Adenosine and Sleep

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The authors dedicate this chapter to the late Prof. Osamu Hayaishi, whose demise saddened everyone who knew him as a great scientist and extraordinary individual.

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H.-P. Landolt, D.-J. Dijk (eds.), *Sleep-Wake Neurobiology and Pharmacology*,
Handbook of Experimental Pharmacology 253, DOI 10.1007/164_2017_36

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Abstract

The classic endogenous somnogen adenosine promotes sleep via A_1 and A_{2A} receptors. In this chapter, we present an overview of the current knowledge regarding the regulation of adenosine levels, adenosine receptors, and available pharmacologic and genetic tools to manipulate the adenosine system. This is followed by a summary of current knowledge of the role of adenosine and its receptors in the regulation of sleep and wakefulness. Despite strong data implicating numerous brain areas, including the basal forebrain, the tuberomammillary nucleus, the lateral hypothalamus, and the nucleus accumbens, in the adenosinergic control of sleep, the complete neural circuitry in the brain involved in the sleep-promoting effects of adenosine remains unclear. Moreover, the popular demand for natural sleep aids has led to a search for natural compounds that can promote sleep via adenosine receptor activation. Finally, we discuss the effects of caffeine in man and the possible use of more selective adenosine receptor drugs for the treatment of sleep disorders.

Keywords

Adeno-associated virus • Astrocytes • CGS 21680 • DREADD • Istradefylline • Modafinil • Non-rapid eye movement sleep • Optogenetics • Prostaglandin D_2 • Slow-wave sleep

1 The Concept of a Sleep Substance

The neural and cellular basis of the need for sleep or, alternatively, the "sleep drive" remains unresolved, but can be conceptualized as a homeostatic pressure that builds up during the waking period and dissipates during sleep. One potential mechanism is that the gradual accumulation of one or more endogenous somnogenic factors during wake is the underpinning of sleep homeostatic pressure. Rosenbaum presented the first formal hypothesis that sleep is regulated by humoral factors in 1892 (Rosenbaum 1892), and Ishimori (Ishimori 1909; Kubota 1989) and Pieron (Legendre and Pieron 1913) independently demonstrated the existence of sleep-promoting chemicals a few years later. Both Ishimori and Pieron proposed, and indeed established, the presence of hypnogenic substances or "hypnotoxins" in the cerebrospinal fluid of sleep-deprived dogs (Inoué et al. 1995). Over the past century, several additional putative hypnogenic substances implicated in the sleep homeostatic process have been identified [for review, see Urade and Hayaishi (2011)], including prostaglandin D_2 (Qu et al. 2006; Ueno et al. 1982) [for review,

see Urade and Lazarus (2013)], cytokines (Krueger et al. 1984) [for review, see Krueger et al. (2011)], adenosine (Porkka-Heiskanen et al. 1997), anandamide (Garcia-Garcia et al. 2009), and the urotensin II peptide (Huitron-Resendiz et al. 2005). Extensive evidence suggests that sleep regulation is interrelated with components of the host defense (immune) system, such as pro-inflammatory cytokines (Krueger and Majde 2003; Krueger et al. 2001; Mullington et al. 2000, 2001) and prostaglandins (Lazarus et al. 2007; Oishi et al. 2015; Urade and Lazarus 2013; Ushikubi et al. 1998). Several excellent reviews of the different theories of how neural switching occurs between sleep and wakefulness are available [for example, Fuller et al. (2015); Saper et al. (2005, 2010)]. In the present chapter, we focus on the possible role of adenosine as a sleep substance.

2 Adenosine in Physiology and Pathophysiology

Adenosine is a neuromodulator and not a neurotransmitter. Although it is released from nerve endings, its formation can be increased by various processes in all types of cells, and in all parts of these cells. Furthermore, the basal level of adenosine depends only on fundamental cell biology and is independent of nerve activity. Adenosine acts on four evolutionarily well-conserved receptors that are present on most if not all cells. Adenosine fulfills physiologic and pathophysiologic functions (Fredholm 2014).

2.1 Regulation of Adenosine Levels

Adenosine is formed by hydrolysis of adenosine monophosphate (AMP) or *S*-adenosylhomocysteine (Fredholm 2007; Schrader 1983). Adenosine is formed from *S*-adenosylhomocysteine by the enzyme *S*-adenosylhomocysteine hydrolase, which can also act to trap adenosine in the presence of excess L-homocysteine. This takes place intracellularly and the fact that the enzyme is bidirectional ensures the constant presence of a finite concentration of adenosine in the cell. The formation of adenosine from 5′-AMP can occur both intracellularly and extracellularly, mediated by different enzymes. The intracellular 5′nucleotidase generates adenosine, which can be used to generate AMP by adenosine kinase. This bidirectional reaction ensures the constant presence of a finite intracellular concentration of adenosine in the range of 10 to a few hundred nanomolar (nM) under physiologic conditions (Ballarin et al. 1991).

The fact that the intracellular concentration of adenosine is not zero ensures that there is also a not insubstantial extracellular concentration of adenosine, because all cells appear to possess one or more equilibrative purine transporters (Geiger and Fyda 1991). Extracellular adenosine is increased when an adenine nucleotide is released. Extracellular adenosine is formed by the conversion of ATP to adenosine by a series of ecto enzymes on the cell surface. Extracellular ATP can be released from various cell types by multiple mechanisms, including co-release from storage

vesicles together with other hormones (neurotransmitter), a "kiss-and-run" mechanism (MacDonald et al. 2006), lysosome exocytosis (Zhang et al. 2007), controlled release through pannexin hemichannels (Chekeni et al. 2010; Elliott et al. 2009), release from inflammatory cells or vascular endothelia through connexin hemichannels and channels such as P2X7 receptors (Chen et al. 2006; Faigle et al. 2008; Linden 2006), and uncontrolled leakage from necrotic cells (Eltzschig 2009). Extracellular ATP and adenosine diphosphate (ADP) are broken down to AMP via many different ecto enzymes, especially CD39 (Yegutkin 2008). In the brain, the AMP formed is then broken down to adenosine only via ecto-5′-nucleotidase, CD73 (Resta et al. 1998). Importantly, the levels of extracellular adenine nucleotides are particularly high when cell membranes are broken, which allows the high intracellular content to escape. Thus, trauma in any form is associated with elevated levels of adenine nucleotides, as is blood sampling because most methods for this lead to a breakdown of blood platelets. AMP is also released directly from apoptotic cells (Yamaguchi et al. 2014).

ADP is released by platelets (Hollopeter et al. 2001), and ATP can be released by many different cells, including endothelial cells (Bodin and Burnstock 1998), astrocytes (Guthrie et al. 1999), and neurons (Fields and Stevens 2000), via many different mechanisms (Burnstock and Verkhratsky 2012). In the brain, extracellular adenosine might originate from neurons (both nerve terminals and postsynaptic components) and from surrounding non-neuronal cells such as glial cells (Halassa et al. 2007, 2009). For example, using inducible, astrocyte-specific transgenic dominant negative SNARE mouse approaches, Haydon's group suggested that astrocytes are an important source of extracellular adenosine via gliotransmission (Halassa et al. 2009). ATP released from neurons (both nerve terminals and postsynaptic components) also contributes to extracellular adenosine production via the CD73 enzyme, the only enzyme that degrades AMP to adenosine in the brain (Lovatt et al. 2012; Wall and Dale 2013). In striatal neurons, extracellular adenosine formed via CD73 may preferentially act at the A_{2A} receptor as extracellular CD73 is selectively co-expressed (Ena et al. 2013) and is physically associated with A_{2A} receptors in striatopallidal neurons (Augusto et al. 2013). Under pathologic conditions, such as cortical seizures, adenosine-mediated synaptic depression is independent of CD73 activity and not a consequence of astrocytic (or neuronal) ATP release, but is due to the activation of postsynaptic neurons, which leads to the release of adenosine, thus constituting an autonomic feedback mechanism that suppresses excitatory transmission during prolonged activity (Lovatt et al. 2012). It may also be that under physiologic conditions, such as those involved in sleep and wakefulness, adenosine is generated in a similar CD73-independent manner.

Adenosine levels are decreased by the enzyme adenosine deaminase (ADA; this enzyme is particularly important when adenosine levels are high) and by uptake into cells other than those that produced it. In these cells, the adenosine taken up is rapidly phosphorylated to AMP by adenosine kinase. The formation and removal of extracellular adenosine determine its levels. Under basal conditions, these levels are low, usually in the order of 30–300 nM (Ballarin et al. 1991). Under more extreme conditions, such as mild hypoxia or strenuous exercise, the levels can approach

1 μM or more, and in severely traumatic situations, including local ischemia, can reach up to several tens of μM (Fredholm 2007).

To link adenosine levels to sleep, one must be able to measure adenosine levels in the brain but adenosine levels rapidly change in both the blood and tissue upon sampling and tissue samples must be frozen within a second or less to preserve in vivo levels. Such rapid inactivation is difficult to achieve, even with focused microwave techniques, and hence measuring regional adenosine brain levels by sampling tissue is highly problematic. Microdialysis could be a feasible method, but as already demonstrated in the first reports using this technique, it takes a long time to overcome the consequences of the initial traumatization required to insert the microdialysis probes (Ballarin et al. 1991; Benveniste et al. 1989; Zetterstrom et al. 1982). Furthermore, if the probe is allowed to remain in the tissue too long it will be covered with glial cells that hamper the exchange of purines (Benveniste et al. 1989). Electrochemical methods were recently used to measure local adenosine levels (Dale and Frenguelli 2012), but this method is also associated with caveats. Thus, reported adenosine levels in sleep and wakefulness should not be uncritically accepted.

2.2 Adenosine Receptors

Extracellular adenosine reacts with one of the four adenosine receptors, A_1, A_{2A}, A_{2B}, and A_3 (Fredholm et al. 2011). If these receptors are expressed at the same level (~200,000 receptors/cell), adenosine appears to be equally potent at A_1, A_{2A}, and A_3 receptors (Fig. 1), and the levels of adenosine occurring under basal physiologic conditions are sufficient to activate these receptors. The data suggest that higher concentrations of adenosine are needed to activate A_{2B} receptors. Nevertheless, it is important to remember that the potency of an agonist such as adenosine on its receptor depends on the number of receptors available, i.e., in the presence of only a few receptors higher adenosine concentrations are required to see an effect. Local expression of the A_1 and A_{2A} receptors appears to be higher than that of the other two receptors (Fredholm et al. 2005a). Thus, these two receptor types may be primarily involved in sleep regulation.

First, we briefly discuss how the role(s) of adenosine in physiology and pathophysiology can be determined.

3 How Do We Learn About the Roles of Adenosine?

3.1 Receptor Antagonists Including Caffeine

To assess the in vivo actions of adenosine receptors, selective pharmacologic tools are crucial. Over the last 20 years, medicinal chemistry has generated agonists and antagonists with high affinity (Kd values in the low nM range) and selectivity (>100–200-fold over other adenosine receptor subtypes) for the human variants of

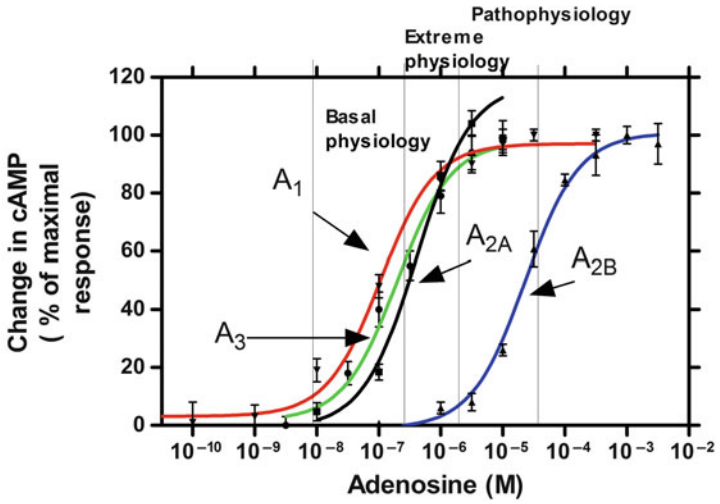

Fig. 1 Schematic illustration of the ability of adenosine to activate the four adenosine receptors. Note that A_1, A_{2A}, and A_3 receptors are activated by basal levels of adenosine at sites where the receptor number is high. In contrast, A_{2B} receptors are mostly activated in pathologic conditions

each of the four receptors (Fredholm et al. 2011). Most of the known adenosine receptor agonists are derivatives of purine nucleosides, either adenosine or xanthosine, while adenosine receptor antagonists have diverse structures (Müller and Jacobson 2011). Many A_{2A}-selective antagonists from different structural classes have been developed, including 8-(3-chlorostyryl)caffeine, MSX-2, and its water-soluble prodrugs MSX-3, ZM 241385, SCH-58261, and KW6002. In addition, radioactive, and more recently, fluorescent, ligands of adenosine receptors were also developed and introduced for drug screening and monitoring in vivo receptor occupancy in humans.

Caffeine, the most widely consumed arousal-promoting psychostimulant, is a classic nonselective adenosine receptor antagonist, although it is rather weakly potent at adenosine receptors ($K_i \approx 10$ μM). At doses commonly consumed by humans, caffeine produces its profound arousal effect by partial (estimated to be 25–50%) and nonselective (similar affinity for both A_1 and A_{2A} receptors) blockade of adenosine receptors (Fredholm et al. 1999). Caffeine is metabolized to paraxanthine and theophylline (Arnaud 2011). These metabolites are more potent than caffeine as inhibitors of A_1 and A_{2A} receptors. Therefore, elimination of caffeine does not predict the elimination of adenosine receptor blockade and hence the effects of caffeine administration.

Importantly, several A_{2A} receptor antagonists are in clinical trials for Parkinson's disease (PD), including istradefylline (KW6002), SYN-115, and preladenant (SCH-442416). Phase IIB and III clinical trials with A_{2A} receptor antagonists showed a very consistent and excellent safety profile in more than 3,000 patients with advanced PD (Hauser et al. 2011; Jenner et al. 2009). The safety profile of these

A_{2A} receptor antagonists is entirely consistent with the widespread use of the nonselective adenosine receptor antagonist caffeine in 70% of the human population. Importantly, this provides an opportunity to rapidly translate A_{2A} receptor antagonists to achieve pharmacologic control of the sleep–wake cycle.

3.2 Receptor Knockouts and Other Genetic Targeting Techniques

Over the past two decades, genetic knockout (KO) models for all four G-protein-coupled adenosine receptors were generated by targeted deletion of critical exons (Fredholm et al. 2005b; Wei et al. 2011). These adenosine receptor KO models have provided insights into the physiologic function of modulation of the sleep–wake cycle by overcoming the limitations of pharmacologic agents with partial specificity and by targeting the adenosine receptor in defined cellular populations. For example, the use of A_{2A} receptor KO models can overcome concerns about the partial specificity of A_{2A} receptor antagonists (particularly after focal injection at relatively high concentrations), and convincingly demonstrated that the sleep-promoting effect of A_{2A} receptor agonists and caffeine-induced arousal effect are mediated by A_{2A} receptors (not A_1 receptors). Global A_1 and A_{2A} receptor KO approaches, however, have intrinsic limitations of the confounding developmental effect and lack of cell-type specificity (Fredholm et al. 2005b). To overcome these limitations, conditional KO of some adenosine receptor genes in defined brain regions (e.g., forebrain versus striatum) and cell-type (e.g., neurons versus astrocytes) has been achieved using the Cre-*loxP* system [for review see Fuller et al. (2015); Wei et al. (2011)]. Brain-regional deletion of A_{2A} receptors has been achieved in the forebrain (i.e., striatum, cortex, hippocampus) (Bastia et al. 2005; Yu et al. 2008) and striatum (Shen et al. 2008). Local deletion of A_1 receptors in hippocampal CA1 or CA3 neurons and A_{2A} receptors in the nucleus accumbens (NAc) has also been achieved by local injection of adeno-associated virus (AAV) vectors containing the *cre* transgene into the brains of mice carrying *loxP*-flanked A_1 receptor (Scammell et al. 2003) or A_{2A} receptor (Lazarus et al. 2011) genes. The conditional KO strategy permits a temporal and regional specificity that has uncovered previously under-appreciated functions of adenosine receptors in the basal ganglia for controlling the sleep–wake cycle (see detailed discussion below). In addition, the development of AAV carrying short-hairpin RNA targeted to produce site-specific silencing of the A_{2A} receptor gene allowed for the clear demonstration in rats that the arousal effect of caffeine is mediated by A_{2A} receptors in the NAc shell (Lazarus et al. 2011). Lastly, the recent development of optogenetics based on specific local modulation of neuronal activity using genetically engineered optical switches (e.g., channelrhodopsin) (Boyden et al. 2005; Deisseroth 2014; Yizhar et al. 2011) or chemogenetics to study G-protein signaling in freely behaving animals by the directed molecular evolution of designer receptors exclusively activated by designer dugs (DREADD) (Farrell et al. 2013; Giguere et al. 2014) has refined our understanding of novel brain circuits underlying the sleep–wake

cycle (Fuller et al. 2015). Recently, a probe for selective optogenetic control of A_{2A} receptor signaling (optoA_{2A} receptor) was developed (Li et al. 2015).

4 Adenosine and Sleep

4.1 Adenosine Levels During Sleep and Wakefulness

Adenosine has long been known to represent a state of relative energy deficiency: ATP depletion and the elevation of extracellular adenosine levels are positively correlated (Kalinchuk et al. 2003) and positively associated with sleep (Porkka-Heiskanen et al. 1997). Adenosine levels in samples collected from several brain areas of cats during spontaneous sleep–wake cycles by in vivo microdialysis were higher during non-rapid eye movement (non-REM, NREM) sleep than wakefulness for all probed brain areas (Porkka-Heiskanen et al. 1997, 2000). Moreover, in vivo microdialysis experiments in the brain of cats also revealed that adenosine concentrations specifically increase twofold in the basal forebrain (BF) during a prolonged 6-hour period of wakefulness compared with that at the beginning of sleep deprivation (Porkka-Heiskanen et al. 1997, 2000).

Sixty years have passed since the discovery of the hypnotic effect of adenosine in the mammalian brain (Feldberg and Sherwood 1954); however, the brain cell types involved in the sleep-promoting effects of adenosine remain unclear. In principle, adenosine (and ATP, which is rapidly degraded to adenosine) can be released from neurons or glia cells. Genetically engineered mice that selectively express a dominant negative SNARE domain in astrocytes to nonspecifically block the release of ATP exhibit decreased concentrations of extracellular adenosine (Pascual et al. 2005). Although the amount of wakefulness, NREM, and REM sleep in these mice is indistinguishable from that in wild-type mice, these mice exhibit reduced slow-wave activity and recovery sleep after sleep deprivation (Halassa et al. 2009), suggesting that adenosine released from astrocytes is involved in the accumulation of sleep pressure. Direct proof is still lacking, however, and thus the exact sources of adenosine remain unknown.

The late Miodrag Radulovacki and colleagues extensively investigated the effects of adenosine on wakefulness. They used the ADA inhibitor deoxycoformycin to increase the levels of adenosine in the central nervous system of rats and found that REM and NREM sleep were increased (Radulovacki et al. 1983), further supporting a hypnotic role for adenosine.

Adenosine is reported to promote sleep by acting through A_1 or A_{2A} receptors, but the relative contribution of these receptors to sleep induction remains controversial (Basheer et al. 2004; Huang et al. 2007). Indirect evidence by comparison of the effects of caffeine, the A_1 receptor antagonist 8-cyclopentyltheophylline, and the nonselective A_1/A_{2A} receptor antagonist alloxazine on sleep in rats (Virus et al. 1990) might partially account for the prevailing opinion that the A_1 receptor is more important in sleep–wake regulation than the A_{2A} receptor. The aforementioned pharmacologic approach and related studies, however, have non-trivial limitations,

particularly with respect to data interpretation. For example, receptor antagonists are difficult to compare due to differences in solubility, blood–brain-barrier permeability, and neuropharmacodynamics, and most importantly, have "off-target" effects, especially at higher concentrations. Moreover, the diffuse expression of inhibitory A_1 receptors in the brain may have differential effects on sleep and wakefulness in a region-specific manner (Ochiishi et al. 1999a, b; Reppert et al. 1991; Rivkees et al. 1995). The advent of genetically engineered systems, including transgenic animals and recombinant viral vectors, and findings in humans have convincingly established over the last decade a pivotal role of A_{2A} receptors in the regulation of sleep and wakefulness (Holst and Landolt 2015; Lazarus et al. 2012, 2013).

4.2 Effects of A_1 Receptors

The A_1 receptor agonist N^6-cyclopentyladenosine produces dose-dependent increases in slow-wave activity in electroencephalography during NREM sleep when administered systemically or intracerebroventricularly in rats (Benington et al. 1995), but lateral ventricle infusions of N^6-cyclopentyladenosine in mice do not change the amounts of observed NREM and REM sleep (Urade et al. 2003), which may indicate opposing effects on sleep and wakefulness in different areas of the brain. For example, adenosine acting via A_1 receptors induces sleep by inhibiting arousal-related cell groups in the BF, such as the horizontal limb of the diagonal band of Broca and the substantia innominata (Fig. 2a) (Alam et al. 1999; Strecker et al. 2000). Moreover, adenosine may promote sleep by A_1 receptor-mediated inhibition of glutamatergic inputs to cortically projecting cholinergic and γ-aminobutyric acid (GABA) neurons of the BF (Yang et al. 2013). Adenosine could also promote sleep by suppressing hypocretin/orexin neurons in the lateral hypothalamus, because an A_1 receptor agonist produced NREM and REM sleep and the receptor's antagonist induced wakefulness (Fig. 2b) (Thakkar et al. 2008). ADA is predominantly localized in the tuberomammillary nucleus (TMN) of the brain and the TMN is enriched in histamine neurons containing A_1 receptors, thereby suggesting that the histaminergic arousal system is actively regulated by adenosine in the TMN. In fact, bilateral injections of the A_1 receptor agonist N^6-cyclopentyladenosine into the rat TMN significantly increase the amount of NREM sleep (Fig. 2c) (Oishi et al. 2008). Moreover, bilateral injections of adenosine or the ADA inhibitor coformycin into the rat TMN also increase NREM sleep, which is completely abolished by co-administration of the selective A_1 receptor antagonist 1,3-dimethyl-8-cyclopenthylxanthine. These results indicate that endogenous adenosine in the TMN suppresses the histaminergic system via A_1 receptors to promote NREM sleep. Interestingly, single-nucleotide polymorphism analyses have identified a human genetic ADA variant with low enzymatic activity that is linked to the enhancement of deep sleep and slow-wave activity during sleep (Bachmann et al. 2012; Mazzotti et al. 2012; Rétey et al. 2005). By contrast, activation of A_1 receptors in the lateral preoptic area of the hypothalamus by

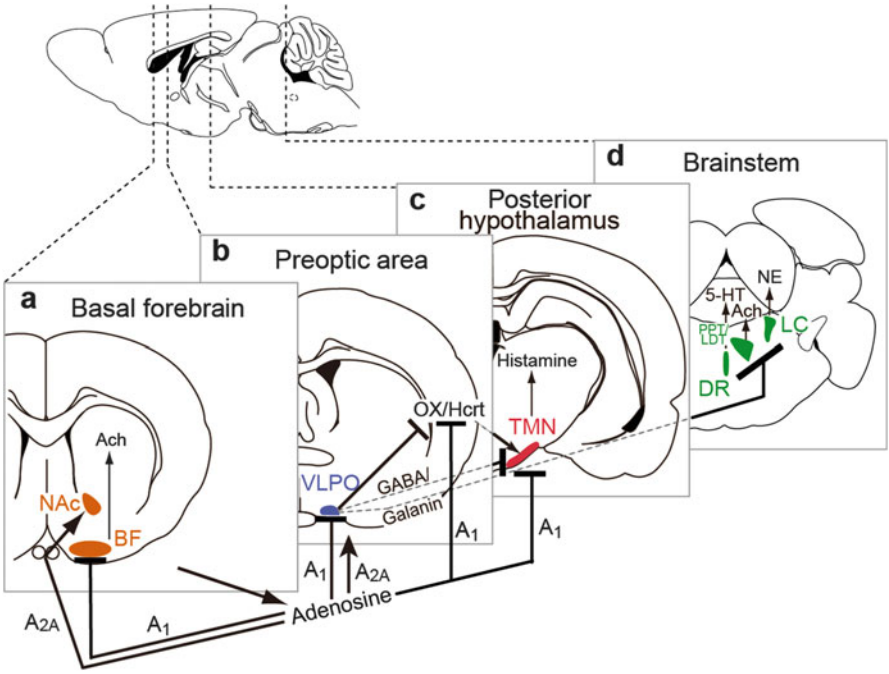

Fig. 2 Circuit basis of sleep–wake regulation. Model 1 (shown in panel **a**): adenosine inhibits the release of acetylcholine from the basal forebrain (BF) cholinergic neurons to produce slow-wave sleep. Model 2 (shown in panels **b**–**d**): a flip–flop switching mechanism involving mutually inhibitory interactions between sleep-promoting neurons in the ventrolateral preoptic area (VLPO) and wake-promoting neurons in the hypothalamus [i.e., histaminergic tuberomammillary nucleus (TMN)], and brainstem [i.e., noradrenergic locus coeruleus (LC), serotonergic dorsal raphe nucleus (DR), and cholinergic laterodorsal tegmental nucleus (LDT)]. The flip-flop switch between the VLPO and hypothalamus and brainstem is stabilized by orexin/hypocretin (OX/Hcrt) inputs from the lateral hypothalamus (LHA). Adenosine acts as an endogenous somnogen and promotes sleep via inhibitory A_1 receptors (A_1) in the basal forebrain, VLPO, LHA, and TMN and excitatory A_{2A} receptors (A_{2A}) in the nucleus accumbens (NAc) and VLPO (Huang et al. 2007, 2011; Lazarus et al. 2012, 2013). Other abbreviations: *Ach* acetylcholine, *5-HT* serotonin, *NE* norepinephrine

local infusion of an A_1 receptor agonist promotes wakefulness (Methippara et al. 2005).

4.3 Effects of A_{2A} Receptors

CGS 21680, a highly selective A_{2A} receptor agonist, produces profound increases in NREM and REM sleep after infusion into the subarachnoid space underlying the ventral surface region of the rostral BF in rats or into the lateral ventricle of mice (Satoh et al. 1996; Urade et al. 2003). In vivo microdialysis experiments demonstrated that infusions of CGS 21680 into the BF inhibit the release of

histamine in both the frontal cortex and medial preoptic area in a dose-dependent manner, and increase the release of GABA in the TMN of the hypothalamus, but not in the frontal cortex (Hong et al. 2005). CGS 21680-induced blocking of histamine release is antagonized when the TMN is perfused with the GABA antagonist picrotoxin, suggesting that the A_{2A} receptor agonist induces sleep by inhibiting the histaminergic system through an increase in GABA release in the TMN. It was previously proposed that sleep is promoted by activating sleep neurons in the ventrolateral preoptic area (VLPO) and reciprocal suppression of histaminergic wake neurons in the TMN through GABAergic and galaninergic inhibitory projections (Sherin et al. 1996, 1998). The existence of two distinct types of VLPO neurons in terms of their responses to serotonin and adenosine was demonstrated by intracellular recordings of VLPO neurons in rat brain slices (Fig. 2b). VLPO neurons are uniformly inhibited by the arousing neurotransmitters noradrenaline and acetylcholine, and primarily inhibited by an A_1 receptor agonist. Serotonin inhibits type-1 neurons but excites type-2 neurons, whereas an A_{2A} receptor agonist postsynaptically excites type-2, but not type-1 neurons. These results implicate the involvement of type-2 neurons in the initiation of sleep, whereas type-1 neurons contribute to sleep consolidation as they are only activated in the absence of inhibitory effects from the arousal systems (Gallopin et al. 2005).

The administration of CGS 21680 into the rostral BF, however, produces c-fos expression not only in the VLPO, but also within the NAc shell and the medial portion of the olfactory tubercle (Satoh et al. 1999; Scammell et al. 2001). Interestingly, direct perfusion of the A_{2A} receptor agonist into the NAc induces NREM and REM sleep that corresponds to about three-quarters of the amount of sleep measured when the A_{2A} receptor agonist is infused into the subarachnoid space (Satoh et al. 1999). These results may indicate that A_{2A} receptors within or close to the NAc predominantly promote sleep (Fig. 2a). Acting opposite to adenosine, caffeine enhances wakefulness because it acts as an antagonist of both A_1 and A_{2A} receptor subtypes (Fredholm et al. 1999). Experiments using global genetic KOs of the A_1 and A_{2A} receptors revealed that A_{2A} receptors, but not A_1 receptors, mediate the arousal-inducing effect of caffeine (Huang et al. 2005). The specific role of A_{2A} receptors in the basal ganglia (BG) was investigated using powerful tools for site-specific gene manipulations, such as conditional KO mice of the A_{2A} receptor based on the Cre/lox technology or local infection with AAV carrying short-hairpin RNA of A_{2A} receptors to silence the expression of the receptor subtype (Lazarus et al. 2011). Deletion of A_{2A} receptors selectively in the NAc shell blocked caffeine-induced wakefulness (Fig. 3). Excitatory A_{2A} receptors within the NAc shell must be tonically activated by adenosine for caffeine to be effective as an A_{2A} receptor antagonist. This tonic activation probably occurs in the NAc shell because sufficient levels of adenosine are available under basal conditions and A_{2A} receptors are abundantly expressed throughout the striatum, including the NAc shell (Rosin et al. 1998; Svenningsson et al. 1999). Thus, activation of A_{2A} receptors in the NAc shell contributes to the restraint of the arousal system, whereby caffeine overrides the "adenosine brake" to promote wakefulness. Interestingly, deletion of the dopamine transporter (DAT), which is responsible for the re-uptake of dopamine (Giros and

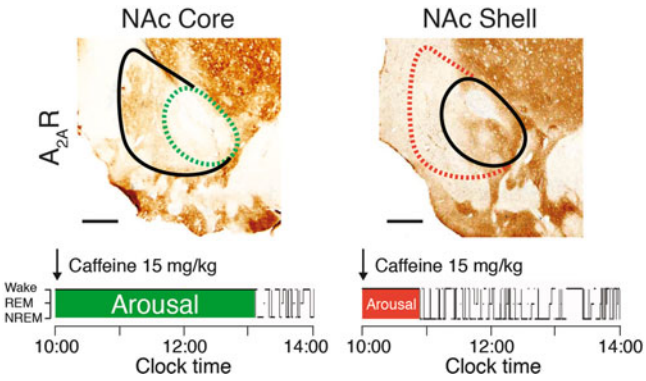

Fig. 3 The arousal effects of caffeine are abolished in rats with site-specific deletion of A_{2A} receptors ($A_{2A}R$) in the shell of the nucleus accumbens (NAc). To identify the neurons on which caffeine acts to produce arousal, A_{2A} receptors were focally depleted by bilateral injections of adeno-associated virus carrying short-hairpin RNA for the A_{2A} receptor into the core (*dashed green line* in the *left panel*) or shell (*dashed red line* in the *right panel*) of the nucleus accumbens of rats (Lazarus et al. 2011). Typical hypnograms that show changes in wakefulness and in rapid eye movement (REM) and non-REM (NREM) sleep after administration of caffeine at a dose of 15 mg/kg indicate that rats with shell, but not core, knockdown of the A_{2A} receptors showed a strongly attenuated caffeine arousal. *Green* and *red* areas in the hypnograms represent wakefulness after caffeine administration that correspond to the depletion of A_{2A} receptors in the core and shell of the nucleus accumbens, respectively

Caron 1993), in mice reduces NREM sleep, increases wakefulness, and unmasks hypersensitivity to the wake-promoting effects of caffeine (Wisor et al. 2001). The last observation may indicate that the expression of NAc D_2 receptors working opposite to A_{2A} receptors is involved in the arousal effect of modafinil, a wakefulness-promoting compound. Despite the fact that stimulating A_{2A} receptors leads to decreased affinity for dopamine at D_2 receptors via intramembrane interactions and to a reduction in Gi-protein coupling of the D_2 receptor for the inhibition of cAMP production (Fuxe et al. 2003), adenosine and its antagonists, such as caffeine, can modulate the activity of medium spiny projection neurons in the striatum via A_{2A} receptors independently of D_2 receptors (Aoyama et al. 2000; Chen et al. 2001). Interestingly, humans with a genetic reduction of striatal DAT show an elevated sensitivity to caffeine stimulation and increased homeostatic response when they are sleep deprived (Holst and Landolt 2015).

The study of NAc adenosine-mediated modulation of the sleep–wake cycle led to a new proposal that the BG represents a key structural element for the control of sleep and wakefulness (Lazarus et al. 2011, 2012). Dysfunction in the BG, such as PD and Huntington's disease and lesions in the BG, results in a wide range of disorders of movement, cognition, and sleep–wake function (Adler and Thorpy 2005; Dale et al. 2004; Goodman and Barker 2010; Obeso et al. 2000; Wetter et al. 2000). In fact, bilateral lesions using ibotenic acid to kill intrinsic neurons in the striatum (caudoputamen), internal and external globus pallidus (GPe), subthalamic nucleus, substantia nigra (pars reticulata or compacta), or thalamus revealed that

bilateral lesions made in the striatum or specifically in the NAc result in a significant reduction in time spent in wakefulness and fragmentation of both sleep and wakefulness (Qiu et al. 2010). Only lesions in the caudate–putamen and globus pallidus increased sleep by 10% and wake by 50%, respectively (Qiu et al. 2010). Moreover, the complete deletion of D_2 receptors, which are prominently, albeit not exclusively, expressed in the BG, significantly decreases wakefulness with a concomitant increase in NREM and REM sleep and a drastic decrease in the NREM sleep delta power (Qu et al. 2010). Excessive sleepiness in PD and other sleep disorders are commonly treated with modafinil (Hogl et al. 2002; Minzenberg and Carter 2007) and interestingly, the arousal effect of modafinil is exclusively mediated by D_1 and D_2 receptors, with D_2 receptors being of primary importance (Qu et al. 2008). Based on these findings, it was proposed that activation of A_{2A} receptors leads to enhanced activity of GABAergic output neurons in the striatopallidal pathway and subsequently arousal systems in the thalamus, hypothalamus, brainstem, and ultimately the cerebral cortex are maintained under a tight inhibitory control. In fact, stereotaxic-based brain microinjections of Cre-recombinase-dependent AAV vectors carrying channelrhodopsin or DREADD into the NAc of transgenic mice in which Cre-recombinase is expressed under the A_{2A}-receptor promoter robustly induced NREM sleep during selective activation of striatopallidal neurons by light or the small molecule clozapine-N-oxide (Oishi Y, Xu Q, et al., unpublished).

Moreover, a recent study found that blocking A_{2A} receptors or A_{2A} receptor-expressing neurons in the olfactory bulb of rodents increases REM sleep, suggesting the possibility that the olfactory bulb is a key site for regulating REM sleep by the adenosine/A_{2A} receptor system (Wang et al. 2016). Because olfactory dysfunction can be ameliorated with an A_{2A} receptor antagonist, for example, caffeine or ZM 241385 (Prediger et al. 2005), it is possible that REM sleep and the perception of odors are linked in the olfactory bulb. Interestingly, the ability to smell is reduced in patients with REM sleep behavior disorder (Stiasny-Kolster et al. 2007).

4.4 Effects of Natural Compounds on Sleep and Wakefulness via Adenosine Receptors

Several studies recently demonstrated that a variety of natural compounds promote sleep via adenosine receptor activation. In strong support of the role of A_{2A} receptors in the regulation of sleep, Japanese sake yeast supplementation improves the quality of sleep in humans (Monoi et al. 2016) and sake yeast-induced NREM sleep was abolished in mice by pretreatment with the A_{2A} receptor antagonist ZM 241385 (Nakamura et al. 2016). Because sake yeast, but not other *Saccharomyces cerevisiae* yeasts (e.g., baker's and brewer's yeast), contains a large amount of *S*-adenosyl-L-methionine and the *S*-adenosyl-L-methionine metabolite methylthioadenosine, Urade and colleagues suggested that the sleep-inducing effect of sake yeast is likely due to the activation of A_{2A} receptors by *S*-adenosyl-L-methionine or methylthioadenosine.

In contrast, paeoniflorin, one of the principal active ingredients of *Paeonia Radix*, shortens sleep latency and increases the amount of NREM sleep exclusively via the activation of A_1 receptors, a conclusion based on the finding that paeoniflorin effects can be blocked by treatment with an A_1 receptor antagonist and are absent in A_1 receptor-KO mice (Chen et al. 2015). In addition, paeoniflorin significantly increases the mechanical pain threshold, prolongs the thermal latency, and increases NREM sleep in partial sciatic nerve ligation mice, a mouse neuropathic pain model characterized by persistent pain and insomnia (Yin et al. 2015). Therefore, the A_1 receptor-mediated analgesic and hypnotic effects of paeoniflorin may be of potential use for the treatment of neuropathic pain and associated insomnia.

Moreover, N^6-(4-hydroxybenzyl) adenine riboside isolated from *Gastrodia elata* has hypnotic effects in mice (Zhang et al. 2012) and may dose-dependently increase NREM sleep via mechanisms that involve A_1 and A_{2A} receptors. Finally, cordycepin (3-deoxyadenosine), an adenosine analogue isolated from *Cordyceps* fungi, promotes NREM sleep in rats, but it remains unclear if the sleep-inducing effect is, in fact, mediated by adenosine receptors (Hu et al. 2013).

5 Effects of Caffeine in Man and the Possible Role of More Selective Adenosine Receptor Drugs

Whereas the above data linking adenosine to sleep were obtained from animal experiments, the evidence suggests that this link also holds true in humans. This is largely due to the well-known effects of caffeine on sleep. Caffeine is the most consumed psychoactive compound in the world. It is readily available through dietary products, such as coffee, tea, soft drinks, and chocolate, but it is also added to non-prescription medications, such as pain-relievers and cold remedies. Regardless of the source, worldwide average caffeine consumption is estimated to be just under 80 mg/d, although the levels of intake in countries such as Sweden and Finland are in the range of 400 mg caffeine per day (Fredholm et al. 1999). Caffeine is widely used to promote wakefulness and to counteract fatigue in doses that are well in the range where adenosine antagonism is the dominant effect. Some individuals, however, experience anxiety and panic attacks (Chait 1992; Evans and Griffiths 1991) at normal consumption levels, and this is more common at higher doses. One study found that people with polymorphisms at the A_{2A}-receptor-gene are at risk of experiencing increased anxiety when consuming coffee, tea, energy drinks, or other caffeine-containing products (Alsene et al. 2003). A_{2A} receptor polymorphisms also consistently modulate the objective and subjective effects of caffeine on sleep quality and electroencephalogram (Bodenmann et al. 2012; Byrne et al. 2012; Rétey et al. 2007).

Whether caffeine affects circadian rhythm and thereby alters the timing of sleep is widely unknown; however, recent developments revealed caffeine effects on the mammalian circadian clock. For example, caffeine delays the human circadian melatonin rhythm by blocking A_1 receptors (Burke et al. 2015). Chronic treatment

with caffeine lengthens the circadian period of molecular oscillations in human osteosarcoma U2OS cells expressing clock gene luciferase reporters. Further, application of pharmacologic tools and small-interfering RNA knockdown revealed that the effect of caffeine on molecular oscillation is attenuated by perturbation of A_1 receptor signaling but not ryanodine receptor or phosphodiesterase activity. This finding establishes a possible molecular mechanism for the clinical observation in a double-blind, placebo-controlled, ~49-day long, within-subject study that bedtime caffeine consumption induces a ~40-min phase delay of the circadian melatonin rhythm in humans. Another study revealed that caffeine increases the light sensitivity of the mouse circadian clock (van Diepen et al. 2014).

Society demands the means to bend sleep to the needs of modern lifestyle instead of the other way around and thus sleep-avoidance has become a popular research topic. Scientists and clinicians worldwide are searching for new methods of keeping people alert on limited sleep. Much more about the effects of coffee and other beverages containing caffeine on sleep in man will be covered elsewhere in this book [for review, see Clark and Landolt (2017)]. Moreover, consistent with the fact that the arousal effect of caffeine in mice is exclusively mediated by A_{2A} receptors, emerging evidence supports the modulation of the sleep–wake cycle by A_{2A} receptor antagonists. For example, the newly developed dual adenosine A_{2A}/A_1 receptor antagonist JNJ-40255293 enhances wakefulness (Atack et al. 2014). Moreover, since the clinical approval of the A_{2A} receptor antagonist istradefylline (KW-6002) for motor improvement in PD in Japan in 2013, a report of four cases indicated that evening treatment with this antagonist reduces sleep duration in the evening and increases daytime sleepiness in patients (Matsuura and Tomimoto 2015). Thus, A_{2A} receptor antagonists may have considerable potential as eugeroics (wakefulness enhancing drugs) while avoiding some of the aforementioned A_{2A}-independent side effects of caffeine (such as anxiety and disturbance of the circadian rhythm) or negative effects of other psychostimulants, including dependence.

The possibility that stimulation of adenosine receptors could be used to promote sleep should also be considered. Currently, there are 60 million prescriptions for sleeping pills in the USA each year, 43 million of which are for the nonbenzodiazepine zolpidem, also known as Ambien. Benzodiazepines and nonbenzodiazepines, both of which enhance the effect of the neurotransmitter GABA at the $GABA_A$ receptor, are used for the treatment of insomnia and poor sleep quality despite their wide range of disadvantages and safety issues, ranging from low sleep quality by increasing light sleep at the expense of physiological deep sleep to side effects (e.g., next-day sedation, cognitive impairment, and amnesic effects) and the development of tolerance and dependence by long-term administration. Because an A_{2A} receptor agonist strongly increases sleep in wild-type mice (Satoh et al. 1996; Urade et al. 2003), pharmacologic A_{2A} receptor activation may be an alternative strategy for the treatment of insomnia. Due to the lack of brain-permeability, however, not all currently existing A_{2A} receptor agonists are suitable for treating the nervous system. If the observation in animals that adenosine levels are elevated during prolonged wakefulness holds also true for humans, a freely penetrating allosteric modulator may effectively enhance the

sleep-inducing effect of endogenous adenosine and help people with insomnia to fall asleep.

6 Conclusion

Here we demonstrated that adenosine is indeed one of the several somnogenic substances that act in concert to ensure normal sleep–wake patterns. Adenosine tends to increase sleep, but the source of the adenosine is still poorly understood. Many cells and processes could play a role. Similarly, adenosine promotes sleep by several mechanisms, in several locations, via A_1 or A_{2A} receptors. We emphasized A_1 receptor-mediated effects on histamine neurons and the A_{2A} receptor-mediated effects in the NAc. Both of these receptors are antagonized by caffeine – to a large extent explaining the awakening effect of this common drug.

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