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Commentary

Sleep homeostasis: A role for adenosine in humans?

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ABSTRACT

Sleep is not the mere absence of wakefulness, but an active state which is finely regulated. The homeostatic facet of sleep–wake regulation is keeping track of changes in 'sleep propensity' (or 'sleep need'), which increases during wakefulness and decreases during sleep. Increased sleep propensity following extended prior wakefulness (sleep deprivation) is counteracted by prolonged sleep duration, but also by enhanced non-rapid-eye-movement (nonREM) sleep intensity as measured by electroencephalographic (EEG) slow-wave activity (SWA, power within ~1–4 Hz). This highly reliable regulatory feature of nonREM sleep may be the most important aspect of sleep in relation to its function. The neurochemical mechanisms underlying nonREM sleep homeostasis are poorly understood. Here we provide compelling and convergent evidence that adenosinergic neurotransmission plays a role in nonREM sleep homeostasis in humans. Specifically, a functional polymorphism in the adenosine metabolizing enzyme, adenosine deaminase, contributes to the high inter-individual variability in deep slow-wave sleep duration and intensity. Moreover, the adenosine receptor antagonist, caffeine, potently attenuates the EEG markers of nonREM sleep homeostasis during sleep, as well as during wakefulness. Finally, adenosinergic mechanisms modulate individual vulnerability to the detrimental effects of sleep deprivation on neurobehavioral performance, and EEG indices of disturbed sleep after caffeine consumption. While these convergent findings strongly support an important contribution of adenosine and adenosine receptors to nonREM sleep homeostasis, further research is needed to elucidate the underlying mechanisms that mediate the actions of adenosine on sleep and the sleep EEG.

1. Introduction

Coffee- and caffeine-containing beverages are among the most widely consumed stimulants worldwide. Nearly a century ago, an FDA lawsuit accusing Coca-Cola company of marketing a product with caffeine as a deleterious ingredient led to the studies by Harry Hollingworth on the behavioral effects of the xanthine in humans [1]. These studies set a then new standard for psychopharmacological research, including blind and "placebo"-controlled experimental design [2]. With respect to the effects of caffeine on sleep, Hollingworth published the results of his research 1 year following the trial. He concluded that the drug does not produce appreciable sleep disturbance except in a few individual cases [1]. During the 96 years since this publication, caffeine has arguably become the most

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often investigated psychoactive substance in animals and humans.

The primary impetus today for studying the effects of caffeine on sleep has been the realization that this central nervous system (CNS) stimulant acts through blocking the actions of the endogenous neuromodulator adenosine [3]. Pharmacological studies and recent insights from genetically modified mice suggest that adenosine acts not only as a neuroprotective agent in situations of an imbalance between energy supply and energy demand. In addition, this nucleoside and its receptors are involved in basal physiological functions, in particular in the nervous and cardiovascular systems. The wide variety of adenosine actions and the potential of adenosine receptors as targets for therapeutic agents to treat human diseases were the topic of recent extensive overviews (e.g. [4–6]). They cannot be covered by this commentary, which focuses primarily on a role for adenosine in sleep–wake regulation in humans.

2. Sleep states and sleep regulation in humans

The electroencephalogram (EEG) recorded from the scalp is the most important method to study the physiological and biochemical processes underlying human sleep. Distinct changes in EEG, electrooculogram (EOG) and electromyogram (EMG) serve to discriminate between wakefulness, non-rapid-eye-movement (nonREM) sleep, and rapid-eye-movement (REM) sleep [7–9]. Apart from behavioral arousal, active wakefulness is characterized by a low-amplitude, fast-frequency EEG. In quiet wakefulness with closed eyes, the EEG shows in many individuals regular alpha (~10 Hz) activity. Nocturnal sleep in healthy humans is typically initiated with nonREM sleep stage 1, which is recognized by a pattern of theta (~5–9 Hz) activity and slowly rolling eye movements. The EEG in nonREM sleep stage 2 is characterized by the occurrence of phasic events representing sleep spindles (~11–15 Hz, sigma frequency range) and K-complexes. Based on the prevalence of EEG high-amplitude, slow waves in the delta frequency range (~1–4 Hz), nonREM sleep is further subdivided into the stages 3 and 4 (referred to as ''slow-wave sleep''). The state of REM sleep is identified by rapid eye movements, atonia in anti-gravity muscles and desynchronized EEG activity. Distinct episodes of REM sleep occur periodically during the night.

Salient features of undisturbed human sleep occurring under conditions entrained to the 24-h light/dark cycle include a declining trend in EEG slow-wave activity (SWA, spectral power within 0.75–4.5 Hz), and a decrease in the ratio between nonREM sleep and REM sleep in the course of the night. These characteristics reflect the influence of three basic processes that are assumed to underlie sleep–wake regulation [10] (Fig. 1). (1) A *homeostatic* process keeping track of 'sleep propensity' or 'sleep need', which accumulates during wakefulness and dissipates during sleep. (2) A *circadian* process reflecting the output of an oscillator with an endogenous period of roughly to 24 h (lat. ''circadian'' = approximately 1 day). This process determines the daily phases of high and low propensity for sleep, REM sleep and wakefulness. And (3), an *ultradian* process reflecting the cyclic occurrence of nonREM and REM sleep within a night. According to the two-process model of sleep regulation [11], the interaction between the sleep–wake-dependent, homeostatic *Process S* and the sleep–wake-independent, circadian *Process C* underlies variations in sleep propensity during waking, the alternation between wakefulness and sleep, nonREM sleep intensity, and the timing of REM sleep. In conclusion, sleep is not the mere absence of wakefulness, but an active physiologic process, which is finely and reliably regulated.

In agreement with Hollingworth [1], a recent review of the available literature by the ''Sleep Deprivation and Stimulant Task Force of the American Academy of Sleep Medicine'' concluded that caffeine does not heavily disrupt sleep following 8 h or longer after drug administration [12]. Nevertheless, this review will show that even moderate amounts of caffeine taken as long as 16 or 17 h prior to sleep induce subtle, yet reliable and physiologically meaningful changes in the sleep EEG, in particular in self-rated caffeine-sensitive subjects. The data are consistent with a role for adenosine and adenosine receptors in nonREM sleep homeostasis in humans.

3. Physiological markers of sleep homeostasis

The homeostatic facet of sleep regulation is the most important aspect of sleep in relation to its function. As early

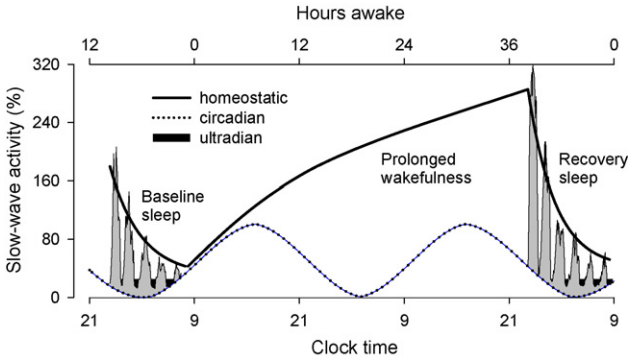

Fig. 1 – Schematic drawing of the physiological processes underlying sleep regulation [11]. (1) A *homeostatic* process (continuous line) keeps track of accumulating 'sleep propensity' during wakefulness and dissipating 'sleep propensity' during sleep. (2) A *circadian* process (dotted line) reflects the output of the circadian oscillator determining the daily phases of high and low propensity for sleep, REM sleep and wakefulness. (3) An *ultradian* process underlies the cyclic occurrence of REM sleep (black). The initial value of EEG slow-wave activity (SWA, spectral power within 0.75–4.5 Hz) and the declining trend of SWA over consecutive nonREM sleep episodes are reliable markers of sleep homeostasis (grey). Mean data of seven habitual long sleepers adapted from Aeschbach et al. [16]. Note the increase of initial SWA from baseline (following 14 h wakefulness) to recovery sleep (following 38 h prolonged wakefulness). In baseline and recovery sleep episodes, the decline of sleep propensity during sleep can be roughly described by an exponential function.

as 1937, Blake and Gerard [13] observed that sleep depth as quantified by the arousal threshold is related to the level of slow waves in the sleep EEG. The global declining trend of SWA within a sleep episode reflects the homeostatic decline of sleep propensity [14]. Sleep deprivation provides a physiological challenge to promote sleep homeostasis. Elevated sleep propensity after prolonged wakefulness is counteracted not only by prolonged sleep duration, but also by enhanced sleep intensity [10]. Today, it is widely accepted that EEG SWA and spindle frequency activity (SFA, power within ~11–15 Hz) serve as reliable markers of nonREM sleep intensity. Initial SWA rises as a function of time awake, while SFA is typically reduced after sleep deprivation [14–19].

A physiological marker of sleep homeostasis can also be tracked during wakefulness. Power in the theta band of the waking EEG increases during prolonged wakefulness [20–24]. The time constant of this increase is similar to that of the wake-dependent increase in delta activity in nonREM sleep [21,22]. This relationship suggests that the rise rate of theta activity during waking and the enhancement of SWA in nonREM sleep after sleep deprivation are closely related [24].

4. Neurochemistry of nonREM sleep homeostasis

While the EEG markers of nonREM sleep homeostasis during sleep and waking are well established, the neurochemical bases underlying these markers are not well understood. Various hormones, peptides, prostaglandins, cytokines and growth factors, including dopamine, norepinephrine, serotonin, histamine, orexin, γ-aminobutyric acid (GABA) and others, promote wakefulness and sleep in animals and/or humans [25–28]. Their roles in sleep homeostasis, however, remain unclear (e.g., [17]). Benington and Heller suggested that amplified neuronal potassium conductance (gK^+) underlies increased SWA and reduced SFA after sleep deprivation [29]. One possibility to promote gK^+ includes the stimulation of inhibitory adenosine receptors, and adenosine may be a likely candidate to mediate the rebound of SWA after sleep deprivation [29].

5. Adenosine, adenosine metabolism, and sleep

Converging lines of evidence indeed support an important role for adenosine in sleep–wake control. Animal studies have long shown that systemic and local administration of adenosine, the adenosine reuptake blocker nitrobenzylthioinosine (NBTI), and adenosine receptor agonists and antagonists modulate the expression of wakefulness and sleep [30–39]. More recently, it has been observed that local adenosine levels rise in certain brain areas in rats and cats during waking and decline during sleep [37,40,41]. Because these changes appear to be more pronounced in the basal forebrain (BF) than in other cerebral regions [42], local release of adenosine in BF was proposed to provide a signal for the homeostatic regulation of nonREM sleep (see [43,44] for reviews). Alternatively, electrophysiological data show that adenosine disinhibits and/or actively excites "sleep-active" neurons in the ventro-lateral preoptic (VLPO) area of the hypothalamus [45–48]. Finally, adenosine may contribute to global cortical disfacilitation, a form of inhibition due to reduced activating input from ascending cholinergic and monoaminergic pathways. As suggested by intracellular recordings in non-anaesthetized cats, the long-lasting hyperpolarizing potentials in nonREM sleep may represent periods of disfacilitation [49].

The extracellular adenosine concentration in the brain increases in activity-dependent manner [50]. Two primary mechanisms underlie the appearance of adenosine in the extracellular space [3,51] (Fig. 2). First, the nucleoside can be released through equilibrative nucleoside transporters. Intracellularly, adenosine is formed from adenosine-mono-phosphate (AMP) by cytosolic 5′-nucleotidase and converted back to AMP by adenosine kinase. Because of the relatively high

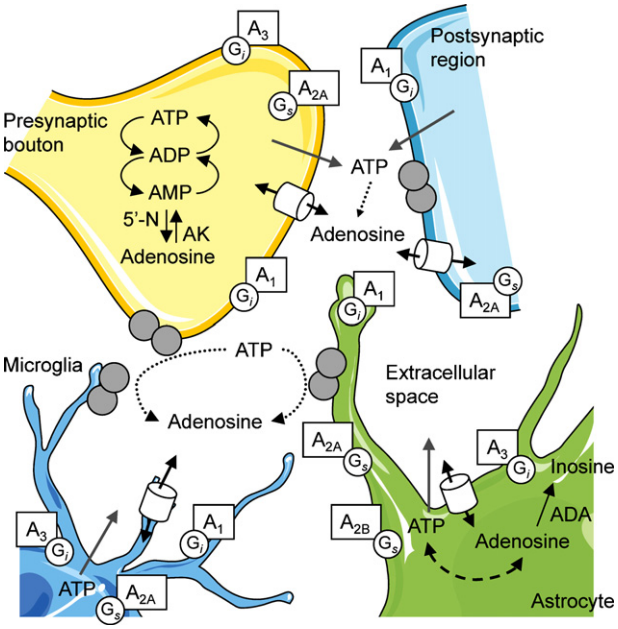

Fig. 2 – Simplified schematic representation of adenosine formation and adenosine actions in different cell types in the brain (adapted from [3]). Microglia and astrocytes, as well as presynaptic boutons and postsynaptic dendrites of neurons can release adenosine and adenosine-tri-phosphate (ATP; grey arrows). All cell types and compartments express equilibrative adenosine transporters (cylinders), ecto-nucleotidases (grey circles) that convert ATP into adenosine (dotted arrows), and G-protein-coupled adenosine receptors (rectangles representing A_1, A_{2A}, A_{2B} and A_3 receptors). They can convert ATP into adenosine-mono-phosphate (AMP), and AMP into ATP (presented in detail in the presynaptic bouton; dashed arrow in astrocyte). 5′-N = cytosolic 5′-nucleotidase. The intracellular metabolism of adenosine following nucleoside transporter-mediated uptake from the extracellular space involves primarily adenosine deaminase (ADA) in astrocytes, and adenosine kinase (AK) in nerve terminals. Activation of adenosine receptors either stimulates ($A_{2A/2B}$ receptors) or inhibits ($A_{1/3}$ receptors) adenylate cyclase and the cyclic AMP pathway.

activity of adenosine kinase, adenosine concentrations inside cells are normally low. Therefore, the net flux through these transporters is inwardly directed. Nevertheless, under conditions of increased energy demand leading to hydrolysis of adenosine-tri-phosphate (ATP) and enhanced intracellular adenosine levels, these transporters can release adenosine. Given that intracellular ATP levels are some 100,000 times higher than adenosine levels, substantial changes in adenosine can occur without major changes in ATP [3]. Second, extracellular adenosine is formed through ecto-nucleotidase-mediated hydrolysis of released adenine nucleotides, especially ATP [52]. These enzymes dephosphorylate adenine nucleotides to AMP, which by the terminal enzymatic step is hydrolyzed by 5′-nucleotidase to adenosine. Ecto-nucleotidases are widely expressed in the brain. For example, ecto-5′-nucleotidase (CD73) is known as a marker of astrocytes (but not neurons) [6]. Recent studies place astrocytes at center stage in the control of adenosine-mediated modulation of neuronal transmission [53].

Clearance of extracellular adenosine mostly occurs through the nonconcentrative nucleoside transporters [3,51]. The main intracellular metabolic pathways of adenosine are the formation of AMP by adenosine kinase, and the irreversible breakdown to inosine by adenosine deaminase (ADA). Extracellularly, ecto-ADA can also deaminate adenosine into inosine. Adenosine kinase appears to be enriched in neurons, whereas ADA appears to be more abundant in astrocytes [3]. The action of the highly active ADA may be particularly important when large amounts of adenosine have to be cleared. Thus, when ADA is pharmacologically blocked [54] or genetically deficient such as in patients with severe combined immunodeficiency disease (SCID), extracellular adenosine levels can markedly rise (cited in [55]). A third enzyme, S-adenosyl-homocysteine hydrolase (SAHH), converts adenosine to S-adenosyl-homocysteine in cardiomyocytes, yet may be less important in the CNS [3].

Diurnal variations in adenosine and its metabolizing enzymes are present in rat cortical tissue, with the highest adenosine levels found at the beginning of the circadian rest period [56,57]. Pharmacological studies revealed that inhibition of adenosine metabolism by blocking adenosine kinase with ABT-702 and ADA with (deoxy)coformycin prolongs sleep and increases SWA in the EEG [54,58,59]. These data from rats are consistent with genetic findings in mice suggesting that a genomic region encoding genes which contribute to the regulation of extracellular adenosine levels – ADA and SAHH – modifies the rate at which nonREM sleep need accumulates during wakefulness [60].

We recently found in humans that a functional genetic variation in ADA has a profound impact on sleep and the sleep EEG [61]. The most frequent variant allele (ADA*2) of ADA that is asymptomatic in heterozygous carriers is caused by a G to A transition at nucleotide 22 of the ADA gene. The G/A genotype is present in roughly 10% of healthy Caucasians, whereas the homozygous A/A genotype occurs in less than 1% of the population [62]. This polymorphism leads to the substitution of asparagine for aspartic acid at codon 8 of the ADA protein [63]. Individuals carrying one copy of the ADA*2 allele (G/A genotype) exhibit 20–30% lower enzymatic activity of ADA in blood cells than individuals with the G/G genotype [64]. In accordance with the hypothesis that genetic variation in ADA affects markers of sleep homeostasis, we revealed that an 8 h nocturnal sleep episode in subjects with the G/A genotype is characterized by 30 min more slow-wave sleep than in subjects with the G/G genotype (92.5 ± 6.2 min *vs.* 63.0 ± 9.3 min) [61]. Moreover, not only the duration of slow-wave sleep is longer, but also its intensity as estimated from SWA is higher in the G/A than in the G/G genotype ($247.8 \pm 23.3\ \mu V^2/Hz$ *vs.* $182.2 \pm 32.0\ \mu V^2/Hz$). The effects of this functional ADA polymorphism are similar in magnitude to the consequences of one night without sleep, and provide the first direct evidence of a role for adenosine in nonREM sleep homeostasis in humans.

Attempts to pharmacologically elevate the extracellular adenosine concentration by inhibiting ADA could, in principle, provide a promising treatment of sleep maintenance insomnia. It should be kept in mind, however, that accumulation of the ADA substrates, adenosine and 2′-deoxyadenosine, and the expression of adenosine receptors on virtually all cells could give rise to multiple unwanted drug reactions [55,65,66].

6. Adenosine receptors and sleep

The cellular effects of adenosine are mediated via four subtypes of G-protein-coupled adenosine receptors (A_1, A_{2A}, A_{2B} and A_3 receptors) [67]. Relatively low amino acid sequence homology is reported among different adenosine receptors within one species, and of the same adenosine receptor between different species [5]. Comparison of certain research findings among different species may, therefore, be difficult. In humans, the most similar are the A_{2A} and A_{2B} receptors (roughly 60% sequence similarity) and the A_1 and A_3 receptors (roughly 50% similarity), respectively [68]. The potency of adenosine for human receptor subtypes expressed in Chinese hamster ovary cells indicates that endogenous adenosine can activate A_1, A_{2A} and A_3 receptors at physiological concentrations in tissues with high receptor expression, whereas pathophysiological conditions are needed to stimulate A_{2B} receptors [66,67].

Each adenosine receptor subtype shows a unique tissue distribution, signaling pathway and pharmacological profile. Even though adenylate cyclase (also known as adenylyl cyclase) and the cyclic adenosine-mono-phosphate (cAMP) pathway is either activated ($A_{2A/2B}$ receptors) or inhibited ($A_{1/3}$ receptors), all adenosine receptors are positively coupled to the extracellular signal-regulated kinases 1 and 2 (ERK1/2) [68]. The ERK1/2 belong to the mitogen-activated protein kinases (MAPKs) and have important roles in cell proliferation and survival [69]. Intriguingly, activation of ERK phosphorylation in *Drosophila* was recently reported to increase sleep in a dose-dependent manner [70].

The A_1 receptors are widely expressed in the brain in cortex, thalamus, hippocampus and basal ganglia [5,68]. Stimulation of these receptors inhibits adenylate cyclase through activation of G_i proteins, activates phospholipase C (PLC), opens several types of K^+ channels, and inactivates Q-, P- and N-type Ca^{2+} channels [3,6]. Because of the widespread distribution of cerebral A_1 receptors and the inhibition of excitatory neurotransmission following presynaptic A_1 receptor activation, it has been

generally assumed that adenosine affects sleep primarily via the A_1 receptor. Some findings from pharmacological studies are compatible with this assumption. For example, i.p. and i.c.v. administration of the selective A_1 receptor agonist N^6-cyclopentyladenosine (CPA) to rats increases nonREM sleep, suppresses REM sleep, and induces changes in the nonREM sleep EEG which are similar to those of prolonged wakefulness [34,35]. Moreover, microdialysis perfusion of the rat basal forebrain with A_1 receptor antisense oligonucleotides reduces nonREM sleep and increases wakefulness [71]. Notwithstanding, a careful study performed in knock-out mice shows that the homeostatic facet of sleep–wake regulation is unaltered in animals lacking A_1 receptors [72]. These data may indicate that compensatory developmental changes occur in the absence of functional A_1 receptors and support the conclusion that A_1 receptors contribute to vigilance states in normal animals, but may not be absolutely necessary for sleep homeostasis.

The A_{2A} receptors are present at high concentration in the central nervous system in striatum, nucleus accumbens and olfactory bulb [5,68]. Stimulation of this receptor subtype increases adenylate cyclase activity through activation of G_s or G_{olf} (in striatum) proteins, induces the formation of inositol phosphates, and activates protein kinase C [3,6]. Evidence accumulated in recent years indicating that also the A_{2A} receptor contributes to the effects of adenosine on sleep. In rats, selective A_{2A} receptor agonists such as CGS21680 administered to the subarachnoid space adjacent to basal forebrain and lateral preoptic area reliably induce nonREM sleep, while infusion of A_1 receptor agonists produces weak and variable effects [48,73–75]. The local application of CGS21680 increases *c-fos* expression in the VLPO [75]. Activation of A_{2A} receptors in nucleus accumbens may underlie this effect. On the other hand, direct activation of sleep-promoting VLPO neurons via postsynaptic stimulation of A_{2A} receptors was recently demonstrated [47]. Interestingly, preliminary data indicate that CGS21680 is ineffective in knock-out mice lacking A_{2A} receptors and that these mice may not show a nonREM sleep rebound following sleep deprivation [76,77].

The A_{2B} receptor is expressed widely, but generally at very low levels [5]. This receptor subtype is positively coupled to both adenylate cyclase and PLC [6]. Little is known about the functional significance of this receptor.

The A_3 receptor appears to be widely distributed in most animals, yet there exist pronounced differences between species [3,5]. The highest message for human A_3 receptors has been found in lung and liver, and lower levels in aorta and brain. This adenosine receptor subtype inhibits adenylate cyclase, stimulates PLC and calcium mobilization, and activates ERK1/2 phosphorylation [3,6]. The A_3 receptor has been primarily implicated in mediating allergic responses [5].

Taken together, the A_1 and A_{2A} receptor subtypes are most likely those to mediate physiological effects of adenosine on sleep, and these effects appear to be site- and receptor-dependent.

7. Caffeine, sleep, and the sleep EEG

Strong support for a role for adenosine receptors in sleep–wake processes comes from the potent stimulant action of caffeine. The average daily caffeine consumption in adults of Western societies leads to low micromolar blood plasma levels [78]. Disturbed sleep after caffeine is among the primary reasons why people voluntarily abstain from the stimulant. It is widely accepted that at micromolar concentration, the stimulant acts primarily as a competitive antagonist at A_1 and A_{2A} receptors [79]. Nevertheless, data from knock-out mice suggest that the A_{2A} receptor is the main target for caffeine-induced wakefulness [80]. This notion is consistent with recent findings in young men demonstrating that a distinct c.1083T>C polymorphism in the A_{2A} receptor gene (*ADORA2A*) modulates individual sensitivity to subjective and objective effects of caffeine on sleep [81].

In keeping with the adenosine hypothesis of sleep, we found in earlier studies that a low dose of caffeine (100 mg), administered immediately prior to sleep, prolongs sleep latency, reduces slow-wave sleep in the first nonREM/REM sleep cycle, and impairs sleep efficiency [82]. The EEG spectral power in the low delta range is decreased, whereas power in the spindle frequency range is increased (Fig. 3A). After early morning caffeine intake (200 mg), remarkably similar effects are observed during nocturnal sleep at a time when the caffeine concentration in saliva is approaching zero [81,83,84]. These caffeine-induced EEG changes in nonREM sleep are comparable in rested (Fig. 3B) and sleep deprived (Fig. 3C) subjects. They are consistently found irrespective of whether the study participants maintain habitual morning caffeine consumption [82,85]), or abstain from caffeine for days [83] and weeks [81,84] prior to the experiments. They cannot, therefore, be explained by reversal of withdrawal effects after experimental caffeine administration [86]. They rather mimic the changes in sleep EEG activity associated with a physiological reduction in nocturnal nonREM sleep propensity.

Some effects, however, which are typically induced by a nap prior to a sleep episode, in particular a reduction in EEG theta activity in nonREM sleep [87], are not observed after caffeine. This discrepancy could be related to the administered (low) doses of the stimulant, or the fact that the substance exerts a non-selective antagonism at both A_1 and A_{2A} adenosine receptors (see [82] for discussion). Nevertheless, together with data in rats [35], the similar caffeine-induced changes in the sleep EEG after evening and morning drug intake are consistent with the hypothesis that the build-up of sleep propensity during wakefulness is attenuated by caffeine. To further investigate this question, mice lacking both A_1 and A_{2A} receptors should be sleep deprived, and determined whether caffeine has an effect on the sleep EEG in these mice. Moreover, it would be of considerable interest to examine in humans whether the effects of caffeine on the sleep EEG are mimicked by selective A_1 and/or A_{2A} receptor antagonists such as KW6002 [88].

8. Does caffeine interact with nonREM sleep homeostasis?

To further test the hypothesis that caffeine interferes with nonREM sleep homeostasis, we examined the effects of caffeine on the evolution of EEG activity during and after sleep deprivation [84]. The time course of theta activity in the

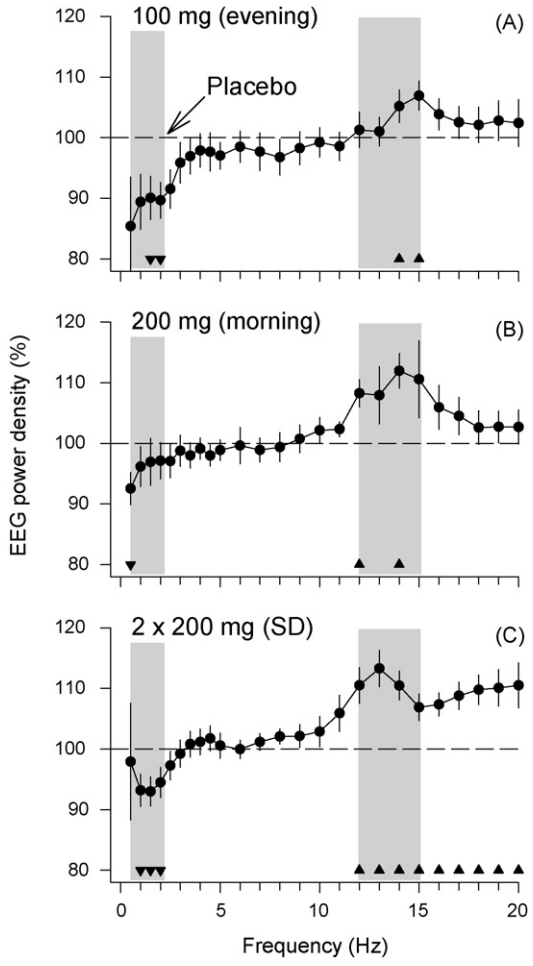

Fig. 3 – Caffeine reduces low-frequency (<2 Hz) activity and enhances spindle frequency (11–15 Hz) activity in nonREM sleep (stages 2, 3 and 4). Relative EEG power density values (±1S.E.M.) after caffeine expressed as a percentage of the corresponding values after placebo (100%, dashed horizontal lines). (A) 100 mg caffeine, administered immediately prior to bedtime (n = 8). Data from Landolt et al. [82]. (B) 200 mg caffeine, administered 16 h prior to bedtime (n = 9). Data from Landolt et al. [83]. (C) 2 × 200 mg caffeine, administered 29 and 17 h prior to bedtime after sleep deprivation (SD; n = 12). Data from Landolt et al. [84]. Triangles above abscissae denote frequency bins for which power differed from placebo ($p < 0.05$, two-tailed, paired t-test). Grey shading overlaying the graph highlights low frequency and spindle frequency activity ranges.

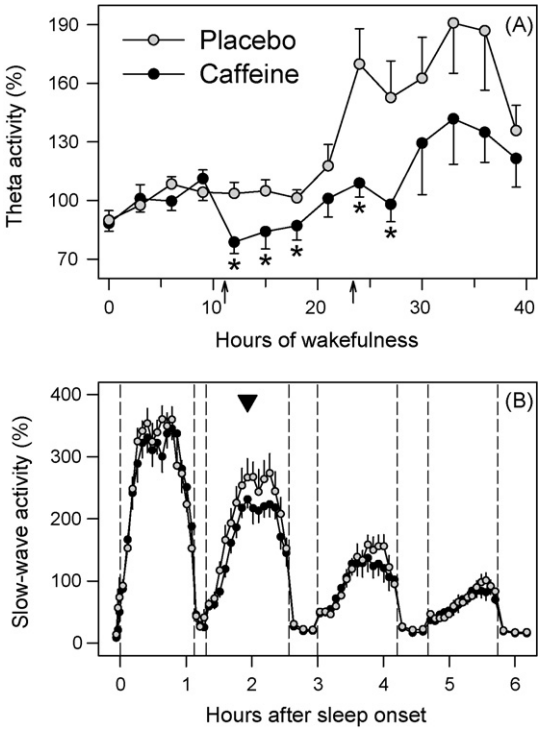

Fig. 4 – Caffeine attenuates EEG markers of sleep homeostasis in waking and sleep. Error bars represent 1S.E.M. (n = 12). (A) Time course of EEG theta activity (5–8 Hz) across 40 h waking. Theta activity was expressed as a percentage of mean theta activity in the first four waking EEG recordings. Vertical arrows below the abscissa indicate caffeine (200 mg) administration. Caffeine attenuates the evolution of theta power ('treatment' × 'time' interaction: $F_{1,10} = 4.8$, $p = 0.05$; see [84] for detailed statistics). Asterisks denote a significant difference between caffeine and placebo ($p < 0.05$, two-tailed, paired t-test). Data from Landolt et al. [84]. (B) Time course of EEG slow-wave activity (0.75–4.5 Hz) in recovery sleep after caffeine and placebo administration during sleep deprivation. Individual nonREM sleep episodes were subdivided into 20, individual REM sleep episodes into 4 equal time bins. For each subject and night, power density values per time bin were expressed as a percentage of the mean nonREM sleep value in baseline. Data were then averaged across subjects and plotted against the mean timing of nonREM and REM sleep episodes. Dashed vertical lines delimit REM sleep episodes. The triangle indicates the nonREM sleep episode in which slow-wave activity was significantly reduced after caffeine when compared to placebo ($p < 0.05$, two-tailed, paired t-test).

waking EEG reflects the increasing duration of wakefulness and also a circadian modulation (Fig. 4A). Compared to placebo, caffeine attenuates the build-up of theta activity associated with prolonged wakefulness. Moreover, the caffeine-induced reduction in theta activity is more pronounced after 23 h than after 11 h of wakefulness. Given that caffeine has only minor effects on the circadian facet of sleep–wake regulation in humans [89], these data suggest that the efficacy of caffeine to reduce theta activity in the waking EEG depends on the duration of prior wakefulness. A similar interaction between the duration of time awake and the effects of caffeine (slow-release formulation, 4 × 300 mg) on EEG-derived markers of vigilance was also found during 64 h of continuous wakefulness [90]. These studies are consistent with the notion that caffeine interacts with homeostatically regulated sleep propensity.

This conclusion is further supported by the time course of caffeine-induced changes in recovery sleep after sleep deprivation. More specifically, SWA in the first nonREM sleep episode does not differ between caffeine and placebo (Fig. 4B). In contrast, caffeine reduces SWA in the second nonREM sleep episode. Thus, a putative residual drug level which would have been highest in the beginning of the recovery night cannot readily account for the reduced SWA in nonREM sleep.

In conclusion, multiple studies consistently demonstrate that pharmacological blockade of adenosine receptors with caffeine interferes with the rise of sleep propensity during wakefulness. While caution is essential when comparing physiological mechanisms of sleep–wake regulation with pharmacological interventions, we found state-specific changes in pre-defined markers of sleep homeostasis in wakefulness and sleep. These findings are highly unlikely to reflect a nonspecific action of caffeine on EEG generation.

9. Caffeine-sensitivity and individual vulnerability to sleep deprivation

Strong evidence suggests that sleep has local and use-dependent facets [91,92]. Regional EEG analyses revealed that the markers of sleep propensity in waking (theta activity) and nonREM sleep (SWA) are largest over frontal cortical areas, especially after sleep deprivation [24,93,94]. These data indicate that frontal parts of the cortex reflect the homeostatic process of sleep–wake regulation more sensitively than other cortical regions. To investigate a possible contribution of adenosinergic mechanisms to these differences, we examined the interaction of sleep deprivation and caffeine on the regional distribution of EEG power in waking and sleep. We observed that during sleep deprivation power in the theta band of the waking EEG increases more in an anterior derivation than in a posterior derivation, primarily in caffeine-sensitive individuals [95]. Caffeine attenuates the waking-induced fronto-occipital power gradient. Intriguingly, the effects of sleep deprivation and caffeine are negatively correlated. A similar relationship between sleep loss- and caffeine-induced changes in the fronto-occipital power distribution is also present in the frequency range of the EEG slow oscillation (<1 Hz) in nonREM sleep. These findings demonstrate that in those subjects in whom prolonged waking induces the largest increase in a fronto-occipital power ratio in the EEG, caffeine most potently reduces this ratio in a state-specific manner in frequencies, which reliably reflect the physiological regulation of sleep.

Large inter-individual differences characterize not only sleep deprivation-induced changes in the waking and sleep EEG, but also in the vulnerability to behavioral impairment from sleep loss [96]. The psychomotor vigilance task (PVT) is highly sensitive to wakefulness-induced impairment of sustained vigilant attention [97]. Prolonged wakefulness impairs optimal PVT performance more in self-rated caffeine-sensitive than in caffeine-insensitive men [95]. Also this difference is counteracted by caffeine. In particular, the effects of sleep deprivation and caffeine are negatively associated. Taken together, these findings suggest that adenosinergic mechanisms contribute to individual differences not only in functional aspects of EEG topography, but also in waking-induced impairment of distinct neurobehavioral functions. This conclusion may not be generalized to other dimensions of neurobehavioral vulnerability, such as working memory or executive functions, because caffeine does apparently not mitigate more complex aspects of impaired cognitive performance during sleep deprivation [98].

10. Conclusions

Taken together, converging lines of evidence, including genetic and pharmacologic data, support a role for adenosinergic neurotransmission in homeostatic sleep–wake regulation in humans. Thus, a functional polymorphism in the adenosine metabolizing enzyme, ADA, contributes to the high inter-individual variability in sleep structure and nonREM sleep intensity. Moreover, the adenosine receptor antagonist, caffeine, potently attenuates the physiological EEG markers of nonREM sleep homeostasis during sleep, as well as during wakefulness. Finally, adenosinergic mechanisms modulate individual vulnerability to the detrimental effects of sleep loss on neurobehavioral performance, as well as disturbed sleep after caffeine consumption.

The exact biochemical mechanisms underlying the effects of adenosine on nonREM sleep homeostasis remain a hotly debated topic (for further discussion, see [99]). In humans, high densities of A_1 receptors are expressed in many brain areas such as cortex, thalamus, striatum and hippocampus [100,101]. Possibly consistent with a role for A_1 receptors in sleep homeostasis, sleep deprivation was recently reported to increase A_1 receptor occupancy throughout cortical and subcortical regions [101].

Another primary possibility for adenosine to modulate sleep and sleep–wake regulation under physiological conditions is via the A_{2A} receptor. A nonREM sleep-related reduction in regional cerebral blood flow is particularly strong in basal ganglia [102], a finding which might reflect the abundant expression of A_{2A} receptors in this brain region. A role for the A_{2A} receptor in nonREM sleep regulation may also be supported by studies in knock-out animals and the effects of caffeine. Nevertheless, it remains to be elucidated whether A_1, A_{2A}, or a combination of A_1 and A_{2A} receptors mediate the actions of caffeine on the sleep and waking EEG in humans. Moreover, to establish adenosine receptor-mediated neuromodulation as possible targets to treat sleep–wake related disorders, it will be essential to carefully study the basic effects on sleep and the sleep EEG of ADA inhibitors, as well as selective A_1 and A_{2A} receptor agonists and antagonists, as they might become available for clinical studies.

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