Published in final edited form as:

Curr Opin Neurobiol. 2013 October ; 23(5): 780–785. doi:10.1016/j.conb.2013.02.001.

Role of the basal ganglia in the control of sleep and wakefulness

Michael Lazarus^{1,2}, Jiang-Fan Chen³, Yoshihiro Urade^{1,2}, and Zhi-Li Huang^{2,4}

¹International Institute for Integrative Sleep Medicine (WPI-IIS), University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8575, Japan

²Department of Molecular Behavioral Biology, Osaka Bioscience Institute, 6-2-4 Furuedai, Suita, Osaka 565-0874, Japan

³Department of Neurology, Boston University School of Medicine, 715 Albany Street, Boston, MA 02118, USA

⁴Department of Pharmacology, Fudan University Shanghai Medical College, 138 Yixueyuan Road, Shanghai 200032, China

Abstract

The basal ganglia (BG) act as a cohesive functional unit that regulates motor function, habit formation, and reward/addictive behaviors; but the debate has only recently started on how the BG maintain wakefulness and suppress sleep to achieve all these fundamental functions of the BG. Neurotoxic lesioning, pharmacological approaches, and the behavioral analyses of genetically modified animals revealed that the striatum and globus pallidus are important for the control of sleep and wakefulness. Here, we discuss anatomical and molecular mechanisms for sleep-wake regulation in the BG and propose a plausible model in which the nucleus accumbens integrates behavioral processes with wakefulness through adenosine and dopamine receptors.

Keywords

indirect pathway; locomotion; caudate-putamen; caffeine; modafinil

Introduction

Sleep is one of the most mysterious of the physiological functions of the brain. Sleep or sleep-like states seem to exist in all complex organisms that have a central nervous system. The sleeping habits of humans, however, are unique in the sense that we often defy sleep and stay awake for occupational or recreational reasons, although we are tired during that time. The motivation to stay awake and active in our modern society is ever growing and often accompanied by the use of psychoactive substances, most prominently caffeine, but also various prescription drugs and substances of abuse. The key area governing these behaviors is the basal ganglia (BG), which are subcortical nuclei involved in motor function, habit formation, and reward/addictive behaviors, all of which depend on wakefulness. Considering the significant influence this behavior has on our lives, it is not surprising that

© 2013 Elsevier Ltd. All rights reserved.

Corresponding authors: Michael Lazarus, phone: 81-6-6872-4851; fax: 81-6-6872-2841; mlazarus@obi.or.jp and Zhi-Li Huang, phone: 86-21-54237043; fax: 86-21-54237103; huangzl@fudan.edu.cn.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

exploration of the neural network through which the BG integrate these fundamental striatal functions with arousal is a rapidly growing field in neurobiology.

One of the mechanisms of sleep induction involves the activation of adenosine A₁ and A_{2A} receptors (A₁Rs and A_{2A}Rs) by adenosine [1–3]. Recent findings indicate that caffeine, an A₁R and A_{2A}R antagonist, induces wakefulness by blocking the action of adenosine on A_{2A}Rs and that A_{2A}Rs in the shell of the nucleus accumbens (NAc) are critical for the arousal effect of caffeine [4,5]. A_{2A}Rs are highly expressed on striatopallidal neurons in the indirect pathway of the BG, in which dopamine D₂ receptors (D₂Rs) are co-expressed with A_{2A}Rs. The high expression levels of adenosine and dopamine receptors in this region provide a plausible framework for the integration of behavioral processes and emotional events to achieve arousal; and, by extension, the motivational state may be a fundamental regulator of sleep and wakefulness. In this review, we describe forthcoming roles of adenosine and dopamine in the BG for sleep-wake regulation and discuss anatomical and molecular mechanistic models of sleep-wake regulation that establish the dorsal striatum, NAc, and globus pallidus (GP) as key structural elements for the control of sleep and wakefulness.

Evidence for roles of the BG in the sleep-wake cycle

The BG consist of four major nuclei, i.e., the striatum, GP, subthalamic nucleus (STN), and substantia nigra (SN) [6]. The BG are strongly connected with the cortex, thalamus, amygdala, as well as with midbrain dopaminergic neurons and act as a cohesive functional unit in the process of optimizing behavior and regulating the vigilance state of wakefulness. Results obtained by neurotoxic lesioning of the striatum, which can be subdivided in rodents into the caudate-putamen (CPu) and ventral striatum, including the NAc, indicate a significant causal role between striatal structures and regulation of the sleep-wake cycle: the dorsal striatum enhances wakefulness and the NAc promotes sleep [7,8]. In these studies, bilateral lesions were made in the striatum that resulted in a significant reduction in time spent in wakefulness and fragmentation of both sleep and wakefulness. The effect of lesions in the striatum on wakefulness was attenuated, when the lesions included the NAc. By contrast, wakefulness was increased and the duration of bouts of non-rapid eye movement (NREM) sleep was reduced, when the NAc was selectively lesioned.

Interestingly, insomnia is observed in rats with cell body-specific lesioning of the external GP leading to a dramatic increase (~45%) in total wakefulness and pronounced fragmentation of NREM sleep and wakefulness [7]. Sleep-wake behavior was also affected by the loss of neurons in the SN leading to increased wakefulness, whereas sleep and wakefulness were unchanged after lesioning the internal GP or STN [7,9]. Interestingly, a generalized slowing of the cortical electroencephalogram (EEG), with less theta and more delta power during wakefulness and REM and NREM sleep is observed in rats with lesions in the CPu, NAc and external GP (GPe). It has been suggested that a dorsostriato-pallido-cortical loop may be the mechanism by which the dorsal striatum regulates sleep-wake behavior and cortical activation [7,10]. In this model, GABAergic neurons in the caudate-putamen (CPu) projects to the GPe, which in turn projects directly to the cerebral cortex. While GABAergic neurons in the adjacent basal forebrain are thought to project to cortical inhibitory interneurons (and thus promote wakefulness), those in the interior of the GPe may inhibit pyramidal cells, and thus promote sleep [7].

The role of the dopaminergic and adenosinergic system in the BG in the sleep-wake cycle

Whereas researchers have long studied the role of the mesolimbic dopamine system from the midbrain to the striatum in locomotion and motivational behavior [11,12], experimental evidence for the roles of adenosine and dopamine in the BG for sleep-wake regulation is finally emerging from obscurity. *In vivo* microdialysis experiments in combination with polysomnographic recording, for instance, have revealed that extracellular dopamine levels in the medial prefrontal cortex (mPFC) and NAc are low during NREM sleep, but significantly elevated during wakefulness and REM sleep [13]. The deletion of dopamine D₂ receptors (D₂Rs) from the entire animal results in a significant decrease in wakefulness, accompanied by an increase in NREM and REM sleep, and in drastically lower NREM sleep delta power [14], suggesting that the D₂R is critical for maintaining wakefulness during the normal wake phase. The D₂R agonist quinlorane, however, directly applied to the NAc increases wakefulness; whereas sleep is observed when the D₂R antagonist is injected into the NAc [15]. Interestingly, sleep deprivation in human study subjects leads to the down-regulation of D₂Rs measured by using positron emission tomography [16]. On the other hand, D₂R agonists, such as piribedil and pramipexole, which are used in the management of Parkinson's disease (PD) and restless legs syndrome, cause sudden sleep attacks or sleepiness in humans [17,18]. D₂R agonists, however, are a double-edged sword, because they may not only activate D₂Rs on striatal neurons, but also reduce dopamine release via presynaptic D₂Rs on dopaminergic axons of mesolimbic and mesocortical systems [19,20]. Modafinil, a wakefulness-promoting compound, is commonly used to treat excessive daytime sleepiness in patients with PD. Although modafinil is known to affect multiple neurotransmitter systems, such as catecholamines, serotonin, glutamate, gamma amino butyric acid (GABA), orexin, and histamine, this drug increases extracellular levels of dopamine in the NAc and mPFC [21] and has no effect in knockout mice for the dopamine transporter through which dopamine is primarily cleared from the synapses [22]. A recent finding by using D₂R knockout mice in combination with a dopamine D₁ receptor (D₁R) antagonist suggests that the arousal effect of modafinil is exclusively mediated by the D₁R and D₂R, with D₂R being the receptor of primary importance [23].

By contrast, the administration of CGS21680, a highly selective A_{2A}R agonist, to the subarachnoid space under the rostral BF produces c-fos expression within the shell of the NAc, the medial portion of the olfactory tubercle and the ventrolateral preoptic area (VLPO) [24]. It is possible that the activation of c-fos in the VLPO was secondary to the effect of activation of A_{2A}Rs in the NAc, especially because the activation of the VLPO in these experiments is more intense than during natural sleep. Moreover, the direct infusion of the same A_{2A}R agonist into the shell portion of the NAc induces NREM and REM sleep [25]. These observations indicate that A_{2A}Rs in or close to the shell portion of the NAc promote sleep.

Caffeine is the world's most widely used psychoactive drug, and it enhances wakefulness. Although this compound acts as an antagonist for both receptor subtypes with very similar affinities, studies using global genetic knockouts of A₁Rs and A_{2A}Rs, in which the receptor is deleted from the entire animal, have found, however, that the A_{2A}R, but not the A₁R, mediates the arousal effect of caffeine [26]. Moreover, using powerful tools for site-specific gene manipulations, including A_{2A}R knockout mice based on the Cre/lox technology and focal A_{2A}R knockdown in rats through local infection with adeno-associated virus carrying short-hairpin RNA specific for the mRNA of A_{2A}Rs [5], we showed that the deletion of the A_{2A}Rs selectively in the NAc shell results in abrogation of caffeine-induced wakefulness. For caffeine to be effective as an antagonist, excitatory A_{2A}Rs must be tonically activated by adenosine. In the NAc shell, this tonic activation is possible because adenosine is

available under the most basal conditions and A_{2A}Rs are highly expressed throughout the striatum. Thus, activation of the GABAergic output neurons on the indirect pathway by A_{2A}Rs results in reduced activity of arousal systems in the thalamus, hypothalamus, brainstem, and ultimately, the cerebral cortex. In fact, after stereotaxic-based brain microinjections of Cre recombinase-dependent, adeno-associated viral vectors carrying light-activated channels (channelrhodopsin) or designer receptors exclusively activated by a designer drug (DREADD) into the NAc of transgenic mice, in which Cre-recombinase is expressed under the A_{2A}R promoter [27], robust induction of NREM sleep can be observed during selective activation of striatopallidal neurons by light or the small molecule clozapine-N-oxide (Q Xu, B Zhang *et al.*, unpublished). By contrast, caffeine can override the “adenosine brake” to promote wakefulness.

A model of NAc involvement in sleep-wake regulation

Several systems of sleep- and wake-active neurons have been proposed to constitute the sleep-wake regulatory network. For instance, one model postulates that sleep results from the inhibition of acetylcholine release by adenosine in the basal forebrain (BF) [28]. Another contemporary model of the sleep-wake regulation describes a “flip-flop” arrangement, in which sleep is promoted by activation of sleep-promoting neurons in VLPO and reciprocal suppression of wake-promoting neurons in the brainstem and hypothalamus, including the tuberomammillary nucleus (TMN), locus coeruleus (LC), dorsal raphe nucleus (DR), and pontine (pedunculopontine and laterodorsal tegmental, PPT/LDT) nuclei [29–31]. During wakefulness, histaminergic neurons in the TMN, noradrenergic neurons in the LC, and serotonergic neurons in the DR exert excitatory effects on arousal systems in the thalamus, hypothalamus, basal forebrain, and cerebral cortex and cause inhibition of sleep-promoting neurons of the VLPO. The VLPO promotes sleep by inhibition of the arousal-promoting regions through GABAergic and galaninergic projections. The “flip-flop” switch model also hypothesizes that orexin neurons of the lateral hypothalamus (LHA) suppress unwanted transitions into sleep and thus stabilize wakefulness; the selective loss of orexin neurons results in narcolepsy, a chronic sleep disorder characterized by excessive sleepiness and sleep attacks at inappropriate times [32].

The NAc has a unique capability to integrate locomotion with motivational behavior through dopaminergic inputs, contextual information from the hippocampus, emotional content from the amygdala and executive/cognitive information from the prefrontal cortex. These multiple and integrated functions may be dissociable at neurotransmitter and neuromodulator levels since dopamine, adenosine and glutamate have been now clearly associated with controlling motor function and modulating learning by feedback reinforcement. Thus far identified efferents make it likely that the NAc is capable of regulating sleep and wakefulness through inhibition of neuronal populations in the VP, the lateral hypothalamus (LHA), the parabrachial nucleus (PB), and the ventral tegmental area (VTA; Figure 1). The circuit originating from the VP includes the thalamus and medial prefrontal cortex (mPFC), a key executive interface between cognition and emotion and uniquely sensitive to sleep and sleep need [33–36]; and it can provide top-down modulation through its descending projections to arousal-promoting neurons in the TMN, the LHA, and the LC. The orexinergic and glutamatergic neurons in the LHA send major projections to the BF and cerebral cortex, but are also reciprocally connected to the NREM/wake flip-flop switch, including the VLPO, the TMN, and the LC [29,37–39]. The NAc shell, but not the NAc core, sends projections to the PB [40,41], which is an important component of the ascending arousal system and is known to be strongly connected to the BF and LHA. The NAc projects to the medial part of the VTA with a field of cortically projecting glutamatergic neurons [37,42], which are likely the tail end of a larger group of neurons of the supramammillary nucleus (SUM). Interestingly, caffeine induces c- fos expression in non-dopaminergic neurons of the medial

VTA [43], but it remains to be clarified if it is possible that the VTA/SUM cell group relays the waking stimulus from the NAc to the cerebral cortex.

Conclusions

Widely accepted concepts of sleep-wake regulation emphasize homeostatic (sleep pressure), circadian (daily rhythms), and allostatic (food availability or behavioral stress) factors that control sleep. The homeostatic process is regulated by the sleep propensity, which builds up during wakefulness and declines during sleep [44]. Thereby, endogenous hypnogenic substances, such as adenosine [1,45,46], prostaglandin D₂ [47,48], cytokines [49], anandamide [50], and peptides including urotensin II [51], are thought to interact with the sleep regulatory network. On the other hand, in the circadian process, the sleep-wake cycle and a wide range of other behaviors and physiological functions during the day and night are controlled by a biological clock in the suprachiasmatic nucleus of the hypothalamus, whereby the timing of sleeping is independent of prior sleep and waking [29,52]. Strong behavioral arousal is required in stressful situations, such as the lack of food, predator confrontation, mating pressure, and seasonal migration, for which neural circuitry in the mPFC, amygdala, hypothalamus, and brain stem have been identified [53,54]. Adenosine and dopamine receptors in the ventral striatum provide molecular systems through which wakefulness is strongly promoted by motivational behavior, but locomotor and arousal systems are inhibited during sleep [55]. In future studies, an important issue is to identify which of the output projections of the striatum and the NAc relay the waking stimulus from the BG to the sleep-wake regulatory network and lead to cortical awakening. This task can be accomplished by a new generation of molecular biological technologies that range from conditional knockout mice based on the Cre/lox technology and RNA interference [5,56] to the optical or chemical modulation of neuronal activity through genetically engineered receptor-channel systems, such as optogenetics, DREADD or ivermectin-gated chloride channels [57–59].

Acknowledgments

We thank Daniel Wachendorf for helpful comments on this manuscript. Our research was supported by Japan Society for the Promotion of Science Grant 24300129 (to M.L.) and 22300133 (to Y.U.); World Premier International Research Center Initiative (WPI) from the Ministry of Education, Culture, Sports, Science, and Technology (to M.L. and Y.U.); a grant from the Ministry of Health, Labor and Welfare (to Y.U.); grants from Ono Pharmaceutical Co. (to Y.U.), Takeda Pharmaceutical Co. (to Y.U.), and Osaka City (to M.L., Z-L.H., and Y.U.); Grants-in-Aid for Scientific Research from the National Natural Science Foundation of China (31171010 and 31121061 to Z-L.H.); grants from the National Basic Research Program of China Grants (2009CB5220004, 2011CB711000, and 2009ZX09303-006 to Z-L.H.); by funding from the Shanghai Leading Academic Discipline Project (B119 to Z-L. H.); by National Institutes of Health Grant NS041083 (to J-F.C.); and by a grant from the Cogan Family Foundation (to J-F.C.).

References

1. Huang ZL, Urade Y, Hayaishi O. The role of adenosine in the regulation of sleep. *Curr Top Med Chem.* 2011; 11:1047–1057. [PubMed: 21401496]
2. Basheer R, Strecker RE, Thakkar MM, McCarley RW. Adenosine and sleep-wake regulation. *Prog Neurobiol.* 2004; 73:379–396. [PubMed: 15313333]
3. Brown RE, Basheer R, McKenna JT, Strecker RE, McCarley RW. Control of Sleep and Wakefulness. *Physiol Rev.* 2012; 92:1087–1187. [PubMed: 22811426]
- 4•• Huang Z-L, Qu W-M, Eguchi N, Chen J-F, Schwarzschild MA, Fredholm BB, Urade Y, Hayaishi O. Adenosine A_{2A}; but not A₁; receptors mediate the arousal effect of caffeine. *Nat Neurosci.* 2005; 8:858–859. Caffeine increases wakefulness in wild-type and A₁ receptor KO mice; but not in A_{2A} receptor KO mice. Thus; the arousal effect of caffeine depends on adenosine A_{2A} receptors. [PubMed: 15965471]

- 5••. Lazarus M, Shen H-Y, Cherasse Y, Qu W-M, Huang Z-L, Bass CE, Winsky-Sommerer R, Semba K, Fredholm BB, Boison D, et al. Arousal Effect of Caffeine Depends on Adenosine A_{2A} Receptors in the Shell of the Nucleus Accumbens. *J Neurosci*. 2011; 31:10067–10075. A study that demonstrated that the arousal effect of caffeine is mediated by adenosine A_{2A} receptors on neurons in the shell of the nucleus accumbens. This study used powerful tools for site-specific gene manipulations; including A_{2A} receptor knockout mice based on the Cre/lox technology and focal A_{2A} receptor knockdown in rats through local infection with adeno-associated virus carrying short-hairpin RNA against A_{2A} receptors mRNA. [PubMed: 21734299]
6. Crittenden JR, Graybiel AM. Basal ganglia disorders associated with imbalances in the striatal striosome and matrix compartments. *Front Neuroanat*. 2011;10.3389/fnana.2011.00059
- 7•. Qiu M-H, Vetrivelan R, Fuller PM, Lu J. Basal ganglia control of sleep–wake behavior and cortical activation. *Eur J Neurosci*. 2010; 31:499–507. A neurotoxic lesion study documents that the dorsal striatum enhances wakefulness; that the nucleus accumbens promotes sleep; and that lesioning of the external globus pallidus leads to a substantial increase in wakefulness. [PubMed: 20105243]
8. Qiu M-H, Liu W, Qu W-M, Urade Y, Lu J, Huang Z-L. The Role of Nucleus Accumbens Core/Shell in Sleep-Wake Regulation and their Involvement in Modafinil-Induced Arousal. *PLoS ONE*. 2012; 7:e45471. [PubMed: 23029032]
9. Gerashchenko D, Blanco-Centurion CA, Miller JD, Shiromani PJ. Insomnia following hypocretin2-saporin lesions of the substantia nigra. *Neuroscience*. 2006; 137:29–36. [PubMed: 16289583]
10. Vetrivelan R, Qiu M-H, Chang C, Lu J. Role of basal ganglia in sleep-wake regulation: neural circuitry and clinical significance. *Front Neuroanat*. 2010; 410.3389/fnana.2010.00145
11. Ikemoto S. Dopamine reward circuitry. Two projection systems from the ventral midbrain to the nucleus accumbens-olfactory tubercle complex. *Brain Res Rev*. 2007; 56:27–78. [PubMed: 17574681]
12. Sesack SR, Grace AA. Cortico-Basal Ganglia Reward Network: Microcircuitry. *Neuropsychopharmacology*. 2009; 35:27–47. [PubMed: 19675534]
13. Léna I, Parrot S, Deschaux O, Muffat-Joly S, Sauvinet V, Renaud B, Suaud-Chagny MF, Gottesmann C. Variations in extracellular levels of dopamine; noradrenaline; glutamate; and aspartate across the sleep–wake cycle in the medial prefrontal cortex and nucleus accumbens of freely moving rats. *J Neurosci Res*. 2005; 81:891–899. [PubMed: 16041801]
14. Qu W-M, Xu X-H, Yan M-M, Wang Y-Q, Urade Y, Huang Z-L. Essential Role of Dopamine D₂ Receptor in the Maintenance of Wakefulness; But Not in Homeostatic Regulation of Sleep; in Mice. *J Neurosci*. 2010; 30:4382–4389. [PubMed: 20335474]
15. Barik S, de Beaurepaire R. Dopamine D₃ modulation of locomotor activity and sleep in the nucleus accumbens and in lobules 9 and 10 of the cerebellum in the rat. *Prog Neuropsychopharmacol Biol Psychiatry*. 2005; 29:718–726. [PubMed: 15913875]
16. Volkow ND, Tomasi D, Wang G-J, Telang F, Fowler JS, Logan J, Benveniste H, Kim R, Thanos PK, Ferré S. Evidence That Sleep Deprivation Downregulates Dopamine D₂R in Ventral Striatum in the Human Brain. *J Neurosci*. 2012; 32:6711–6717. [PubMed: 22573693]
17. Tan EK. Piribedil-induced sleep attacks in Parkinson's disease. *Fundam Clin Pharm*. 2003; 17:117–119.
18. Lipford MC, Silber MH. Long-term use of pramipexole in the management of restless legs syndrome. *Sleep Med*. 2012; 13:1280–1285. [PubMed: 23036265]
19. Monti J, Hawkins M, Jantos H, D'Angelo L, Fernández M. Biphasic effects of dopamine D-2 receptor agonists on sleep and wakefulness in the rat. *Psychopharmacology*. 1988; 95:395–400. [PubMed: 3137628]
20. Sebban C, Zhang XQ, Tesolin-Decros B, Millan MJ, Spedding M. Changes in EEG spectral power in the prefrontal cortex of conscious rats elicited by drugs interacting with dopaminergic and noradrenergic transmission. *Br J Pharmacol*. 1999; 128:1045–1054. [PubMed: 10556942]
21. Murillo-Rodriguez E, Haro R, Palomero-Rivero M, Millan-Aldaco D, Drucker-Colin R. Modafinil enhances extracellular levels of dopamine in the nucleus accumbens and increases wakefulness in rats. *Behav Brain Res*. 2007; 176:353–357. [PubMed: 17098298]

22. Wisor JP, Nishino S, Sora I, Uhl GH, Mignot E, Edgar DM. Dopaminergic Role in Stimulant-Induced Wakefulness. *J Neurosci*. 2001; 21:1787–1794. [PubMed: 11222668]
23. Qu WM, Huang ZL, Xu XH, Matsumoto N, Urade Y. Dopaminergic D₁ and D₂ receptors are essential for the arousal effect of modafinil. *J Neurosci*. 2008; 28:8462–8469. This study investigated the effects of administering dopamine D₁ receptor antagonists to dopamine D₂ receptor knockout mice and found that the arousal effect of modafinil; a wake-promoting compound; is mediated by dopamine D₁ receptors and dopamine D₂ receptors; with dopamine D₂ receptors being of primary importance. [PubMed: 18716204]
24. Scammell TE, Gerashchenko DY, Mochizuki T, McCarthy MT, Estabrooke IV, Sears CA, Saper CB, Urade Y, Hayaishi O. An adenosine A_{2A} agonist increases sleep and induces Fos in ventrolateral preoptic neurons. *Neuroscience*. 2001; 107:653–663. [PubMed: 11720788]
25. Satoh S, Matsumura H, Koike N, Tokunaga Y, Maeda T, Hayaishi O. Region-dependent difference in the sleep-promoting potency of an adenosine A_{2A} receptor agonist. *Eur J Neurosci*. 1999; 11:1587–1597. [PubMed: 10215911]
26. Huang Z-L, Qu W-M, Eguchi N, Chen J-F, Schwarzschild MA, Fredholm BB, Urade Y, Hayaishi O. Adenosine A_{2A}; but not A₁; receptors mediate the arousal effect of caffeine. *Nat Neurosci*. 2005; 8:858–859. [PubMed: 15965471]
27. Durieux PF, Bearzatto B, Guiducci S, Buch T, Waisman A, Zoli M, Schiffmann SN, de Kerchove d'Exaerde A. D₂R striatopallidal neurons inhibit both locomotor and drug reward processes. *Nat Neurosci*. 2009; 12:393–395. [PubMed: 19270687]
28. Jones BE. Activity; modulation and role of basal forebrain cholinergic neurons innervating the cerebral cortex. *Prog Brain Res*. 2004; 145:157–169. [PubMed: 14650914]
29. Saper CB, Fuller PM, Pedersen NP, Lu J, Scammell TE. Sleep State Switching. *Neuron*. 2010; 68:1023–1042. A review that summarizes recent advances in our understanding of the brain circuitry that regulates sleep and wakefulness. It also discusses the mutual inhibition between the arousal- and sleep-producing circuitry that results in the switching from one state to the other and how sleep is regulated by homeostatic; circadian; and allostatic factors. [PubMed: 21172606]
30. Saper CB, Scammell TE, Lu J. Hypothalamic regulation of sleep and circadian rhythms. *Nature*. 2005; 437:1257–1263. [PubMed: 16251950]
31. Sherin JE, Shiromani PJ, McCarley RW, Saper CB. Activation of Ventrolateral Preoptic Neurons During Sleep. *Science*. 1996; 271:216–219. [PubMed: 8539624]
32. Hara J, Beuckmann CT, Nambu T, Willie JT, Chemelli RM, Sinton CM, Sugiyama F, Yagami K-i, Goto K, Yanagisawa M, et al. Genetic Ablation of Orexin Neurons in Mice Results in Narcolepsy; Hypophagia; and Obesity. *Neuron*. 2001; 30:345–354. [PubMed: 11394998]
33. Chuah YML, Venkatraman V, Dinges DF, Chee MWL. The Neural Basis of Interindividual Variability in Inhibitory Efficiency after Sleep Deprivation. *J Neurosci*. 26:7156–7162. [PubMed: 16822972]
34. Muzur A, Pace-Schott EF, Hobson JA. The prefrontal cortex in sleep. *Trends Cogn Sci*. 2002; 6:475–481. [PubMed: 12457899]
35. Chee MWL, Choo WC. Functional Imaging of Working Memory after 24 Hr of Total Sleep Deprivation. *J Neurosci*. 2004; 24:4560–4567. [PubMed: 15140927]
36. Koenigs M, Holliday J, Solomon J, Grafman J. Left Dorsomedial Frontal Brain Damage Is Associated with Insomnia. *J Neurosci*. 2010; 30:16041–16043. [PubMed: 21106842]
37. Hur EE, Zaborszky L. Vglut2 afferents to the medial prefrontal and primary somatosensory cortices: a combined retrograde tracing in situ hybridization study. *J Comp Neurol*. 2005; 483:351–373. [PubMed: 15682395]
38. Yoshida K, McCormack S, España RA, Crocker A, Scammell TE. Afferents to the orexin neurons of the rat brain. *J Comp Neurol*. 2006; 494:845–861. [PubMed: 16374809]
39. Sano H, Yokoi M. Striatal medium spiny neurons terminate in a distinct region in the lateral hypothalamic area and do not directly innervate orexin/hypocretin- or melanin-concentrating hormone-containing neurons. *J Neurosci*. 2007; 27:6948–6955. [PubMed: 17596443]
40. Usuda I, Tanaka K, Chiba T. Efferent projections of the nucleus accumbens in the rat with special reference to subdivision of the nucleus: biotinylated dextran amine study. *Brain Res*. 1998; 797:73–93. [PubMed: 9630528]

41. Li C-S, Chung S, Lu D-P, CHO YK. Descending projections from the nucleus accumbens shell suppress activity of taste-responsive neurons in the hamster parabrachial nuclei. *J Neurophysiol.* 2012; 108:51288–51298.
42. Heimer L, Zahm DS, Churchill L, Kalivas PW, Wohltmann C. Specificity in the projection patterns of accumbal core and shell in the rat. *Neuroscience.* 1991; 41:89–125. [PubMed: 2057066]
43. Deurveilher S, Lo H, Murphy JA, Burns J, Semba K. Differential c-Fos immunoreactivity in arousal-promoting cell groups following systemic administration of caffeine in rats. *J Comp Neurol.* 2006; 498:667–689. [PubMed: 16917819]
44. Borbely AA. A two process model of sleep regulation. *Hum Neurobiol.* 1982; 1:195–204. [PubMed: 7185792]
45. Huang Z-L, Urade Y, Hayaishi O. Prostaglandins and adenosine in the regulation of sleep and wakefulness. *Curr Opin Pharmacol.* 2007; 7:33–38. [PubMed: 17129762]
46. Porkka-Heiskanen T, Kalinchuk AV. Adenosine; energy metabolism and sleep homeostasis. *Sleep Med Rev.* 2011; 15:123–135. [PubMed: 20970361]
47. Urade Y.; Lazarus, M. Prostaglandin D₂ in the regulation of sleep. In: Shaw, PJ.; Tafti, M.; Thorpy, MJ., editors. *The Genetic Basis of Sleep & Sleep Disorders.* Cambridge University Press; 2013. in press
48. Urade Y, Hayaishi O. Prostaglandin D₂ and sleep/wake regulation. *Sleep Med Rev.* 2011; 15:411–418. [PubMed: 22024172]
49. Krueger JM, Clinton JM, Winters BD, Zielinski MR, Taishi P, Jewett KA, Davis CJ. Involvement of cytokines in slow wave sleep. *Prog Brain Res.* 2011; 193:39–47. [PubMed: 21854954]
50. Garcia-Garcia F, Acosta-Pena E, Venebra-Munoz A, Murillo-Rodriguez E. Sleep-inducing factors. *CNS Neurol Disord Drug Targets.* 2009; 8:235–244. [PubMed: 19689305]
51. Huitron-Resendiz S, Kristensen MP, Sánchez-Alavez M, Clark SD, Grupke SL, Tyler C, Suzuki C, Nothacker H-P, Civelli O, Criado JR, et al. Urotensin II Modulates Rapid Eye Movement Sleep through Activation of Brainstem Cholinergic Neurons. *J Neurosci.* 2005; 25:5465–5474. [PubMed: 15944374]
52. Achermann P, Borbely AA. Mathematical models of sleep regulation. *Front Biosci.* 2003; 8:s683–693. [PubMed: 12700054]
53. Cano G, Mochizuki T, Saper CB. Neural Circuitry of Stress-Induced Insomnia in Rats. *J Neurosci.* 2008; 28:10167–10184. [PubMed: 18829974]
54. Yamanaka A, Beuckmann CT, Willie JT, Hara J, Tsujino N, Mieda M, Tominaga M, Yagami K-i, Sugiyama F, Goto K, et al. Hypothalamic Orexin Neurons Regulate Arousal According to Energy Balance in Mice. *Neuron.* 2003; 38:701–713. [PubMed: 12797956]
55. Lazarus M, Huang ZL, Lu J, Urade Y, Chen JF. How do the basal ganglia regulate sleep-wake behavior? *Trends Neurosci.* 2012; 35:723–732. [PubMed: 22858523]
56. Lazarus M, Yoshida K, Coppari R, Bass C, Mochizuki T, Lowell B, Saper C. EP₃ prostaglandin receptors in the median preoptic nucleus are critical for fever responses. *Nat Neurosci.* 2007; 10:1131–1133. [PubMed: 17676060]
57. Rogan SC, Roth BL. Remote Control of Neuronal Signaling. *Pharmacol Rev.* 2011; 63:291–315. [PubMed: 21415127]
58. Lerchner W, Xiao C, Nashmi R, Slimko EM, van Trigt L, Lester HA, Anderson David A J. Reversible Silencing of Neuronal Excitability in Behaving Mice by a Genetically Targeted; Ivermectin-Gated Cl⁻ Channel. *Neuron.* 2007; 54:35–49. [PubMed: 17408576]
59. Adamantidis AR, Zhang F, Aravanis AM, Deisseroth K, de Lecea L. Neural substrates of awakening probed with optogenetic control of hypocretin neurons. *Nature.* 2007; 450:420–424. [PubMed: 17943086]

Highlights

1. The dorsal striatum enhances wakefulness and the nucleus accumbens promotes sleep.
2. The external globus pallidus regulates sleep–wake behavior through cortical activation.
3. Adenosine A₂A receptors in the nucleus accumbens shell are critical for caffeine arousal.
4. The nucleus accumbens has an intrinsic role in the sleep/wake regulatory network.
5. The motivational state is a fundamental regulator of sleep and wakefulness.

Figure 1. A model in which the nucleus accumbens (NAc) has an intrinsic role in the sleep/wake regulatory network

Inhibitory output projections of the NAc modulate activity of neuronal populations in the ventral pallidum (VP), the lateral hypothalamus (LHA), the parabrachial nucleus (PB), and the ventral tegmental area (VTA), which may be a major source of arousal. The NAc can modulate the medial prefrontal cortex (mPFC) via a pathway through the VP and thalamus; and, in turn, the mPFC projects to arousal-promoting neurons in the hypothalamic tuberomammillary nucleus (TMN), the LHA, and the locus coeruleus (LC). Subserving the NAc, the orexinergic and glutamatergic neurons in the LHA send major projections to the basal forebrain (BF) and cerebral cortex. The LHA is also reciprocally connected to the flip-flop switch between non-rapid eye movement sleep and wakefulness (shown in gray), including the ventrolateral preoptic area (VLPO), the TMN, and the LC; and the PB, an important component of the ascending arousal system, is known to be strongly connected to the BF and LHA. Glutamatergic neurons at the border between the VTA and supramammillary nucleus (SUM) may also relay the waking stimulus from the NAc to the cerebral cortex. Adenosine acting on excitatory A_{2A}Rs, opposite to the inhibitory dopamine/D₂R system, can modulate the activity of GABAergic output neurons in the NAc to inhibit arousal and promote sleep. Black arrows, excitation; red round-headed lines, inhibition; lines with two round-headed ends represent reciprocal inhibitory connections; circled areas with green background, neuronal populations with cortical projections (light green arrows).