sleep behavior disorder.[22] It has been proposed that dreams are essentially a passive response to stochastic ascending input from the brainstem REM sleep generator.[23] However, systematic analyses of dreams show them for the most part to be structured with regular developmental characteristics simulating waking experience. This data indicates that, bizarre dream characteristics are relatively rare in contrast to what one might expect from

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pulsatile brainstem activation. Daily events are not typically integrated into dreams but clearly waking concerns and interests shape dreams as they do waking cognition.[24]

Although all brain regions are capable of plasticity a few brain regions including the olfactory bulb and the dentate gyrus of the hippocampus actually generate new neurons throughout the lifespan, likely compensating the relatively rapid loss of old cells in these same structures. Sleep deprivation, particularly REM sleep deprivation, interferes with the neurogenesis either by preventing an essential step in the process of neurogenesis that occurs only during sleep, or by disrupting this process by the stress elicited by the deprivation procedure.[25] However, as pointed out above, total blockade of REM sleep does not interfere with learning.[4]

REM sleep control

Another approach to unraveling the functional paradox of REM sleep is examining its control circuitry. The classic work of Jouvet and others[26–28] established that the pons was both necessary and sufficient for REM sleep. Indeed primitive mammals often show REM sleep only in the brainstem,[20,29] suggesting that forebrain aspects of REM sleep, including dreaming, have evolved relatively recently. Initial work in the cat emphasized the role of acetylcholine.[30] Microinjection of the cholinergic agonist carbachol into the pontine brainstem, particularly in the region ventral to the locus coeruleus can produce, at a latency of seconds, a state with all the characteristics of REM sleep including rapid eye movements, high voltage waves propagating from the pons to the thalamus and then cortex, called PGO spikes, and muscle atonia.[31] Strikingly, this state can last hours or even days after a single injection. Work in the cat and then in the rat showed that glutamatergic projections emanating from the critical pontine zone mediated the muscle tone suppression of REM sleep, acting on neurons in the medial medulla that cause the release of glycine and gamma-Aminobutyric acid (GABA) onto motoneurons.[32–39] This network at the same time caused inactivation of noradrenergic and other monoaminergic neurons which normally facilitated muscle tone.[40] So both disfacilitation by removal of monoamines and inhibition by release of glycine and GABA were linked to the muscle tone suppression of REM sleep.

Luppi and colleagues have focused on localizing the glutamatergic neurons active during REM sleep in the rat and particularly those involved in muscle tone suppression in REM sleep and cataplexy.[10] As in the cat, these neurons are localized to the region ventral to locus coeruleus. In the rat brain atlas used,[41] this subcoeruleus region was named the sublaterodorsal tegmental nucleus. Luppi and colleagues find that neurons containing the inhibitory transmitter GABA prevent the activity of the glutamatergic REM active neurons in the sublaterodorsal nucleus. Therefore the cessation of activity in these GABA neurons can trigger REM sleep. The sublaterodorsal glutamatergic neurons are also excited by glutamate which may be released by neurons whose cell bodies are in the midbrain periaqueductal gray.

It has been found that the noradrenergic neurons that are off in REM sleep and likely inhibit its occurrence, are themselves inhibited by GABA.[42,43] Luppi shows that application of GABA antagonists prevents the cessation of activity in these neurons during REM sleep, supporting the concept that GABA release is responsible for this cessation.

It has been theorized that the cessation of activity of noradrenergic neurons may be an important functional consequence of REM sleep, producing upregulation of noradrenergic receptors, downregulated by the tonic activity of these neurons in waking.[44,45] Mallick and Singh[11] suggest that REM sleep deprivation increases norepinephrine level and that this stimulates Na–K ATPase, an ion pump that moves sodium out of and potassium into neurons. This pump thereby controls the membrane potential of cells.

The unraveling of some to the REM sleep circuitry may give the impression that the paradox of REM sleep has been solved. But, alas, it remains. We do not know what conditions turn REM sleep on and what presumably fulfilled condition turns it off. So we now know many of the “players” in REM sleep control, but we really still don’t know their “game.”

REM sleep and bradyarrhythmia

Fifteen percent of all fatal ventricular arrhythmias occur during sleep. Rapid eye movement related bradyarrhythmia syndrome can occur in individuals without other heart disorders and in the absence of clear-cut sleep disorders such as obstructive sleep apnea. Asystoles lasting longer than 2.5 s and as long as 15 s have been seen during REM sleep.[9] Many such patients have dizziness, syncope and blurred vision upon awakening. The authors speculate that these events have one of three causes: exaggerated vagal tone, withdrawal of sympathetic activity or abnormal baroreceptor reflexes during REM sleep.

Holty and Guilleminault[9] highlight the large magnitude of changes in and the variability of the activity of sympathetic and parasympathetic activity during REM sleep. This illustrates the potential risk of REM sleep without revealing its offsetting benefit, reinforcing the paradoxical nature of the ubiquity of this state across individuals and species.

REM sleep and narcolepsy

Narcolepsy has long been viewed as a disease of REM sleep. This is because cataplexy, its most striking symptom seems physiologically similar to the muscle tone suppression of REM sleep.[46–48] The discovery that loss of cells containing the peptide orexin/hypocretin (two names for the same peptide) underlies most cases of narcolepsy[49,50] has provided a key insight into the sleepiness and cataplexy that define this disorder. Sinton[14] takes on the Herculean task of integrating the more than 2000 publications on orexin/hypocretin since the discovery of this peptide in 1998.[14] Key issues that are explored include the nature of the triggering of REM sleep and the relation of REM sleep signs to symptoms of narcolepsy. Although it has been speculated that offset of activity in orexin/hypocretin neurons is responsible for sleep or REM sleep onset, recordings of the activity of these neurons indicate a more complex process. In normal rats orexin/hypocretin neurons can be silent for long periods of time in waking[51] that are not followed by sleep. In sleep, activity is minimal in nonREM sleep with only a relatively small further decrement in activity in REM and without marked changes at the nonREM–REM transition. This is in keeping with other evidence suggesting a gradual transition between these two sleep states. The gradual transition between nonREM and REM sleep contrasts with the abrupt transition between either of these sleep states and waking whose substrates can be identified in unit recordings.[28]

The link between REM sleep and cataplexy can be seen in unit activity recording in other cell groups. For example the cells in the medulla that are thought to be responsible for the motor inhibition by GABA and glycine seen in REM sleep are maximally active only during REM sleep and cataplexy.[47] Conversely the noradrenergic cells that facilitate muscle tone in waking and to a lesser extent in nonREM sleep are inactive during REM sleep and cataplexy.[46] Serotonergic cells of the dorsal raphe show a similar slowing in cataplexy, but to a lesser extent than locus coeruleus cells.[52] On the other hand, most cells in the brainstem tegmentum that are active during REM sleep are inactive during cataplexy.[53] Thus at the

neuronal level we see aspects of REM sleep occurring during cataplexy, supporting the concept of REM sleep intrusion. However, just as cataplexy differs from REM sleep in its maintenance of consciousness and tracking eye movement, the neuronal activity that accompanies it also differs, most interestingly in the maintenance of activity in histamine cells in cataplexy.[54] We hypothesized that this activity is responsible for the maintenance of consciousness in cataplexy, a key aspect distinguishing it from REM sleep.

Presumably it is the loss of orexin/hypocretin signaling that is responsible for the discoordination of REM sleep signs that produces cataplexy. But it seems unlikely that this is a direct effect, since as mentioned above, long duration cessation of neuronal activity and orexin/hypocretin release in waking is a normal phenomenon, not linked to narcolepsy. However, the death of orexin/hypocretin cells presumably removes trophic effects on other brain systems normally receiving projections from these neurons. The anatomical and physiological changes that result from this produce the symptoms of narcolepsy.

Sinton integrates the sleep pathology caused by orexin/hypocretin cell loss with the larger issue of the adaptive role of the orexin/hypocretin cells. He reviews evidence indicating that these cells are activated and appear to drive adaptive responses to need for food and associated changes in autonomic function.

The maladaptive changes in central nervous system (CNS) structures normally innervated by orexin/hypocretin neurons may be responsible for some aspects of the autonomic changes reviewed by Plazzi et al. in narcoleptics.[13] Plazzi et al. explain the reduction in pupil diameter and increase in low frequency oscillation in pupil diameter in narcolepsy by the loss of the projection of these neurons to the ciliary ganglion. They cite evidence that reduced cardiovascular reflexes occur in narcolepsy and are not due to the chronic use of stimulants. This finding is in accord with data from orexin/hypocretin knock out (KO) mice.[55] Similarly, obesity occurs not only in human narcolepsy but also in KO mice, despite reduced food intake, and this effect is sex dependent.[56–58] Sexual disorders tend to occur many years after the loss of orexin/hypocretin cells and are of uncertain etiology. Plazzi et al. document several other disputed claims of altered autonomic function in narcolepsy. Parallel studies in animal models may help resolve these disputes.

There have been publications claiming a role for orexin/hypocretin in thermoregulation, but the evidence for this stems from injections of large amounts of the peptide into the cerebral ventricles or into relatively small brain regions. Orexin/hypocretin is an excitatory peptide and like glutamate or other excitatory neurotransmitters the effects seen from nonspecific administration have questionable relevance to normal function.

Conclusion

These wide ranging reviews of various aspects of the literature on REM sleep better define its generation mechanism, its relation to cardiac and narcoleptic pathology, and its link to dreaming. Clearly REM sleep dramatically modulates physiological and cognitive states. The adaptive benefits of these modulations remain unclear. Perhaps some other as yet unappreciated parameter will give further insight into the adaptive significance of this state. However, these recent reviews certainly clarify what it is we are trying to understand when we ask the question “why do we have REM sleep?”

References

1. Siegel JM. Sleep viewed as a state of adaptive inactivity. *Nat Rev Neurosci* 2009; **10**:747–53.
2. Matthews P, White C. Discontinuous gas exchange in insects: is it all in their heads? *Am Naturalist* 2011;**177**:130–4.
3. Schweitzer PK. Drugs that disturb sleep and wakefulness. In: Kryger MH, Roth T, Dement WC, editors. *Principles and Practice of Sleep Medicine*. Amsterdam: Elsevier Saunders; 2011. pp. 542–560.
4. Rasch B, Pommer J, Diekelmann S, Born J. Pharmacological REM sleep suppression paradoxically improves rather than impairs skill memory. *Nat Neurosci* 2009;**12**:396–7.
5. Lavie P, Pratt H, Scharf B, Peled R, Brown J. Localized pontine lesion: nearly total absence of REM sleep. *Neurology* 1984;**34**:118–20.
6. Rechtschaffen A, Bergmann BM. Sleep deprivation in the rat: an update of the 1989 paper. *Sleep* 2002;**25**:18–24.
7. Siegel JM. Do all animals sleep? *Trends Neurosci* 2008;**31**:208–13.
8. Roth TC, Lesku JA, Amlaner CJ, Lima SL. A phylogenetic analysis of the correlates of sleep in birds. *J Sleep Res* 2006;**15**:395–402.
9. Holty JE, Guilleminault C. REM-related bradyarrhythmia syndrome. *Sleep Med Rev* 2011;**15**:143–51.
10. Luppi P-H, Clément O, Sapin E, Gervasoni D, Peyron C, Léger L, et al. The neuronal network responsible for paradoxical sleep and its dysfunctions causing narcolepsy and rapid eye movement (REM) behavior disorder. *Sleep Med Rev* 2011;**15**:153–63.
11. Mallick BN, Singh A. REM sleep loss increases brain excitability: role of noradrenalin and its mechanism of action. *Sleep Med Rev* 2011;**15**:165–78.
12. Palagini L, Rosenlicht N. Sleep, dreaming, and mental health: A review of historical and neurobiological perspectives. *Sleep Med Rev* 2011;**15**:179–86.
13. Plazzi G, Moghadam KK, Maggi LS, Donadio V, Vetrugno R, Liguori R, et al. Autonomic disturbances in narcolepsy. *Sleep Med Rev* 2011;**15**:187–96.
14. Sinton CM. Orexin/hypocretin plays a role in the response to physiological disequilibrium. *Sleep Med Rev* 2011;**15**:197–207.
15. Aserinsky E, Kleitman N. Regularly occurring periods of eye motility, and concomitant phenomena, during sleep. *Science* 1953;**118**:273–4.
16. Siegel JM. Clues to the functions of mammalian sleep. *Nature* 2005;**437**:1264–71.
17. Solms M. *The neuropsychlogy of dreams: a clinico-anatomical study*. Mahwah, New Jersey: Lawrence Erlbaum Associates; 1997.
18. Pagel JF. Non-dreamers. *Sleep Med* 2003;**4**:235–41.
19. Foulkes D. *Children's dreaming and the development of consciousness*. Cambridge, MA: Harvard University Press; 2002.
20. Siegel JM, Manger PR, Nienhuis R, Fahringer HM, Shalita T, Pettigrew JD. Sleep in the platypus. *Neurosci* 1999;**91**:391–400.
21. Aserinsky E. Relationship of rapid eye movement density to the prior accumulation of sleep and wakefulness. *Psychophysiol* 1973;**10**:545–58.
22. Leclair-Visonneau L, Oudiette D, Gaymard B, Leu-Semenescu S, Arnulf I. Do the eyes scan dream images during rapid eye movement sleep? Evidence from the rapid eye movement sleep behaviour disorder model. *Brain* 2010;**133**: 1737–46.
23. Hobson JA, McCarley RW. The brain as a dream state generator: an activation-synthesis hypothesis of the dream process. *Am J Psychiatry* 1977;**134**:1335–48.
24. Zadra A, Domhoff GW. Dream content: quantitative findings. In: Kryger MH, Roth T, Dement WC, editors. *Principles and Practice of Sleep Medicine*. St. Louis MO: Elsevier Saunders; 2011. p. 585–94.
25. Guzman-Marin R, Suntsova N, Bashir T, Nienhuis R, Szymusiak R, McGinty D. Rapid eye movement sleep deprivation contributes to reduction of neurogenesis in the hippocampal dentate gyrus of the adult rat. *Sleep* 2008;**31**: 167–75.
26. Siegel JM, Nienhuis R, Tomaszewski KS. REM sleep signs rostral to chronic transections at the pontomedullary junction. *Neurosci Lett* 1984;**45**:241–6.
27. Siegel JM, Tomaszewski KS, Nienhuis R. Behavioral states in the chronic medullary and mid-pontine cat. *Electroenceph Clin Neurophysiol* 1986;**63**: 274–88.
28. Siegel JM. The neurobiology of sleep. *Semin Neurol* 2009;**29**:277–96.
29. Siegel JM, Manger P, Nienhuis R, Fahringer HM, Pettigrew J. The echidna *Tachyglossus aculeatus* combines REM and nonREMs aspects in a single sleep state: implications for the evolution of sleep. *J Neurosci* 1996;**16**:3500–6.
30. George R, Haslett WL, Jenden DJ. A cholinergic mechanism in the brainstem reticular formation: induction of paradoxical sleep. *Int J Neuropharmacol* 1964;**3**:541–52.
31. Shiromani P, Siegel JM, Tomaszewski KS, McGinty DJ. Alterations in blood pressure and REM sleep after pontine carbachol microinfusion. *Exp Neurol* 1986;**91**: 285–92.
32. Lai YY, Siegel JM. Cardiovascular and muscle tone changes produced by microinjection of cholinergic and glutamatergic agonists in dorsolateral pons and medial medulla. *Brain Res* 1990;**514**:27–36.
33. Shiromani PJ, Lai YY, Siegel JM. Descending projections from the dorsolateral pontine tegmentum to the paramedian reticular nucleus of the caudal medulla in the cat. *Brain Res* 1990;**517**:224–8.
34. Lai YY, Siegel JM. Pontomedullary glutamate receptors mediating locomotion and muscle tone suppression. *J Neurosci* 1991;**11**:2931–7.
35. Kodama T, Lai YY, Siegel JM. Enhancement of acetylcholine release during REM sleep in the caudomedial medulla as measured by in vivo microdialysis. *Brain Res* 1992;**580**:348–50.
36. Lai YY, Clements J, Siegel J. Glutamatergic and cholinergic projections to the pontine inhibitory area identified with horseradish peroxidase retrograde transport and immunohistochemistry. *J Comp Neurol* 1993;**336**: 321–30.
37. Kodama T, Lai YY, Siegel JM. Enhanced glutamate release during REM sleep in the rostromedial medulla as measured by in vivo microdialysis. *Brain Res* 1998; **780**:178–81.

38. Reid MS, Nishino S, Tafti M, Siegel JM, Dement WC, Mignot E. Neuropharmacological characterization of basal forebrain cholinergic stimulated cataplexy in narcoleptic canines. *Exp Neurol* 1998;**151**:89–104.
39. Hajnik T, Lai YY, Siegel JM. Atonia-related regions in the rodent pons and medulla. *J Neurophysiol* 2000;**84**:1942–8.
40. Mileykovskiy BY, Kiyashchenko LI, Kodama T, Lai YY, Siegel JM. Activation of pontine and medullary motor inhibitory regions reduces discharge in neurons located in the locus coeruleus and the anatomical equivalent of the midbrain locomotor region. *J Neurosci* 2000;**20**:8551–8.
41. Swanson LW. *Brain maps: structure of the rat brain*. Amsterdam: Elsevier Science; 1998.
42. Nitz D, Siegel JM. GABA release in the dorsal raphe nucleus: role in the control of REM sleep. *Amer J Physiol* 1997;**273**:R451–5.
43. Nitz D, Siegel JM. GABA release in the cat locus coeruleus as a function of the sleep/wake state. *Neurosci* 1997;**78**:795–801.
44. Siegel JM, Rogawski MA. A function for REM sleep: regulation of noradrenergic receptor sensitivity. *Brain Res Rev* 1988;**13**:213–33.
45. Mallick BN, Kaur S, Saxena RN. Interactions between cholinergic and GABAergic neurotransmitters in and around the locus coeruleus for the induction and maintenance of rapid eye movement sleep in rats. *Neurosci* 2001;**104**:467–85.
46. Wu MF, Gulyani SA, Yau E, Mignot E, Phan B, Siegel JM. Locus coeruleus neurons: cessation of activity during cataplexy. *Neurosci* 1999;**91**:1389–99.
47. Siegel JM, Nienhuis R, Fahringer H, Paul R, Shiromani P, Dement WC, et al. Neuronal activity in narcolepsy: identification of cataplexy related cells in the medial medulla. *Science* 1991;**252**:1315–8.
48. Rechtschaffen A, Wolpert EA, Dement WC, Mitchel SA, Fisher C. Nocturnal sleep of narcoleptics. *Electroenceph Clin Neurophysiol* 1963;**15**:599–609.
49. Peyron C, Faraco J, Rogers W, Ripley B, Overeem S, Charnay Y, et al. A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains. *Nat Med* 2000;**6**:991–7.
50. Thannickal TC, Moore RY, Nienhuis R, Ramanathan L, Gulyani S, Aldrich M, et al. Reduced number of hypocretin neurons in human narcolepsy. *Neuron* 2000;**27**:469–74.
51. Mileykovskiy BY, Kiyashchenko LI, Siegel JM. Behavioral correlates of activity in identified hypocretin/orexin neurons. *Neuron* 2005;**46**:787–98.
52. Wu MF, John J, Boehmer LN, Yau D, Nguyen GB, Siegel JM. Activity of dorsal raphe cells across the sleep-waking cycle and during cataplexy in narcoleptic dogs. *J Physiol* 2004;**554**:202–15.
53. Siegel JM, Nienhuis R, Fahringer HM, Chiu C, Dement WC, Mignot E, et al. Activity of medial mesopontine units during cataplexy and sleep-waking states in the narcoleptic dog. *J Neurosci* 1992;**12**:1640–6.
54. John J, Wu M-F, Boehmer LN, Siegel JM. Cataplexy-active neurons in the posterior hypothalamus: implications for the role of histamine in sleep and waking behavior. *Neuron* 2004;**42**:619–34.
55. Kayaba Y, Nakamura A, Kasuya Y, Ohuchi T, Yanagisawa M, Komuro I, et al. Attenuated defense response and low basal blood pressure in orexin knockout mice. *Am J Physiol Regul Integr Comp Physiol* 2003;**285**:R581–93.
56. Siegel JM. Hypocretin (orexin): role in normal behavior and neuropathology. *Annu Rev Psychol* 2004;**55**:125–48.
57. Willie JT, Chemelli RM, Sinton CM, Tokita S, Williams SC, Kisanuki YY, et al. Distinct narcolepsy syndromes in orexin receptor-2 and orexin null mice: molecular genetic dissection of non-REM and REM sleep regulatory processes. *Neuron* 2003;**38**:715–30.
58. Hara J, Beuckmann CT, Nambu T, Willie JT, Chemelli RM, Sinton CM, et al. Genetic ablation of orexin neurons in mice results in narcolepsy, hypophagia, and obesity. *Neuron* 2001;**30**:345–54.

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