REVIEW

Neuronal substrates for initiation, maintenance, and structural organization of sleep/wake states [version 1; referees: 2 approved]

Ada Eban-Rothschild, Luis de Lecea

Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, CA, 94305, USA

v1 **First published:** 03 Mar 2017, **6**(F1000 Faculty Rev):212 (doi: 10.12688/f1000research.9677.1)

Latest published: 03 Mar 2017, **6**(F1000 Faculty Rev):212 (doi: 10.12688/f1000research.9677.1)

Abstract

Animals continuously alternate between sleep and wake states throughout their life. The daily organization of sleep and wakefulness is orchestrated by circadian, homeostatic, and motivational processes. Over the last decades, much progress has been made toward determining the neuronal populations involved in sleep/wake regulation. Here, we will discuss how the application of advanced *in vivo* tools for cell type–specific manipulations now permits the functional interrogation of different features of sleep/wake state regulation: initiation, maintenance, and structural organization. We will specifically focus on recent studies examining the roles of wake-promoting neuronal populations.

Open Peer Review

Referee Status: ✔ ✔

	Invited Referees 1	2
version 1 published 03 Mar 2017	✔	✔

F1000 Faculty Reviews are commissioned from members of the prestigious F1000 Faculty. In order to make these reviews as comprehensive and accessible as possible, peer review takes place before publication; the referees are listed below, but their reports are not formally published.

1 **Jasna Saponjic**, University of Belgrade Serbia

2 **Tononi Guilio**, University of Wisconsin-Madison USA

Discuss this article

Comments (0)

Corresponding author: Luis de Lecea (LLECEA@STANFORD.EDU)

How to cite this article: Eban-Rothschild A and de Lecea L. **Neuronal substrates for initiation, maintenance, and structural organization of sleep/wake states [version 1; referees: 2 approved]** *F1000Research* 2017, **6**(F1000 Faculty Rev):212 (doi: 10.12688/f1000research.9677.1)

Grant information: This work was supported by the Edmond and Lily Safra Center of Brain Science and Katharine McCormick postdoctoral fellowships (to AE-R); the National Institutes of Health grants RO1-MH087592, RO1-MH102638, and RO1-AG04767 (to LdL); a Brain and Behavior Research Foundation (NARSAD) grant (to LdL); and the US Israel Binational Science Foundation (LdL).
The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors declare that they have no competing interests.

First published: 03 Mar 2017, **6**(F1000 Faculty Rev):212 (doi: 10.12688/f1000research.9677.1)

Introduction

Animals—including nematode worms[1,2], bees[3,4], flies[5,6], fish[7,8], rodents, humans, and even birds during migration[9]—alter between wake and sleep states throughout their life. During wakefulness, animals engage in various adaptive and motivated behaviors related to foraging, courting, mating, and predator evading, among many others. Sleep is a state of quiescence with reduced responsiveness to external stimuli yet is restorative and recruits essential mechanisms for homeostatic balance[10–12].

The daily organization of sleep and wake periods is orchestrated by circadian, homeostatic, and motivational processes[13,14]. The circadian clock (about 24 hours long) synchronizes sleep to an appropriate time of day; for example, night in diurnal animals and day in nocturnal animals. The homeostatic process is responsible for compensating sleep loss. In addition, environmental circumstances and internal needs, such as hunger[9,15–18], the presence of a predator[19–23], or mating opportunities[24], can powerfully modulate sleep and wake states.

Sleep is ubiquitous in the animal kingdom, and the molecular pathways associated with sleep in the worm, fly, and mammals show much conservation, suggesting an ancient and common origin for sleep[12,25–27]. For example, in both insects and mammals, histaminergic, noradrenergic, and dopaminergic neurotransmission promotes wakefulness whereas GABAergic and serotonergic neurotransmission promotes sleep[28–42].

Sleep/wake disturbances are a major public health concern and affect 6% to 30% of the general adult population worldwide[43]. Sleep disturbances have numerous deleterious effects, including impaired cognition, reduced immunity, and elevated risks of cancer and heart disease[44,45]. Perturbations of sleep/wake states are also associated with various neuropsychiatric disorders, such as major depression, substance abuse, and anxiety disorders[45]. Increasing evidence suggests that several co-morbid pathologies found in neuropsychiatric disorders arise from a destabilization of sleep mechanisms[44,45]. Elucidating the neurobiological substrates of sleep and wakefulness could not only reveal how the brain orchestrates one of the most striking transitions in behavior and physiology, but could also provide a mechanistic framework for improved intervention with therapeutic purposes.

Neuronal circuitry underlying the regulation of sleep/wake states

In mammals, birds, and reptiles, there are three general states of vigilance: wakefulness, non–rapid eye movement (NREM) sleep, and rapid eye movement (REM) sleep. The different states can be distinguished using electroencephalogram (EEG) and electromyogram recordings, which measure global cortical and muscular activity, respectively. The three vigilance states also differ in various physiological parameters, such as thermoregulation, brain metabolism, and breathing[46]. How does the mammalian brain control sleep and wake states? von Economo[47], Ranson[48], and Moruzzi and Magoun[49] were among the first to examine a neuronal mechanism for sleep/wake regulation. Many subsequent studies have contributed to the identification of distinct neuronal populations across the brain that participate in sleep/wake regulation. It is currently understood that sleep/wake states are regulated by complex interactions between several neuronal populations, which show robust arousal state–dependent alterations in neuronal activity[13]. Subcortical neuromodulatory neurons in the brainstem, midbrain, hypothalamus, and basal forebrain (BF) send widespread projections across the brain and interact with each other, the thalamus, and the cortex to drive behavioral, physiological, and electrocortical sleep/wake states[13,46,50–52]. In this review, we will focus mainly on wake-promoting populations. Key components of the arousal system are the following:

1) Monoaminergic neurons, including the noradrenergic locus coeruleus (LC)[36,53], dopaminergic ventral tegmental area (VTA)[31,32], dopaminergic and serotonergic dorsal raphe nucleus (DRN)[41,54–56], and histaminergic tuberomammillary nucleus (TMN)[38,57] neurons.

2) Cholinergic neurons of the pedunculopontine and laterodorsal tegmental nuclei (PPT/LDT)[58,59] and BF[60,61].

3) Hypocretinergic (Hcrt, also known as orexinergic) neurons of the lateral hypothalamus (LH)[62–64].

In each of these nuclei reside additional populations of GABAergic and glutamatergic neurons that have been shown to participate, or may participate, in sleep/wake regulation (for example,[65]). A balance between the wake-promoting and the sleep-promoting neurons—such as the GABAergic neurons of the ventrolateral preoptic area and the median preoptic area[66–69], the GABAergic neurons of the parafacial zone[70,71], and melanin-concentrating hormone neurons of the LH[72]—has been hypothesized as a theoretical model to understand sleep-to-wake transitions[13]. According to this model, the mutually inhibitory interactions of wake-promoting and sleep-promoting neurons produce a state similar to a flip-flop switch in an electrical circuit[13].

From a functional dynamic perspective, one could identify neuronal circuits involved in the initiation, maintenance, and structural organization of the three vigilance states. With traditional strategies, such as brain lesions, pharmacological interventions, and animal knockout models, it was very difficult to address the causal role of specific populations in the regulation of the different components of vigilance states because they lacked both cellular specificity and temporal resolution. With the application of *in vivo* optogenetic[73] and chemogenetic[74] tools for cell type–specific neural manipulations and genetically encoded calcium indicators[75] for neural activity recordings, it is now possible to functionally interrogate the specific roles of, and interactions between, genetically defined neuronal populations across the brain in sleep/wake regulation.

Initiation of vigilance states

Animals typically wake up rapidly—an adaptive response since they may need to flee or defend themselves when awakened. The transition between sleep and wakefulness has been hypothesized to involve fast glutamate transmission and wake-promoting neuromodulators[13,46,76]. Optogenetic manipulations have demonstrated that increasing activity in noradrenergic LC[77], dopaminergic VTA[31], and cholinergic BF[78–81] neurons during sleep can rapidly

initiate wakefulness. Hcrt LH neurons have been hypothesized to regulate sleep-to-wake transitions based on homeostatic and environmental conditions[82–84]. Hcrt LH neurons are sensitive to diverse peripheral and central signals associated with nutritional state, such as low glucose (for example,[85,86]), and optogenetic stimulation of Hcrt LH neurons during NREM sleep increases the probability for a sleep-to-wake transition[87] only under low sleep pressure[82]. Cholinergic neurons have long been suggested to play a critical role in cortical activation during both wakefulness[88] and REM sleep[51]. Optogenetic stimulation of cholinergic BF neurons during NREM sleep can elicit a transition to either wakefulness or REM sleep[79], whereas optogenetic inhibition prolongs NREM sleep[89]. These findings suggest that BF cholinergic neurons have an important role in NREM sleep termination, allowing the brain to transition to either wake or REM sleep[89].

Transitions from wakefulness to sleep are not instantaneous and can take a few seconds to minutes[13]. With the initiation of NREM sleep, the EEG progressively changes from high-frequency, low-voltage waves characteristic of wakefulness, to higher-voltage, slower waves designating NREM sleep[13,46,90]. Although the physiological and electrophysiological characteristics preceding and accompanying wake-to-NREM sleep transitions have been well studied[90,91], relatively little is known about the neuronal underpinnings of naturalistic behaviors that precede sleep. Animals typically display species-specific behaviors prior to sleep[92–94]; they will search for a safe place, may build a nest, assume a specific body posture[92–94], and engage in other behaviors, such as grooming and drinking[95,96]. A recent study demonstrated that mice drink prior to sleep in anticipation to the sleep period and not as a response to an immediate physiological need[97]. Moreover, drinking prior to sleep is controlled by circadian output from the central clock in the suprachiasmatic nucleus to the organum vasculosum lamina terminalis neurons[97]. We have recently identified a neuronal substrate for sleep-preparatory nest-building[31]. We demonstrated that chemogenetic inhibition of VTA dopaminergic neurons promotes sleep, only in the presence of a nest. In the absence of a nest, the inhibition of VTA dopaminergic neurons first promoted nest-building and only later sleep. Taken together, these findings suggest that electrocortical sleep is coupled with preceding behavioral manifestations, yet the role of this preparatory phase in sleep structure and quality remains to be elucidated.

Maintenance of vigilance states

During a normal sleep phase, animals continuously alternate between short periods of wakefulness, NREM sleep, and REM sleep. Typically, individuals enter NREM sleep from wakefulness and transition from NREM to either REM sleep or wakefulness. In humans, each cycle lasts around 90 minutes, whereas in rodents the cycles are shorter, lasting only several minutes. Once wakefulness, NREM sleep, or REM sleep is initiated, it is maintained for the duration necessary to fulfill its physiological purposes. How is the maintenance of vigilance states attained? One potential mechanism is continuous, tonic, or phasic activity in a certain neuronal population, such as histaminergic TMN neurons (for wakefulness). Activity in these neurons could directly support the maintenance of specific states, or inhibit the initiation of other vigilance states, by specific downstream projections. Another possibility, yet not mutually exclusive, is irregular phasic activity in a neuronal ensemble that initiates and supports a range of behavioral and physiological characteristics via various downstream targets. For example, Hcrt LH neurons are phasically active only during the transitions between sleep and wakefulness and during wakefulness when environmental conditions change[63,64]. This "kickstart" pattern of activity is likely widespread in arousal centers as it allows more adaptive responses to changing environments.

The different arousal systems vary in their capacity to promote wakefulness, and it has been hypothesized that the different neuronal populations have distinct roles in supporting arousal under specific environmental conditions[51]. For example, histaminergic TMN neurons have an important role in maintaining arousal in novel environments[38,98]. Noradrenergic LC neurons promote attention and cognition during wakefulness[99] and have a pivotal role in supporting arousal in threatening circumstances[100,101]. Dopaminergic VTA neurons have a crucial role in wake maintenance in the face of various motivational processes, including mate- and food-seeking and predator evading[31]. Serotonergic DRN neurons have been suggested to support quiet wakefulness, possibly preceding sleep initiation[51,102,103]. A distinct role for each wake-related neuronal population in promoting distinct forms of arousal under specific environmental conditions could clarify the relatively surprising redundancy in wake-promoting circuits[13,51].

It is important to note that specific sleep/wake regulatory populations could have a more complex role than supporting one vigilance state. Histaminergic TMN neurons that have long been implicated in wake maintenance via histamine neurotransmission[13] also release GABA, which rather seems to promote sleep[104], at least via some projections. The co-transmission of histamine and GABA could serve as a break to the wake-promoting effects of histamine[104]. It would be of interest for future studies to further determine the importance of co-transmission in additional sleep/wake neuronal populations and the precise role the neuromodulatory substrates by themselves play in sleep/wake regulation.

Structural organization of vigilance states

Another important feature of sleep/wake regulatory circuits is maintaining the boundaries between vigilance states. A failure to maintain these boundaries could have severe consequences for survival if, for instance, a predator defense behavior were interrupted by an unexpected transition to sleep. In addition, the restorative and memory consolidation functions of sleep are dependent upon proper consolidation of sleep, as demonstrated by the deleterious effects of sleep fragmentation[43,105].

The daily organization of sleep and wake periods is orchestrated by circadian, homeostatic, and motivational processes. The circadian clock (about 24 hours long) synchronizes sleep to an appropriate time of day (that is, night in diurnal animals and day in nocturnal animals). The homeostatic process is responsible for compensating sleep loss following sleep debt. In addition, environmental circumstances and internal needs, here referred to as "motivational processes", can powerfully affect sleep/wake states.

How do regulatory circuits maintain the boundaries between the vigilance states? The hypocretin system is hypothesized to orchestrate the structural organization of sleep/wake states[84,106]. The hypocretins are two neuropeptides, Hcrt-1 and Hcrt-2, produced from the pre-pro-hypocretin precursor, which are expressed solely in a glutamatergic neuronal population in the LH. Hcrt neurons project to diverse areas of the central nervous system, including to major sleep/wake nuclei, such as the LC, TMN, DRN, PPT, LDT, and VTA[62,107], that express the Hcrt receptors, Hcrt-R1 and Hcrt-R2[108]. *In vitro* electrophysiology and histological studies demonstrate that Hcrt neurons are activated by neurotransmitters that promote arousal, including corticotropin-releasing factor[109] and thyrotropin-releasing hormone[110], and inhibited by sleep-promoting substances, including GABA[111] and adenosine[112].

Hcrt LH neurons are essential for the stability of arousal and malfunction of the Hcrt network fragments sleep and wake states. The loss of Hcrt neurons, or its receptors, in rodents[113–115], canines[116], and humans[117–119] is associated with narcolepsy with cataplexy, a neurological disorder characterized by an inability to control the boundaries between sleep/wake states. In narcoleptics, periods of wakefulness are interrupted by unexpected sleep episodes, and REM-like episodes coexist with conscious wakefulness[120]. Similarly, Hcrt knockout or Hcrt-R2-deficient mice show increased arousal state–transitions but do not vary in the total daily duration of sleep and wake states from control animals. Lastly, optogenetic stimulation of Hcrt LH neurons during sleep, in rodents, increases the probability for a sleep-to-wake transition[87]. Together, these findings support the premise that under physiological conditions Hcrt LH neurons are important in maintaining the boundaries between sleep/wake states.

It is also important to note that the three vigilant states are not always mutually exclusive, and different dissociated states exist in humans as well as other animals. Slow-wave sleep can occur locally in cortical areas[121–123] as well as in individual neurons while animals are behaviorally awake[124]. In addition, unihemispheric slow-wave sleep (USWS) has been documented in a number of aquatic mammals[125] and birds[126]. During USWS, the eye contralateral to the awake hemisphere is open and could monitor the environment. This plasticity could permit birds to defend themselves from predators or continuously fly during long migration periods and aquatic mammals to breathe or take care of their young during critical periods[126].

Conclusions and perspectives

During the last decade, major advances have been made in characterizing the neuronal populations participating in sleep/wake regulation. However, it is still unclear how the brain integrates information from diverse populations to control overt arousal. Are the different arousal populations promoting wakefulness in different ecological contexts? How does the brain prioritize arousal based on environmental circumstances and homeostatic needs? In addition, future studies should further examine the role of distinct subpopulations of GABAergic, glutamatergic, and peptidergic neurons in sleep/wake regulatory nuclei.

Competing interests

The authors declare that they have no competing interests.

Grant information

This work was supported by the Edmond and Lily Safra Center of Brain Science and Katharine McCormick postdoctoral fellowships (to AE-R); the National Institutes of Health grants RO1-MH087592, RO1-MH102638, and RO1-AG04767 (to LdL); a Brain and Behavior Research Foundation (NARSAD) grant (to LdL); and the US Israel Binational Science Foundation (LdL).

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgments

We thank William J. Giardino, Suszie Tyree and the referees for their helpful comments on this manuscript.

References

F1000 recommended

1. F Raizen DM, Zimmerman JE, Maycock MH, *et al.*: **Lethargus is a *Caenorhabditis elegans* sleep-like state.** *Nature.* 2008; **451**(7178): 569–72.
PubMed Abstract | Publisher Full Text | F1000 Recommendation
2. van Buskirk C, Sternberg PW: **Epidermal growth factor signaling induces behavioral quiescence in *Caenorhabditis elegans*.** *Nat Neurosci.* 2007; **10**(10): 1300–7.
PubMed Abstract | Publisher Full Text
3. Kaiser W, Steiner-Kaiser J: **Neuronal correlates of sleep, wakefulness and arousal in a diurnal insect.** *Nature.* 1983; **301**(5902): 707–9.
PubMed Abstract | Publisher Full Text
4. Eban-Rothschild A, Bloch G: **Social influences on circadian rhythms and sleep in insects.** *Adv Genet.* 2012; **77**: 1–32.
PubMed Abstract | Publisher Full Text
5. Hendricks JC, Finn SM, Panckeri KA, *et al.*: **Rest in *Drosophila* is a sleep-like state.** *Neuron.* 2000; **25**(1): 129–38.
PubMed Abstract | Publisher Full Text
6. Shaw PJ: **Correlates of sleep and waking in *Drosophila melanogaster*.** *Science.* 2000; **287**(5459): 1834–7.
PubMed Abstract | Publisher Full Text
7. Zhdanova IV, Wang SY, Leclair OU, *et al.*: **Melatonin promotes sleep-like state in zebrafish.** *Brain Res.* 2001; **903**(1–2): 263–8.
PubMed Abstract | Publisher Full Text
8. Prober DA, Rihel J, Onah AA, *et al.*: **Hypocretin/orexin overexpression induces an insomnia-like phenotype in zebrafish.** *J Neurosci.* 2006; **26**(51): 13400–10.
PubMed Abstract | Publisher Full Text
9. Rattenborg NC, Voirin B, Cruz SM, *et al.*: **Evidence that birds sleep in mid-flight.** *Nat Commun.* 2016; **7**: 12468.
PubMed Abstract | Publisher Full Text | Free Full Text
10. Cirelli C, Tononi G: **Is sleep essential?** *PLoS Biol.* 2008; **6**(8): e216.
PubMed Abstract | Publisher Full Text | Free Full Text
11. Mignot E: **Why we sleep: the temporal organization of recovery.** *PLoS Biol.* 2008; **6**(4): e106.
PubMed Abstract | Publisher Full Text | Free Full Text
12. Allada R, Siegel JM: **Unearthing the phylogenetic roots of sleep.** *Curr Biol.* 2008;

18(15): R670–R679.
PubMed Abstract | Publisher Full Text | Free Full Text

13. Saper CB, Fuller PM, Pedersen NP, *et al.*: **Sleep state switching.** *Neuron.* 2010; **68**(6): 1023–42.
PubMed Abstract | Publisher Full Text | Free Full Text

14. Borbély AA, Achermann P: **Sleep homeostasis and models of sleep regulation.** *J Biol Rhythms.* 1999; **14**(6): 557–568.
PubMed Abstract | Publisher Full Text

15. Borbély AA: **Sleep in the rat during food deprivation and subsequent restitution of food.** *Brain Res.* 1977; **124**(3): 457–71.
PubMed Abstract | Publisher Full Text

16. Danguir J, Nicolaidis S: **Dependence of sleep on nutrients' availability.** *Physiol Behav.* 1979; **22**(4): 735–40.
PubMed Abstract | Publisher Full Text

17. Dewasmes G, Duchamp C, Minaire Y: **Sleep changes in fasting rats.** *Physiol Behav.* 1989; **46**(2): 179–84.
PubMed Abstract | Publisher Full Text

18. Jacobs BL, McGinty DJ: **Effects of food deprivation on sleep and wakefulness in the rat.** *Exp Neurol.* 1971; **30**(2): 212–22.
PubMed Abstract | Publisher Full Text

19. Lima SL, Rattenborg NC, Lesku JA, *et al.*: **Sleeping under the risk of predation.** *Anim Behav.* 2005; **70**(4): 723–36.
Publisher Full Text

20. Lesku JA, Bark RJ, Martinez-Gonzalez D, *et al.*: **Predator-induced plasticity in sleep architecture in wild-caught Norway rats (*Rattus norvegicus*).** *Behav Brain Res.* 2008; **189**(2): 298–305.
PubMed Abstract | Publisher Full Text

21. Lendrem DW: **Sleeping and vigilance in birds, II. An experimental study of the Barbary dove (*Streptopelia risoria*).** *Anim Behav.* 1984; **32**(1): 243–8.
Publisher Full Text

22. Gauthier-Clerc M, Tamisier A, Cezilly F: **Sleep-vigilance trade-off in Green-winged Teals (*Anas crecca crecca*).** *Can J Zool.* 1998; **76**(12): 2214–8.
Publisher Full Text

23. Dominguez J: **Sleeping and vigilance in Black-tailed Godwit.** *J Ethol.* 2003; **21**(1): 57–60.
Publisher Full Text

24. F Lesku JA, Rattenborg NC, Valcu M, *et al.*: **Adaptive sleep loss in polygynous pectoral sandpipers.** *Science.* 2012; **337**(6102): 1654–8.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

25. Cirelli C: **The genetic and molecular regulation of sleep: from fruit flies to humans.** *Nat Rev Neurosci.* 2009; **10**(8): 549–60.
PubMed Abstract | Publisher Full Text | Free Full Text

26. Sehgal A, Mignot E: **Genetics of sleep and sleep disorders.** *Cell.* 2011; **146**(2): 194–207.
PubMed Abstract | Publisher Full Text | Free Full Text

27. Greenspan RJ, Tononi G, Cirelli C, *et al.*: **Sleep and the fruit fly.** *Trends Neurosci.* 2001; **24**(3): 142–5.
PubMed Abstract | Publisher Full Text

28. Andretic R, van Swinderen B, Greenspan RJ: **Dopaminergic modulation of arousal in *Drosophila*.** *Curr Biol.* 2005; **15**(13): 1165–75.
PubMed Abstract | Publisher Full Text

29. F Kume K, Kume S, Park SK, *et al.*: **Dopamine is a regulator of arousal in the fruit fly.** *J Neurosci.* 2005; **25**(32): 7377–84.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

30. Pimentel D, Donlea JM, Talbot CB, *et al.*: **Operation of a homeostatic sleep switch.** *Nature.* 2016; **536**(7616): 333–7.
PubMed Abstract | Publisher Full Text | Free Full Text

31. Eban-Rothschild A, Rothschild G, Giardino WJ, *et al.*: **VTA dopaminergic neurons regulate ethologically relevant sleep-wake behaviors.** *Nat Neurosci.* 2016; **19**(10): 1356–66.
PubMed Abstract | Publisher Full Text

32. Dahan L, Astier B, Vautrelle N, *et al.*: **Prominent burst firing of dopaminergic neurons in the ventral tegmental area during paradoxical sleep.** *Neuropsychopharmacology.* 2007; **32**(6): 1232–41.
PubMed Abstract | Publisher Full Text

33. Monti JM, Monti D: **The involvement of dopamine in the modulation of sleep and waking.** *Sleep Med Rev.* 2007; **11**(2): 113–33.
PubMed Abstract | Publisher Full Text

34. Nall A, Sehgal A: **Monoamines and sleep in *Drosophila*.** *Behav Neurosci.* 2014; **128**(3): 264–72.
PubMed Abstract | Publisher Full Text

35. F Taylor NE, van Dort CJ, Kenny JD, *et al.*: **Optogenetic activation of dopamine neurons in the ventral tegmental area induces reanimation from general anesthesia.** *Proc Natl Acad Sci U S A.* 2016; pii: 201614340.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

36. Aston-Jones G, Bloom FE: **Activity of norepinephrine-containing locus coeruleus neurons in behaving rats anticipates fluctuations in the sleep-waking cycle.** *J Neurosci.* 1981; **1**(8): 876–886.
PubMed Abstract

37. Crocker A, Sehgal A: **Octopamine regulates sleep in *drosophila* through protein kinase A-dependent mechanisms.** *J Neurosci.* 2008; **28**(38): 9377–85.
PubMed Abstract | Publisher Full Text | Free Full Text

38. Parmentier R, Ohtsu H, Djebbara-Hannas Z, *et al.*: **Anatomical, physiological, and pharmacological characteristics of histidine decarboxylase knock-out mice: evidence for the role of brain histamine in behavioral and sleep-wake control.** *J Neurosci.* 2002; **22**(17): 7695–7711.
PubMed Abstract

39. Oh Y, Jang D, Sonn JY, *et al.*: **Histamine-HisCl1 receptor axis regulates wake-promoting signals in *Drosophila melanogaster*.** *PLoS One.* 2013; **8**(7): e68269.
PubMed Abstract | Publisher Full Text | Free Full Text

40. F Agosto J, Choi JC, Parisky KM, *et al.*: **Modulation of $GABA_A$ receptor desensitization uncouples sleep onset and maintenance in *Drosophila*.** *Nat Neurosci.* 2008; **11**(3): 354–9.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

41. McGinty DJ, Harper RM: **Dorsal raphe neurons: Depression of firing during sleep in cats.** *Brain Res.* 1976; **101**(3): 569–75.
PubMed Abstract | Publisher Full Text

42. Yuan Q, Joiner WJ, Sehgal A: **A sleep-promoting role for the *Drosophila* serotonin receptor 1A.** *Curr Biol.* 2006; **16**(7): 1051–62.
PubMed Abstract | Publisher Full Text

43. Roth T: **Insomnia: definition, prevalence, etiology, and consequences.** *J Clin Sleep Med.* 2007; **3**(5 Suppl): S7–10.
PubMed Abstract | Free Full Text

44. Mignot E, Taheri S, Nishino S: **Sleeping with the hypothalamus: emerging therapeutic targets for sleep disorders.** *Nat Neurosci.* 2002; **5**(Suppl): 1071–5.
PubMed Abstract | Publisher Full Text

45. Wulff K, Gatti S, Wettstein JG, *et al.*: **Sleep and circadian rhythm disruption in psychiatric and neurodegenerative disease.** *Nat Rev Neurosci.* 2010; **11**(8): 589–99.
PubMed Abstract | Publisher Full Text

46. Brown RE, Basheer R, McKenna JT, *et al.*: **Control of sleep and wakefulness.** *Physiol Rev.* 2012; **92**(3): 1087–187.
PubMed Abstract | Publisher Full Text | Free Full Text

47. Economo CV: **Sleep as a problem of localization.** *J Nerv Ment Dis.* 1930; **71**(3): 249–59.
Publisher Full Text

48. Ranson SW: **Somnolence caused by hypothalamic lesions in the monkey.** *Arch NeurPsych.* 1939; **41**(1): 1–23.
Publisher Full Text

49. Moruzzi G, Magoun HW: **Brain stem reticular formation and activation of the EEG.** *Electroencephalogr Clin Neurophysiol.* 1949; **1**(4): 455–73.
PubMed Abstract | Publisher Full Text

50. Luppi PH, Peyron C, Fort P: **Not a single but multiple populations of GABAergic neurons control sleep.** *Sleep Med Rev.* 2016. pii: S1087-0792(16)00025-3.
PubMed Abstract | Publisher Full Text

51. Jones BE: **Arousal systems.** *Front Biosci.* 2003; **8**: s438–451.
PubMed Abstract | Publisher Full Text

52. Jouvet M: **The role of monoamines and acetylcholine-containing neurons in the regulation of the sleep-waking cycle.** *Ergeb Physiol.* 1972; **64**: 166–307.
PubMed Abstract

53. Takahashi K, Kayama Y, Lin JS, *et al.*: **Locus coeruleus neuronal activity during the sleep-waking cycle in mice.** *Neuroscience.* 2010; **169**(3): 1115–26.
PubMed Abstract | Publisher Full Text

54. Lu J, Jhou TC, Saper CB: **Identification of wake-active dopaminergic neurons in the ventral periaqueductal gray matter.** *J Neurosci.* 2006; **26**(1): 193–202.
PubMed Abstract | Publisher Full Text

55. Guzmán-Marín R, Alam MN, Szymusiak R, *et al.*: **Discharge modulation of rat dorsal raphe neurons during sleep and waking: effects of preoptic/basal forebrain warming.** *Brain Res.* 2000; **875**(1–2): 23–34.
PubMed Abstract | Publisher Full Text

56. Sakai K, Crochet S: **Serotonergic dorsal raphe neurons cease firing by disfacilitation during paradoxical sleep.** *Neuroreport.* 2000; **11**(14): 3237–41.
PubMed Abstract | Publisher Full Text

57. F Takahashi K, Lin JS, Sakai K: **Neuronal activity of histaminergic tuberomammillary neurons during wake-sleep states in the mouse.** *J Neurosci.* 2006; **26**(40): 10292–8.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

58. el Mansari M, Sakai K, Jouvet M: **Unitary characteristics of presumptive cholinergic tegmental neurons during the sleep-waking cycle in freely moving cats.** *Exp Brain Res.* 1989; **76**(3): 519–29.
PubMed Abstract | Publisher Full Text

59. Boucetta S, Jones BE: **Activity profiles of cholinergic and intermingled GABAergic and putative glutamatergic neurons in the pontomesencephalic tegmentum of urethane-anesthetized rats.** *J Neurosci.* 2009; **29**(14): 4664–74.
PubMed Abstract | Publisher Full Text

60. Cape EG, Jones BE: **Effects of glutamate agonist versus procaine microinjections into the basal forebrain cholinergic cell area upon gamma and theta EEG activity and sleep-wake state.** *Eur J Neurosci.* 2000; **12**(6): 2166–84.
PubMed Abstract | Publisher Full Text

61. Kaur S, Junek A, Black MA, *et al.*: **Effects of ibotenate and 192IgG-saporin lesions of the nucleus basalis magnocellularis/substantia innominata on spontaneous sleep and wake states and on recovery sleep after sleep deprivation in rats.** *J Neurosci.* 2008; **28**(2): 491–504.
PubMed Abstract | Publisher Full Text

62. Peyron C, Tighe DK, van den Pol AN, *et al.*: **Neurons containing hypocretin (orexin) project to multiple neuronal systems.** *J Neurosci.* 1998; **18**(23): 9996–10015.
PubMed Abstract

63. F Mileykovskiy BY, Kiyashchenko LI, Siegel JM: **Behavioral correlates of activity in identified hypocretin/orexin neurons.** *Neuron.* 2005; **46**(5): 787–98.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

64. Lee MG, Hassani OK, Jones BE: **Discharge of identified orexin/hypocretin neurons across the sleep-waking cycle.** *J Neurosci.* 2005; **25**(28): 6716–20.
PubMed Abstract | Publisher Full Text

65. Anaclet C, Pedersen NP, Ferrari LL, *et al.*: **Basal forebrain control of wakefulness and cortical rhythms.** *Nat Commun.* 2015; **6**: 8744.
PubMed Abstract | Publisher Full Text | Free Full Text

66. Alam MA, Kumar S, McGinty D, *et al.*: **Neuronal activity in the preoptic hypothalamus during sleep deprivation and recovery sleep.** *J Neurophysiol.* 2014; **111**(2): 287–99.
PubMed Abstract | Publisher Full Text | Free Full Text

67. Sherin JE, Shiromani PJ, McCarley RW, *et al.*: **Activation of ventrolateral preoptic neurons during sleep.** *Science.* 1996; **271**(5246): 216–9.
PubMed Abstract | Publisher Full Text

68. John J, Kumar VM: **Effect of NMDA lesion of the medial preoptic neurons on sleep and other functions.** *Sleep.* 1998; **21**(6): 587–598.
PubMed Abstract | Publisher Full Text

69. Lu J, Greco MA, Shiromani P, *et al.*: **Effect of lesions of the ventrolateral preoptic nucleus on NREM and REM sleep.** *J Neurosci.* 2000; **20**(10): 3830–3842.
PubMed Abstract

70. Batini C, Moruzzi G, Palestini M, *et al.*: **Presistent patterns of wakefulness in the pretrigeminal midpontine preparation.** *Science.* 1958; **128**(3314): 30–2.
PubMed Abstract | Publisher Full Text

71. Anaclet C, Ferrari L, Arrigoni E, *et al.*: **The GABAergic parafacial zone is a medullary slow wave sleep-promoting center.** *Nat Neurosci.* 2014; **17**(9): 1217–24.
PubMed Abstract | Publisher Full Text | Free Full Text

72. Jego S, Glasgow SD, Herrera CG, *et al.*: **Optogenetic identification of a rapid eye movement sleep modulatory circuit in the hypothalamus.** *Nat Neurosci.* 2013; **16**(11): 1637–43.
PubMed Abstract | Publisher Full Text | Free Full Text

73. Tye KM, Deisseroth K: **Optogenetic investigation of neural circuits underlying brain disease in animal models.** *Nat Rev Neurosci.* 2012; **13**(14): 251–66.
PubMed Abstract | Publisher Full Text

74. Sternson SM, Roth BL: **Chemogenetic tools to interrogate brain functions.** *Annu Rev Neurosci.* 2014; **37**: 387–407.
PubMed Abstract | Publisher Full Text

75. Resendez SL, Stuber GD: ***In vivo* calcium imaging to illuminate neurocircuit activity dynamics underlying naturalistic behavior.** *Neuropsychopharmacology.* 2015; **40**(1): 238–9.
PubMed Abstract | Publisher Full Text | Free Full Text

76. Richter C, Woods IG, Schier AF: **Neuropeptidergic control of sleep and wakefulness.** *Annu Rev Neurosci.* 2014; **37**: 503–31.
PubMed Abstract | Publisher Full Text

77. F Carter ME, Yizhar O, Chikahisa S, *et al.*: **Tuning arousal with optogenetic modulation of locus coeruleus neurons.** *Nat Neurosci.* 2010; **13**(12): 1526–33.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

78. Han Y, Shi YF, Xi W, *et al.*: **Selective activation of cholinergic basal forebrain neurons induces immediate sleep-wake transitions.** *Curr Biol.* 2014; **24**(6): 693–8.
PubMed Abstract | Publisher Full Text

79. Irmak SO, de Lecea L: **Basal forebrain cholinergic modulation of sleep transitions.** *Sleep.* 2014; **37**(12): 1941–51.
PubMed Abstract | Publisher Full Text | Free Full Text

80. Xu M, Chung S, Zhang S, *et al.*: **Basal forebrain circuit for sleep-wake control.** *Nat Neurosci.* 2015; **18**(11): 1641–7.
PubMed Abstract | Publisher Full Text

81. Zant JC, Kim T, Prokai L, *et al.*: **Cholinergic Neurons in the Basal Forebrain Promote Wakefulness by Actions on Neighboring Non-Cholinergic Neurons: An Opto-Dialysis Study.** *J Neurosci.* 2016; **36**(6): 2057–67.
PubMed Abstract | Publisher Full Text | Free Full Text

82. F Carter ME, Adamantidis A, Ohtsu H, *et al.*: **Sleep homeostasis modulates hypocretin-mediated sleep-to-wake transitions.** *J Neurosci.* 2009; **29**(35): 10939–49.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

83. Adamantidis A, Carter MC, de Lecea L: **Optogenetic deconstruction of sleep-wake circuitry in the brain.** *Front Mol Neurosci.* 2010; **2**: 31.
PubMed Abstract | Publisher Full Text | Free Full Text

84. Sutcliffe JG, de Lecea L: **The hypocretins: setting the arousal threshold.** *Nat Rev Neurosci.* 2002; **3**(5): 339–49.
PubMed Abstract | Publisher Full Text

85. Acuna-Goycolea C, van den Pol A: **Glucagon-like peptide 1 excites hypocretin/orexin neurons by direct and indirect mechanisms: implications for viscera-mediated arousal.** *J Neurosci.* 2004; **24**(37): 8141–52.
PubMed Abstract | Publisher Full Text

86. Rao Y, Lu M, Ge F, *et al.*: **Regulation of synaptic efficacy in hypocretin/orexin-containing neurons by melanin concentrating hormone in the lateral hypothalamus.** *J Neurosci.* 2008; **28**(37): 9101–10.
PubMed Abstract | Publisher Full Text | Free Full Text

87. F Adamantidis AR, Zhang F, Aravanis AM, *et al.*: **Neural substrates of awakening probed with optogenetic control of hypocretin neurons.** *Nature.* 2007; **450**(7168): 420–4.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

88. Lin SC, Brown RE, Hussain Shuler MG, *et al.*: **Optogenetic Dissection of the Basal Forebrain Neuromodulatory Control of Cortical Activation, Plasticity, and Cognition.** *J Neurosci.* 2015; **35**(41): 13896–903.
PubMed Abstract | Publisher Full Text | Free Full Text

89. F Shi YF, Han Y, Su YT, *et al.*: **Silencing of Cholinergic Basal Forebrain Neurons Using Archaerhodopsin Prolongs Slow-Wave Sleep in Mice.** *PLoS One.* 2015; **10**(7): e0130130.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

90. Wright KP Jr, Badia P, Wauquier A: **Topographical and temporal patterns of brain activity during the transition from wakefulness to sleep.** *Sleep.* 1995; **18**(10): 880–889.
PubMed Abstract | Publisher Full Text

91. Ogilvie RD: **The process of falling asleep.** *Sleep Med Rev.* 2001; **5**(3): 247–70.
PubMed Abstract | Publisher Full Text

92. Hediger H: **Comparative observations on sleep.** *Proc R Soc Med.* 1969; **62**(2): 153–156.
PubMed Abstract | Free Full Text

93. Meddis R: **On the function of sleep.** *Anim Behav.* 1975; **23**(3): 676–91.
PubMed Abstract | Publisher Full Text

94. Moruzzi G: **Sleep and instinctive behavior.** *Arch Ital Biol.* 1969; **107**(2): 175–216.
PubMed Abstract

95. Spiteri NJ: **Circadian patterning of feeding, drinking and activity during diurnal food access in rats.** *Physiol Behav.* 1982; **28**(1): 139–47.
PubMed Abstract | Publisher Full Text

96. Johnson RF, Beltz TG, Thunhorst RL, *et al.*: **Investigations on the physiological controls of water and saline intake in C57BL/6 mice.** *Am J Physiol Regul Integr Comp Physiol.* 2003; **285**(2): R394–403.
PubMed Abstract | Publisher Full Text

97. F Gizowski C, Zaelzer C, Bourque CW: **Clock-driven vasopressin neurotransmission mediates anticipatory thirst prior to sleep.** *Nature.* 2016; **537**(7622): 685–8.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

98. Anaclet C, Parmentier R, Ouk K, *et al.*: **Orexin/hypocretin and histamine: distinct roles in the control of wakefulness demonstrated using knock-out mouse models.** *J Neurosci.* 2009; **29**(46): 14423–38.
PubMed Abstract | Publisher Full Text | Free Full Text

99. Sara SJ: **The locus coeruleus and noradrenergic modulation of cognition.** *Nat Rev Neurosci.* 2009; **10**(3): 211–23.
PubMed Abstract | Publisher Full Text

100. Hobson JA, McCarley RW, Wyzinski PW: **Sleep cycle oscillation: reciprocal discharge by two brainstem neuronal groups.** *Science.* 1975; **189**(4196): 55–8.
PubMed Abstract | Publisher Full Text

101. Aston-Jones G, Cohen JD: **An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance.** *Annu Rev Neurosci.* 2005; **28**: 403–50.
PubMed Abstract | Publisher Full Text

102. Sommerfelt L, Ursin R: **Behavioral, sleep-waking and EEG power spectral effects following the two specific 5-HT uptake inhibitors zimeldine and alaproclate in cats.** *Behav Brain Res.* 1991; **45**(2): 105–15.
PubMed Abstract | Publisher Full Text

103. Ursin R: **The effects of 5-hydroxytryptophan and L-tryptophan on wakefulness and sleep patterns in the cat.** *Brain Res.* 1976; **106**(1): 105–15.
PubMed Abstract | Publisher Full Text

104. F Yu X, Ye Z, Houston CM, *et al.*: **Wakefulness Is Governed by GABA and Histamine Cotransmission.** *Neuron.* 2015; **87**(1): 164–78.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

105. F Rolls A, Colas D, Adamantidis A, *et al.*: **Optogenetic disruption of sleep continuity impairs memory consolidation.** *Proc Natl Acad Sci U S A.* 2011; **108**(32): 13305–10.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

106. de Lecea L, Kilduff TS, Peyron C, *et al.*: **The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity.** *Proc Natl Acad Sci U S A.* 1998; **95**(1): 322–7.
PubMed Abstract | Publisher Full Text | Free Full Text

107. Sakurai T, Mieda M: **Connectomics of orexin-producing neurons: interface of systems of emotion, energy homeostasis and arousal.** *Trends Pharmacol Sci.* 2011; **32**(8): 451–62.
PubMed Abstract | Publisher Full Text

108. Carter ME, Schaich Borg J, de Lecea L: **The brain hypocretins and their receptors: mediators of allostatic arousal.** *Curr Opin Pharmacol.* 2009; **9**(1): 39–45.
PubMed Abstract | Publisher Full Text | Free Full Text

109. F Winsky-Sommerer R, Yamanaka A, Diano S, *et al.*: **Interaction between the corticotropin-releasing factor system and hypocretins (orexins): a novel circuit mediating stress response.** *J Neurosci.* 2004; **24**(50): 11439–48.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

110. Hara J, Gerashchenko D, Wisor JP, *et al.*: **Thyrotropin-releasing hormone increases behavioral arousal through modulation of hypocretin/orexin neurons.** *J Neurosci.* 2009; **29**(12): 3705–14.
PubMed Abstract | Publisher Full Text | Free Full Text

111. Xie X, Crowder TL, Yamanaka A, *et al.*: **$GABA_B$ receptor-mediated modulation of hypocretin/orexin neurones in mouse hypothalamus.** *J Physiol.* 2006; **574**(Pt 2): 399–414.
PubMed Abstract | Publisher Full Text | Free Full Text

112. Liu ZW, Gao XB: **Adenosine inhibits activity of hypocretin/orexin neurons by the A1 receptor in the lateral hypothalamus: a possible sleep-promoting effect.** *J Neurophysiol.* 2007; **97**(1): 837–48.
PubMed Abstract | Publisher Full Text | Free Full Text

113. F Mochizuki T, Arrigoni E, Marcus JN, *et al.*: **Orexin receptor 2 expression in the posterior hypothalamus rescues sleepiness in narcoleptic mice.** *Proc Natl Acad Sci U S A.* 2011; **108**(11): 4471–6.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

114. Mochizuki T, Crocker A, McCormack S, *et al.*: **Behavioral state instability in orexin knock-out mice.** *J Neurosci.* 2004; **24**(28): 6291–300.
PubMed Abstract | Publisher Full Text

115. Chemelli RM, Willie JT, Sinton CM, *et al.*: **Narcolepsy in *orexin* knockout mice: molecular genetics of sleep regulation.** *Cell.* 1999; **98**(4): 437–51.
PubMed Abstract | Publisher Full Text

116. Lin L, Faraco J, Li R, *et al.*: **The sleep disorder canine narcolepsy is caused by a mutation in the *hypocretin* (*orexin*) *receptor 2* gene.** *Cell.* 1999; **98**(3): 365–76.
PubMed Abstract | Publisher Full Text

117. Nishino S, Ripley B, Overeem S, *et al.*: **Hypocretin (orexin) deficiency in human narcolepsy.** *Lancet.* 2000; **355**(9197): 39–40.
PubMed Abstract | Publisher Full Text

118. Peyron C, Faraco J, Rogers W, *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**(9): 991–7.
PubMed Abstract | Publisher Full Text

119. Thannickal TC, Moore RY, Nienhuis R, *et al.*: **Reduced number of hypocretin neurons in human narcolepsy.** *Neuron.* 2000; **27**(3): 469–74.
PubMed Abstract | Publisher Full Text

120. de Lecea L: **Optogenetic control of hypocretin (orexin) neurons and arousal circuits.** *Curr Top Behav Neurosci.* 2015; **25**: 367–78.
PubMed Abstract | Publisher Full Text | Free Full Text

121. F Huber R, Ghilardi MF, Massimini M, *et al.*: **Local sleep and learning.** *Nature.* 2004; **430**(6995): 78–81.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

122. Krueger JM, Rector DM, Roy S, *et al.*: **Sleep as a fundamental property of neuronal assemblies.** *Nat Rev Neurosci.* 2008; **9**(12): 910–9.
PubMed Abstract | Publisher Full Text | Free Full Text

123. Nir Y, Staba RJ, Andrillon T, *et al.*: **Regional slow waves and spindles in human sleep.** *Neuron.* 2011; **70**(1): 153–69.
PubMed Abstract | Publisher Full Text | Free Full Text

124. F Vyazovskiy VV, Olcese U, Hanlon EC, *et al.*: **Local sleep in awake rats.** *Nature.* 2011; **472**(7344): 443–7.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

125. Lyamin OI, Manger PR, Ridgway SH, *et al.*: **Cetacean sleep: an unusual form of mammalian sleep.** *Neurosci Biobehav Rev.* 2008; **32**(8): 1451–84.
PubMed Abstract | Publisher Full Text

126. Rattenborg NC, Amlaner CJ, Lima SL: **Behavioral, neurophysiological and evolutionary perspectives on unihemispheric sleep.** *Neurosci Biobehav Rev.* 2000; **24**(8): 817–42.
PubMed Abstract | Publisher Full Text

Open Peer Review

Current Referee Status: ✔ ✔

Editorial Note on the Review Process

F1000 Faculty Reviews are commissioned from members of the prestigious F1000 Faculty and are edited as a service to readers. In order to make these reviews as comprehensive and accessible as possible, the referees provide input before publication and only the final, revised version is published. The referees who approved the final version are listed with their names and affiliations but without their reports on earlier versions (any comments will already have been addressed in the published version).

The referees who approved this article are:

Version 1

1 **Tononi Guilio**, University of Wisconsin-Madison, Madison, WI, USA
Competing Interests: No competing interests were disclosed.

1 **Jasna Saponjic**, University of Belgrade, Belgrade, Serbia
Competing Interests: No competing interests were disclosed.