Role of the basal ganglia in the control of sleep and wakefulness
Michael Lazarus¹,², Jiang-Fan Chen³, Yoshihiro Urade¹,² and Zhi-Li Huang²,⁴

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.

Addresses
¹ International Institute for Integrative Sleep Medicine (WPI-III5), University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8575, Japan
² Department of Molecular Behavioral Biology, Osaka Bioscience Institute, 6-2-4 Furuedai, Suita, Osaka 565-0874, Japan
³ Department of Neurology, Boston University School of Medicine, 715 Albany Street, Boston, MA 02118, USA
⁴ Department of Pharmacology, Fudan University Shanghai Medical College, 138 Yixueyuan Road, Shanghai 200032, China

Corresponding authors: Lazarus, Michael (mlazarus@obi.or.jp) and Huang, Zhi-Li (huangzl@fudan.edu.cn)

Evidence for roles of the BG in the sleep–wake cycle
The BG consist of four major nuclei, that is, 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 (GPe) leading to a dramatic increase (∼45%) in total wakefulness and pronounced fragmentation of NREM sleep and wakefulness [77]. 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 [77,9]. Interestingly, a generalized slowing of the cortical electroencephalogram, with less theta and more delta power during wakefulness and rapid eye movement (REM) and NREM sleep is observed in rats with lesions in the CPu, NAc and GPe. It has been suggested that a dorsorostral–pallidio–cortical loop may be the mechanism by which the dorsal striatum regulates sleep–wake behavior and cortical activation [77,10]. In this model, gamma amino butyric acid (GABA)ergic neurons in the CPu projects to the GPe, which in turn projects directly to the cerebral cortex. While GABAergic neurons in the adjacent basal forebrain (BF) 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 [77].

## 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 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 quinolinorane, 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 downregulation 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, 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 A2AR 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 A2ARs 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 A2AR agonist into the shell portion of the NAc induces NREM and REM sleep [25]. These observations indicate that A2ARs 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 A2ARs, in which the receptor is deleted from the entire animal have found, however, that the A2AR, but not the A1R, mediates the arousal effect of caffeine [4**]. Moreover, using powerful tools for site-specific gene manipulations, including A2AR knockout mice based on the Cre/lox technology and focal A2AR knockout in rats through local infection with adeno-associated virus carrying short-hairpin RNA specific for the mRNA of A2ARs [5**], we showed that the deletion of the A2ARs selectively in the NAc shell results in abrogation of caffeine-induced wakefulness. For caffeine to be effective as an antagonist, excitatory A2ARs 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 A2ARs are highly expressed throughout the striatum. Thus, activation of the GABAergic output neurons on the indirect pathway by A2ARs 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 A2aR promoter [26], 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-J Zhang et al., unpublished data). By contrast, caffeine can override the ‘adenosine brake’ to promote wakefulness.

A model of NAc involvement in sleep–wake regulation
Several systems of sleep-active 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 BF [27]. 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 pedunculopontine and laterodorsal tegmental nuclei [28,29,30]. 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, BF, 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 [31].

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 neuropeptide populations in the ventral pallidum (VP), the LHA, the parabrachial nucleus (PB), and the ventral tegmental area (VTA; Figure 1). The circuit

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 more or less major sources 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 nonrapid 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 subparabrachial nucleus (SUM) may also relay the waking stimulus from the NAc to the cerebral cortex. Adenosine acting on excitatory A1 and A2A receptors (A1R, A2AR), opposite to the inhibitory dopamine D2R receptor (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).
originating from the VP includes the thalamus and mPFC, a key executive interface between cognition and emotion and uniquely sensitive to sleep and sleep need [32–35], 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 not only send major projections to the BF and cerebral cortex, but are also reciprocally connected to the BF and NREM/wake flip-flop switch, including the VLPO, the TMN, and the LC [28*, 36–38]. The NAc shell, but not the NAc core, sends projections to the PB [39, 40], 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 [36, 41], which are likely the tail end of a larger group of neurons of the supramammillary nucleus (SUM). Interestingly, caffeine induces c-fos expression in nondopaminergic neurons of the medial VTA [42], 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 [43]. Thereby, endogenous hypnogenic substances, such as adenosine [1, 44, 45], prostaglandin D2 [46, 47], cytokines [48], anandamide [49], and peptides including urotensin II [50], 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 [28*, 51]. 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 [52, 53]. 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 [54]. 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*, 55] to the optical or chemical modulation of neuronal activity through genetically engineered receptor-channel systems, such as optogenetics, DREADD or ivermectin-gated chloride channels [56–58].

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest


Caffeine increases wakefulness in wild-type and A1 receptor knockout mice, but not in A2A receptor knockout mice. Thus, the arousal effect of caffeine depends on adenosine A2A receptors.


A study that demonstrated that the arousal effect of caffeine is mediated by adenosine A2A receptors on neurons in the shell of the nucleus accumbens. This study used powerful tools for site-specific gene manipulations, including A2A receptor knockout mice based on the Cre/lox technology and focal A2A receptor knockdown in rats through local injection with adeno-associated virus carrying short-hairpin RNA against A2A receptors mRNA.


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