Received: 17 March 2022 | Accepted: 18 March 2022

DOI: 10.1111/jsr.13597

REVIEW ARTICLE

Adenosine, caffeine, and sleep–wake regulation: state of the science and perspectives

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Funding information
Gertrud Thalmann Fonds

Summary

For hundreds of years, mankind has been influencing its sleep and waking state through the adenosinergic system. For ~100 years now, systematic research has been performed, first started by testing the effects of different dosages of caffeine on sleep and waking behaviour. About 70 years ago, adenosine itself entered the picture as a possible ligand of the receptors where caffeine hooks on as an antagonist to reduce sleepiness. Since the scientific demonstration that this is indeed the case, progress has been fast. Today, adenosine is widely accepted as an endogenous sleep-regulatory substance. In this review, we discuss the current state of the science in model organisms and humans on the working mechanisms of adenosine and caffeine on sleep. We critically investigate the evidence for a direct involvement in sleep homeostatic mechanisms and whether the effects of caffeine on sleep differ between acute intake and chronic consumption. In addition, we review the more recent evidence that adenosine levels may also influence the functioning of the circadian clock and address the question of whether sleep homeostasis and the circadian clock may interact through adenosinergic signalling. In the final section, we discuss the perspectives of possible clinical applications of the accumulated knowledge over the last century that may improve sleep-related disorders. We conclude our review by highlighting some open questions that need to be answered, to better understand how adenosine and caffeine exactly regulate and influence sleep.

KEYWORDS
chronic caffeine, circadian, genetics, sleep deprivation, sleep homeostasis, sleep–wake disorder

1 | INTRODUCTION

Adenosine is widely accepted as an important sleep regulatory substance. Figure 1 illustrates a timeline of selected key discoveries in humans and animal models that accumulated over the last century providing evidence for a role of adenosine in sleep–wake regulation. The first scientific insights regarding this role date back to the years 1911/1912, when Harry Levi Hollingworth published a series of studies on behavioural effects of caffeine, including the quality of sleep. Hollingworth established for the first time a double-blind and placebo-controlled experimental design, which is the "gold standard" scientific

Carolin Franziska Reichert, Tom Deboer, and Hans-Peter Landolt contributed equally to this work.

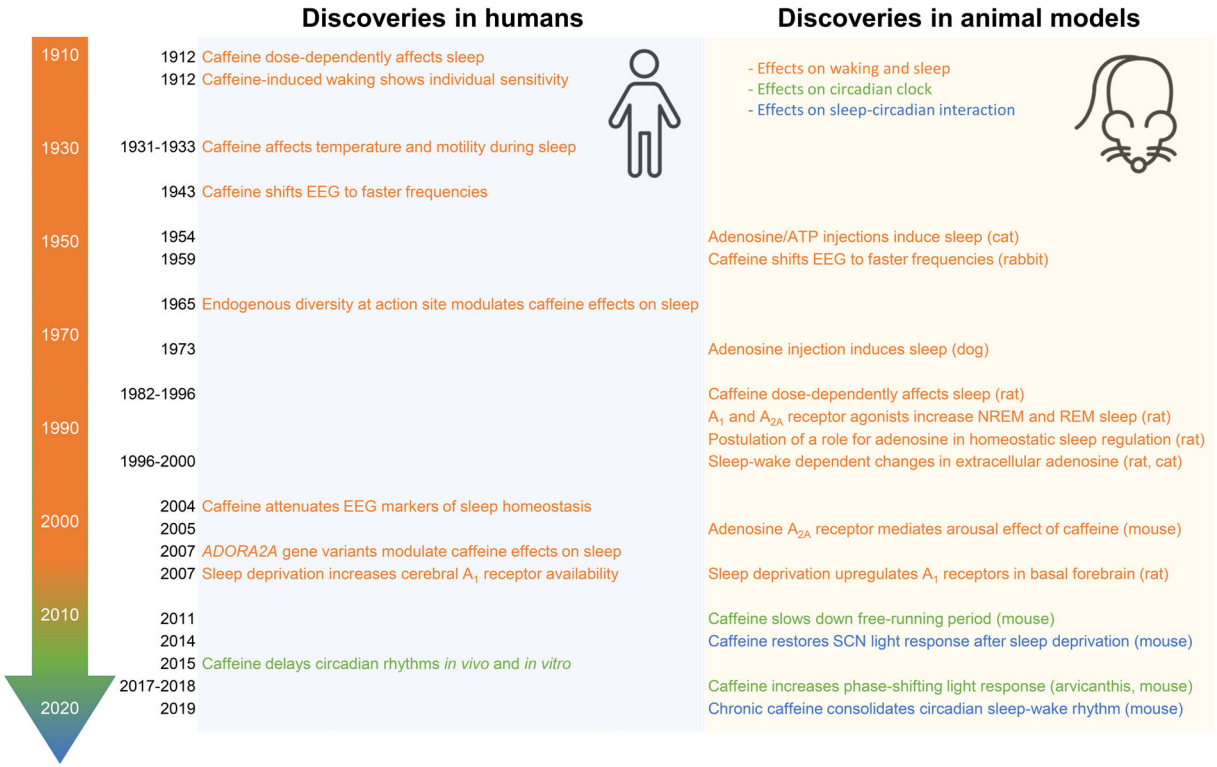

FIGURE 1 Timeline of sleep and circadian research discoveries demonstrating a role for adenosine in sleep–wake regulation (see text). ATP, adenosine triphosphate; EEG, electroencephalography; (N)REM, (non-) rapid eye movement

approach in pharmacology until today, and subjected 16 participants to 40 controlled "full-time" study days in a dedicated laboratory. Although he noticed large inter-individual differences in self-reported sleep impairments, he concluded that caffeine doses higher than "6 grains" disturb sleep in most participants (Hollingworth, 1912). Today we know that at the doses of habitual human consumption, the methylxanthines caffeine, theophylline, and paraxanthine act as adenosine receptor antagonists (Biaggioni et al., 1991), and that the trait-like individual differences in the effects of caffeine on sleep have a biological basis in genetic variants coding for adenosine receptors (Retey et al., 2007). Important insights following Hollingworth's pioneering work also included the early finding that caffeine accelerated brain electrical activity in humans and animals (Gibbs & Maltby, 1943; Krupp et al., 1959). On the contrary, brain administration of adenosine and adenosine triphosphate (ATP) in cats and dogs produced behavioural sleep (Feldberg & Sherwood, 1954; Haulica et al., 1973). Inspired by these early insights, and based on their own findings in rats that different adenosine analogues dose-dependently increased the durations of non-rapid-eye-movement (NREM) and rapid-eye-movement (REM) sleep, Radulovacki and colleagues were the first to suggest a role for adenosine in the regulation of sleep (Radulovacki, 1985; Radulovacki et al., 1984; Yanik & Radulovacki, 1987).

Support for this hypothesis came from the observations that extracellular adenosine levels in different brain areas in rats and cats tended to increase during wakefulness, decrease during sleep, and to be enhanced after prolonged wakefulness (Huston et al., 1996; Porkka-Heiskanen et al., 1997; Porkka-Heiskanen et al., 2000). Huston and co-workers suggested that "adenosine's sleep promoting effects result from its signaling to cease behavioral activity in order to prevent excessive activity related changes, and thus allow other restorative sleep-related processes to take over" (Huston et al., 1996). The link between the actions of adenosine and electroencephalography (EEG) markers of sleep homeostasis was made through experiments, in which a remarkable similarity between the sleep EEG responses to adenosine analogues and the sleep EEG spectral profile after prolonged wakefulness was noted (Benington et al., 1995; Porkka-Heiskanen et al., 1997; Schwierin et al., 1996). By contrast, in both rats and humans, caffeine attenuated EEG markers of sleep homeostasis after sleep deprivation in wakefulness and sleep (Landolt et al., 2004; Schwierin et al., 1996). Taken together, convergent evidence in animals and humans supported a role for adenosine and its receptors in sleep homeostasis.

More recent experiments indicated that adenosine may also affect the circadian clock and the interaction between the circadian clock and sleep homeostatic mechanisms. In humans, ~200 mg caffeine ingested in the early evening delayed the endogenous melatonin rhythm by roughly 40 min, nearly half of the delay caused by bright light exposure at bedtime (Burke et al., 2015). Convergent pharmacological, genetic, and immunochemical data in vitro suggested that these effects were mediated by an A_1 receptor-, cAMP-dependent mechanism (Burke et al., 2015). In mice, the period of rest–activity in constant conditions became longer, suggesting that the clock slows

down under the influence of caffeine (Oike et al., 2011; Ruby et al., 2018; van Diepen et al., 2014). Thus, caffeine possibly also affects sleep through changes in circadian clock functioning.

Here, we aim at reviewing the current state of the science on the role of adenosine in sleep–wake regulation. More specifically, we addressed the following questions: does adenosine provide important feedback signals to the homeostatic and circadian facets of sleep–wake regulation; does caffeine interfere with sleep–wake regulation, and are the effects of caffeine on different sleep variables mediated by specific subtypes of adenosine receptors; does acute and chronic caffeine intake differently affect sleep measures; does genetic variation in the adenosinergic system contribute to individual variation in sleep–wake phenotypes; and, does the adenosine neuromodulatory system provide a promising possible target to ameliorate sleep–wake disturbances and sleep-associated disorders. We conclude the narrative review by offering our perspectives on important open questions that could shape a future research agenda, to further establish the exact roles of adenosine in sleep–wake regulation.

2 | ADENOSINE ORIGIN, TRANSPORT, AND METABOLISM

The intra- and extracellular concentrations of adenosine are tightly controlled by complex regulatory processes that depend on the metabolic state of both neurones and astrocytes. Specific enzymes and transporters catalyse the formation and the breakdown of adenosine from and to ATP (via adenosine diphosphate [ADP] and adenosine monophosphate [AMP]) and S-adenosylhomocysteine and control the release into and the uptake of these molecules from the extracellular space. The major source of extracellular adenosine is the catalytic product of 5′-ecto-nucleotidases (5′-ENs) that degrade adenine nucleotides (ATP) released together with glutamate to adenosine. The release of ATP and glutamate from activated astrocytes has been referred to as "gliotransmission" and is triggered by astroglial Ca^{2+} signals in proportion to sleep need (Ingiosi et al., 2020). Adenosine kinase (AdK) effectively controls the intra- and extracellular adenosine concentration by phosphorylating adenosine to AMP. High extracellular adenosine levels are also reduced by adenosine deaminase (ADA) or taken up into the intracellular compartment by bi-directional equilibrative nucleoside transporters (ENTs 1–4). The ADA irreversibly breaks down adenosine to inosine and plays an important role in removing physiologically elevated adenosine concentrations such as after sleep deprivation (Borea et al., 2018). Under conditions of raised adenosine levels, the ENTs also have an important role in regulating the extracellular adenosine concentration (Borea et al., 2018). Thus, the availability of adenosine at the site of its receptors on the cell surface is regulated by complex biological processes of adenosine formation and removal (Figure 2).

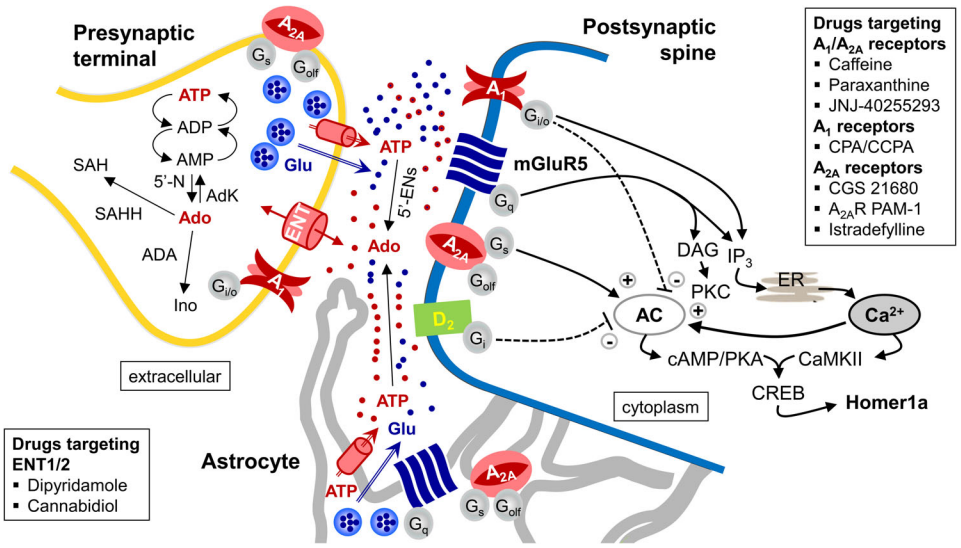

FIGURE 2 Simplified schematic representation of adenosine formation, transport and metabolism in a hypothetical tripartite synapse consisting of a presynaptic terminal, a postsynaptic spine, and an astrocyte. Only selected processes and pathways mentioned in the text are shown (please see text for more detailed information). Neurones, astrocytes, and microglia can release adenosine and adenosine triphosphate (ATP). The unique co-localisation and functional interactions among the G-protein coupled adenosine (red), dopamine (green) and metabotropic glutamate receptors (blue) on striato-pallidal neurones and circuits suggest a hypothesised integration of adenosine-dopamine-glutamate signalling and synaptic plasticity. 5′-ENs, 5′-ecto-nucleotidases; 5′-N, 5′-nucleotidase; A_1, A_{2A}, adenosine A_1 and A_{2A} receptors; AC, adenylyl cyclase; ADA, adenosine deaminase; AdK, adenosine kinase; Ado, adenosine (red dots); ADP, adenosine diphosphate; AMP, adenosine monophosphate; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; cAMP, cyclic adenosine monophosphate; CCPA, 2-chloro-N^6-cyclopentyladenosine; CPA, N^6-cyclopentyladenosine; CREB, cAMP responsive element binding protein; D_2, dopamine D_2 receptor; DAG, diacylglycerol; EEG, electroencephalography; ENT, equilibrative nucleoside transporters; ER, endoplasmic reticulum; Glu, glutamate (blue dots); Ino, inosine; IP_3, inositol-tri-phosphate; mGluR5, metabotropic glutamate receptor of subtype-5; PKC, PKA, protein kinase C and A; SAH, S-adenosyl-homocysteine; SAHH, S-adenosyl-homocysteine hydrolase

3 | DOES ADENOSINE PROVIDE A NEUROCHEMICAL FEEDBACK SIGNAL FOR SLEEP HOMEOSTASIS?

Adenosine is a breakdown product of the depletion of ATP in the brain. The ATP levels in wake-active brain regions in rats are elevated during spontaneous sleep and reduced during sleep deprivation (Dworak et al., 2010). After prolonged neuronal activity during wakefulness, ATP accumulates in the extracellular space and is degraded by 5′-EN to adenosine (Blutstein & Haydon, 2013; Dunwiddie et al., 1997). Adenosine is thought to increase in the extracellular space in the course of prolonged waking, and has been proposed as a homeostatic accumulator of the need to sleep (Benington & Heller, 1995; Brown et al., 2012; Landolt, 2008). Some authors suggested that particularly the level of adenosine in the basal forebrain is important for sleep–wake regulation (Porkka-Heiskanen et al., 1997; Porkka-Heiskanen et al., 2000). In several regions of the brain, stimulation of adenosine A_1 receptors depresses glutamate release, reducing the amplitude of postsynaptic currents (Barrie & Nicholls, 1993; Dolphin & Prestwich, 1985; Oliet & Poulain, 1999). The accumulation of adenosine, but also other sleep promoting substances (Krueger et al., 2008), may therefore reduce the activity of wake promoting areas and, in this way, disinhibit sleep promoting areas. Among the four different subclasses of adenosine receptors (A_1, A_{2A}, A_{2B}, and A_3 receptors), not only the A_1 receptor but also the A_{2A} receptor appears to be important for sleep–wake control (Lazarus et al., 2019). Both, pharmacological stimulation of A_1 and A_{2A} receptors with specific agonists increases slow-wave sleep and EEG slow-wave activity (SWA; spectral power in the ~1–4 Hz range) in NREM sleep (Benington et al., 1995; Satoh et al., 1996; Scammell et al., 2001; Schwierin et al., 1996).

In the conceptual framework of the two-process model, EEG slow-waves in NREM sleep are thought to reflect sleep homeostatic mechanisms (Borbely, 1982; Borbely et al., 2016; Daan et al., 1984). A central role of adenosine in homeostatic sleep regulation would suggest that adenosine must show a daily modulation, in parallel with the daily changes in NREM sleep EEG power density in the slow-wave range. The changes in EEG SWA are relatively slow, involving many hours of slow increase during the main waking period and an almost equally slow decreasing process during the main sleep period, independent of the species investigated (Deboer, 2015; Huber et al., 2000). Therefore, it may be expected that adenosine shows a daily modulation with similar time constants. However, the experimental results until now do not support this slow kinetics in adenosine levels. Based on data obtained from brain sampling and microdialysis in rats, it seems that at the transition from the rest to the active phase there is an abrupt increase in adenosine, in parallel with the abrupt change in the amount of sleep and waking. But during the subsequent consolidation of increased waking in the course of the active phase, no further rise in adenosine is observed (Chagoya de Sanchez et al., 1993; Murillo-Rodriguez et al., 2004). The opposite is true at the start of the rest phase. At that moment an acute reduction in adenosine is seen, followed by a consolidation of this level throughout the rest phase. The shape of the curve resembles a square wave with a period of 24 h, whereas a triangle wave, with a peak at the onset of the rest phase and a through at the end, would be expected on the basis of the shape of the changes in EEG SWA. Recently it became possible to monitor adenosine levels in the mouse brain at a time resolution of seconds (Peng et al., 2020). The data confirmed the findings obtained with microdialysis and show that the time constant of changes in adenosine, in response to changes in vigilance states, lies in the order of minutes rather than hours. This can result in higher levels of adenosine during periods of increased waking and lower levels during rest/sleep. However, the observed kinetics suggest that extracellular adenosine is unlikely responsible for the diurnal changes in sleepiness and sleep pressure observed under undisturbed baseline conditions. Notwithstanding, adenosine may still play a role when waking is prolonged beyond the normal daily duration and add to increased sleep pressure and EEG slow waves under those conditions.

4 | DOES CAFFEINE INTERFERE WITH SLEEP HOMEOSTASIS?

4.1 | Effects of acute caffeine administration on sleep

Caffeine is a potent adenosine receptor antagonist with roughly equally high affinity for both A_1 and A_{2A} receptors. Work in mice provided strong evidence that caffeine promotes wakefulness primarily by blocking the A_{2A} subtype of adenosine receptors (Huang et al., 2005). While caffeine (at a dose of 15 mg/kg) failed to disrupt sleep in mice with genetically-abolished A_{2A} receptor function, the stimulant promoted wakefulness in wild-type mice as well as in transgenic mice without functional A_1 receptors. Subsequent experiments revealed that specifically the genetic deletion of A_{2A} receptors in the shell of the nucleus accumbens blocked caffeine-induced wakefulness (Lazarus et al., 2011).

Research in humans typically relied on the study of caffeine, to investigate the role of adenosine on sleep homeostasis. Polysomnographic measures of sleep latency were consistently prolonged (Brezinova, 1974; Drapeau et al., 2006; Karacan et al., 1976; Landolt, Dijk, et al., 1995; Okuma et al., 1982; Paterson et al., 2009; Robillard et al., 2015; Youngstedt et al., 2000) and sleep efficiency was reduced (Bonnet & Arand, 2003; Drapeau et al., 2006; Karacan et al., 1976; Landolt, Dijk, et al., 1995; Okuma et al., 1982; Paterson et al., 2009; Robillard et al., 2015) when caffeine was administered in the evening close to bedtime. Several studies also showed reduced SWA and increased activity in the frequency range of sleep spindles (~12–15 Hz; sigma range) (Drapeau et al., 2006; Landolt, Dijk, et al., 1995; Robillard et al., 2015) even after long periods of wakefulness (Carrier et al., 2009; Landolt et al., 2004; Landolt, Werth, et al., 1995). Significant reductions in the SWA range were, however, in some cases restricted to a single bin (Landolt, Werth, et al., 1995; Robillard et al., 2015), only detectable in the first NREM sleep episode (Carrier et al., 2009), or even absent (Paterson et al., 2009). Additionally, it has

not been elucidated whether adenosine receptor antagonism with caffeine affects the time course of the SWA decline during night-time sleep. To our knowledge, there exists at present no evidence to suggest a compensatory mechanism in the EEG within one sleep episode after caffeine ingestion (such as a SWA rebound in the second or third sleep cycle compensating for a caffeine-induced SWA reduction in the first sleep cycle or data suggesting caffeine-induced SWA differences at the end of night-time sleep). It remains to be tested if we can assume that baseline levels of sleep pressure at the start of the next waking episode are independent of prior evening caffeine intake. In this case, a homeostatic decrease of sleep pressure or sleep need could take place, probably independent of caffeine-induced adenosine antagonism and even if caffeine hampers the expression of SWA at the beginning of night-time sleep.

4.2 | Effects of chronic caffeine administration on sleep

During daily intake of caffeine the situation changes. As summarised in Figure 3, the continuous presence of caffeine and its main metabolite paraxanthine most likely trigger changes in the adenosine system, which may in turn affect sleep. Investigating the effects of regular daily intake in humans is challenging, because it is still unclear for how

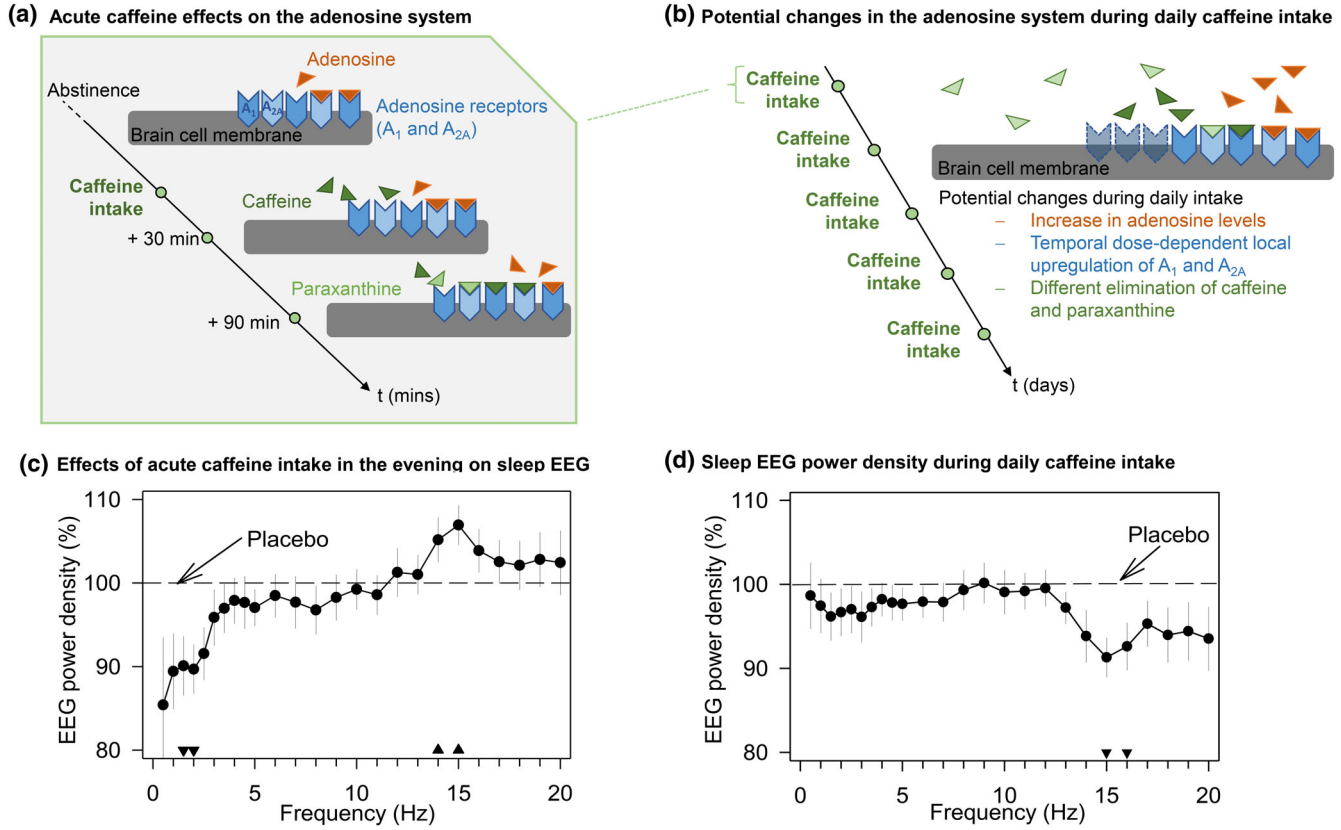

FIGURE 3 Simplified illustration of the impact of caffeine intake in the brain. (a) Approximately 30 min after oral intake, caffeine reaches the central nervous system and blocks adenosine A_1 and A_{2A} receptors. There is evidence in the animal domain that caffeine's main metabolite paraxanthine has similar affinity as caffeine (Snyder et al., 1981) to both receptors (Chou & Vickroy, 2003) and disturbs NREM sleep (Okuro et al., 2010). Beside caffeine itself, paraxanthine may therefore contribute to the wake-promoting potential. (b) Typical reduction of SWA and increased sigma frequency activity in NREM sleep after acute caffeine intake (data from Landolt, Dijk, et al., 1995). Black triangles denote frequency bins in which power density after caffeine intake significantly differed from placebo ($p < 0.05$, paired t tests). (c) during daily repeated caffeine intake, the adenosine system may adapt to the daily presence of the stimulant. Animal studies suggest that plasma adenosine levels rise during daily intake (Conlay et al., 1997). Additionally, some studies suggest an upregulation in A_1 receptors (Boulenger & Marangos, 1989; Ramkumar et al., 1988; Shi et al., 1993; but also see Espinosa et al., 2013; Johansson et al., 1996; Johansson et al., 1997; Nabbi-Schroeter et al., 2018). To our knowledge, an upregulation of A_{2A} receptors has not been observed (Espinosa et al., 2013; Johansson et al., 1996; Shi et al., 1993). The effects of regular caffeine consumption on its own metabolism are controversial and need to be further investigated. The available studies reported either no influence on, stimulation or inhibition of caffeine pharmacokinetic measures by chronic caffeine intake (Nehlig, 2018). We hypothesise that both pharmacodynamic and pharmacokinetic changes could underlie the different effects of caffeine on the sleep EEG during daily (versus acute) intake of the stimulant. (d) NREM sleep EEG SWA in human volunteers was not significantly reduced during daily caffeine intake, whereas sigma activity was lower compared to placebo intake (data from Weibel et al., 2021; statistics adapted regarding conditions). Black triangles indicate frequency bins in which paired t tests revealed a significant difference between caffeine and placebo ($p < 0.05$, paired t tests). EEG, electroencephalography; (N)REM, (non-) rapid eye movement; SWA, slow-wave activity

long an individual must abstain from caffeine to reach a state that is no longer confounded by the prior intake (James, 2014). On the other hand, comparing habitual consumers with non-consumers may be biased by group differences such as differences in caffeine sensitivity and associated genetic variants in the adenosine system (Retey et al., 2007). The currently available evidence indicates that sleep latency and efficiency during night-time sleep adapt to daily caffeine intake in humans (Bonnet & Arand, 1992; Weibel et al., 2021). Sleep in cats under chronic caffeine was shown to normalise in the course of several days after an initial acute increase in waking, but the amount of the deepest stage of sleep remained lower than during baseline (Sinton & Petitjean, 1989). In humans, EEG activity in the SWA range during night-time sleep did not differ after 9 days of caffeine intake (3 × 150 mg/day) when compared to placebo intake for the same duration (Weibel et al., 2021). Similarly, chronic caffeine intake in adult mice, but not in pubertal rats (Olini et al., 2013), did not elicit clear-cut differences in NREM sleep SWA compared to a control condition (Panagiotou et al., 2019). Surprisingly, chronic caffeine ingestion even induced a higher percentage of NREM sleep during the rest phase of the animals (Panagiotou et al., 2019). Together, the findings indicate that sleep SWA, the classical marker of sleep homeostasis, is not chronically altered during daily caffeine intake. Sleep homeostasis most likely preserves its functions over longer periods of adenosine antagonism. Still, the daily presence of caffeine and metabolites alters sleep EEG power density in other frequency ranges (Panagiotou et al., 2019; Weibel et al., 2021), suggesting that the continuous presence of an adenosine antagonist affects sleep apart from a clear-cut sleep-homeostatic effect. Given the observation that an adaptation to daily caffeine was not observed when sleep was scheduled at the wrong circadian phase, such as after an eastward transmeridian travel (Beaumont et al., 2004), further indicates that caffeine affects sleep not only by acting on the homeostatic facet of sleep–wake regulation.

The normalisation in the course of the chronic consumption could be caused by changes in sensitivity or tolerance to caffeine (Bhorkar et al., 2014; Bonnet & Arand, 1992; Dall'Igna et al., 2003; Dubroqua et al., 2014; Sinton & Petitjean, 1989). As illustrated in Figure 3, changes in adenosine levels or adenosine receptors could contribute to the observed adaptive effects. It has been shown in rats that adenosine levels were increased under chronic caffeine conditions (Conlay et al., 1997). Furthermore, chronic caffeine administration increased the number of adenosine receptors in rats and mice (Boulenger et al., 1983; reviewed by Nehlig et al., 1992). In a recent mouse study, the mice stopped drinking at the start of the rest phase (Panagiotou et al., 2019). When subsequently the absorbed caffeine is cleared from the system relatively fast, this would markedly decrease the caffeine availability. If adenosine and/or its receptors are increased under the influence of chronic caffeine in mice, this reduction in caffeine would enable the physiological expression of the available adenosine. This then may explain the increased sleep and EEG SWA after the start of the light period.

Similar to the state of research in animals, the extent of tolerance development is still controversial and not clearly established also in humans (Roehrs & Roth, 2008). A complicating factor in humans is that, in contrast to the experimental protocols used in animals, humans have the possibility to switch to an alternative beverage and to avoid being exposed to caffeine, when adverse effects of caffeine on behaviour or sleep are experienced. Therefore, physiological information on the effects of chronic caffeine on sleep likely stems from individuals who tolerate caffeine relatively well. Nevertheless, epidemiological studies support the idea that increased caffeine use is associated with less sleep or more disturbed sleep, also when caffeine is used chronically (Clark & Landolt, 2017; Roehrs & Roth, 2008).

4.3 | Effects of caffeine on subjective sleepiness

Differences between acute and chronic caffeine intake have also been observed on self-reported sleepiness. Depending on the duration of prior abstinence and the actual sleep pressure level, caffeine can reduce subjective estimates of sleepiness. These effects are particularly prominent when caffeine administration occurs after >24 h of abstinence and when sleep pressure is high (i.e., during sleep deprivation or after sleep restriction) (Aggarwal et al., 2011; Beaumont et al., 2001; Dagan & Doljansky, 2006; Hansen et al., 2019; Killgore et al., 2006; Killgore et al., 2012; Killgore & Kamimori, 2020; Kohler et al., 2006; Landolt et al., 2004; Lieberman et al., 2002; Paech et al., 2016; Patat et al., 2000; Penetar et al., 1993; Wright, Badia, Myers, & Plenzler, 1997). When abstinence is <24 h, caffeine has still the potential to elicit feelings of improved alertness, but mainly under conditions of unusually high sleep pressure (Biggs et al., 2007; De Valck et al., 2003; De Valck & Cluydts, 2001; Reyner & Horne, 2000; but see Lohi et al., 2007) and not under normal sleep–wake conditions (Bragg et al., 2017; Kim et al., 2013; Lane, 1994; but see Hammami et al., 2010). Consistent therewith, self-reported caffeine consumption during "typical days" (Chaudhary et al., 2016) was not associated with daytime sleepiness in a representative sample (Chaudhary et al., 2016). However, it is important to note that an extra dose of caffeine during regular intake and normal sleep–wake conditions can still induce an acute reduction of subjective sleepiness (Adan et al., 2008; Hayashi et al., 2003; Mets et al., 2012; Rogers et al., 2013). Taken together, the current evidence suggests that caffeine can reduce subjective sleepiness particularly under conditions, which do not regularly occur and where the adenosine system is not accustomed to. Otherwise, the system most likely adapts to regular intake, such that the psychostimulant cannot elicit strong net effects in subjective sleepiness after a certain phase of daily consumption.

Accordingly, when caffeine intake was allowed before sleep deprivation (Erblang et al., 2021; Hartley et al., 2013; Walsh et al., 1990) or given over several days (Ataka et al., 2008; Beaumont et al., 2004; James, 1998; Weibel et al., 2020), caffeine did not significantly change subjective sleepiness compared to placebo. Similarly, caffeine intake over several days of sleep restriction did not clearly mitigate increased feelings of sleepiness or reduced vigour (Baur et al., 2020; Doty et al., 2017; James & Gregg, 2004) nor continuously reduced sleepiness across consecutive simulated night shifts (Schweitzer

et al., 2006). There exists even empirical evidence for higher sleepiness during daily caffeine intake (Bonnet & Arand, 1992; James & Gregg, 2004; Wyatt et al., 2004), a phenomenon which echoes early clinical case reports of pathological sleepiness during excessive caffeine use (Regestein, 1989). As outlined above, we cannot readily explain these apparently paradoxical effects with caffeine-induced sleep disturbances, because sleep appears to adapt to regular intake over time. As unintentional sleep onsets during long periods of scheduled wakefulness were reduced during chronic caffeine intake (Wyatt et al., 2004), a higher sleepiness in these participants may be related to the reduced probability to decrease sleep pressure during short periods of unintentional sleep. Alternatively, the higher sleepiness during chronic intake may mirror a state of withdrawal, which regularly comes to light within the 24-h cycle, most likely dependent on the pattern of consumption and the individual speed of metabolism. It may reflect a compensatory mechanism of adaptation within the adenosine neuromodulatory system to the sustained presence of an adenosine receptor antagonist.

5 | DOES ADENOSINE INFLUENCE CIRCADIAN CLOCK FUNCTIONING?

The central circadian pacemaker, located in the suprachiasmatic nuclei (SCN) of the hypothalamus is the main regulator of daily changes in physiology and behaviour, including sleep. Light is the most powerful synchroniser of the circadian clock. Light information reaches the SCN through the retino-hypothalamic tract (Vansteensel et al., 2008), which releases glutamate at its nerve terminals (Ding et al., 1994; Johnson et al., 1988). The glutamate release leads to increased neuronal activity in the SCN (Meijer et al., 1998; van Diepen et al., 2013; van Diepen et al., 2014; van Diepen et al., 2021). The application of glutamate to the SCN mimics this effect (Ding et al., 1994). Next to serotonin, adenosine is an obvious candidate that may influence SCN neuronal activity (Deboer, 2018). Adenosine is known to increase during prolonged waking (Porkka-Heiskanen et al., 1997; Porkka-Heiskanen et al., 2000) and generally induces a suppression of neuronal activity. Within the SCN, adenosine acts on the light-receiving ventro-lateral area and inhibits retino-hypothalamic tract activity. Stimulation of A_1 receptors inhibits excitatory synaptic transmission by blocking the intracellular build-up of Ca^{2+} (Chen et al., 1997; Hallworth et al., 2002). In accordance with this, on the behavioural level, application of an adenosine agonist attenuates light-induced phase shifts. This attenuation can, in the same experiment, be reversed by an A_1 receptor antagonist (Elliott et al., 2001; Sigworth & Rea, 2003).

Neuronal activity in the SCN can be recorded in vivo with electrophysiological techniques. The data obtained with these techniques show that in constant darkness, the electrical spiking activity of the SCN neurones is high during the subjective day and low during the subjective night, both in diurnal and nocturnal animals (Vansteensel et al., 2008). In addition, neuronal activity in the SCN increases when the eyes of the animals are exposed to light. This neuronal activity is enhanced for the duration of the light pulse (Meijer et al., 1998; van Diepen et al., 2014). When SCN neuronal activity is recorded simultaneously with EEG and electromyography, it was shown in rats that SCN neuronal activity depends on the vigilance state. The activity increases during waking and REM sleep and decreases during NREM sleep (Deboer et al., 2003) The ultradian changes across the vigilance states are visible on top of the circadian modulation of SCN neuronal activity.

Several experimental results have been published showing an interactive effect of sleep deprivation and caffeine on the functioning of the central circadian pacemaker. Sleep deprivation led to lower SCN neuronal activity compared to baseline sleep, reducing its circadian amplitude. In parallel to the decrease in EEG SWA in NREM sleep, SCN neuronal activity gradually returned to baseline values in the course of recovery sleep (Deboer et al., 2007) (Figure 4, middle panel). The results suggest that there is a negative relationship between SCN electrical neuronal activity and depth of sleep or sleep homeostatic pressure. There is evidence that this negative relationship also exists in humans. The SCN is small and difficult to investigate in humans, however, it has been shown that the functional magnetic resonance imaging (fMRI) blood-oxygen-level-dependent (BOLD) signal in humans, recorded during a psychomotor vigilance test, declined in the area around the SCN in individuals with higher sleep pressure (Schmidt et al., 2009). This change in the BOLD signal, measured in the evening, correlated with SWA in the first nocturnal NREM sleep episode preceding that measurement. Thus, the circadian pacemaker in the SCN is able to obtain feedback on the status of homeostatic sleep pressure, in a way that increased pressure reduces SCN neuronal activity and the circadian amplitude of the output of the SCN. Moreover, a 6-h sleep deprivation reduced the electrophysiological responses of increased neuronal activity to light in the SCN. Given that caffeine was able to restore these responses (van Diepen et al., 2014), increased adenosine during sleep deprivation may be the working mechanism through which sleep deprivation changes circadian clock responses. This hypothesis is in accordance with experiments in several different species showing that phase shifts in rest–activity rhythms in response to light were reduced after sleep deprivation (Burgess, 2010; Challet et al., 2001; Mistlberger et al., 1997; van Diepen et al., 2014). On the other hand, caffeine treatment increased the phase shifting response to light (Jha et al., 2017; Ruby et al., 2018) (Figure 4, right panel). In contrast, the electroretinogram does not change after sleep deprivation (Schoonderwoerd et al., 2022) (Figure 4, left panel). Although this does not represent all the possible responses to light in the retina, it makes it unlikely that the reduction in phase-shifting responses is caused by changes in the processing of light information by the eye.

Therefore, sleep deprivation may reduce the phase-shifting capacity of the circadian pacemaker by diminishing the strength of the photic signal from the retino-hypothalamic tract, through blocking of glutamate release. The inhibition is reduced by caffeine and therefore probably caused by an adenosinergic mechanism. The conclusion would be that sleep homeostatic pressure due to increased waking is translated into increased adenosine levels in the SCN, which reduces the light responsiveness of the circadian clock in mammals on the input side of the circadian clock. It may therefore be that adenosine is part of the mechanism through which sleep homeostatic mechanisms influence circadian clock functioning (Deboer, 2018).

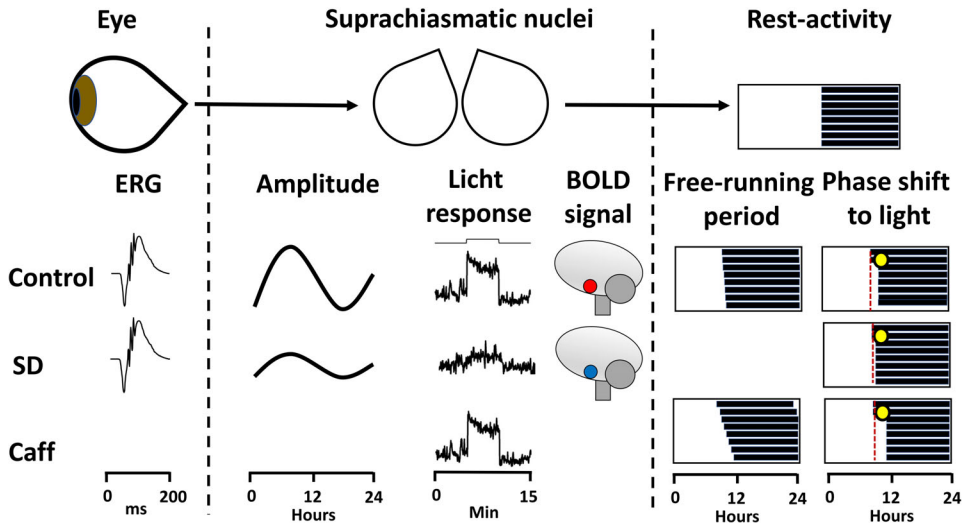

FIGURE 4 Effects of sleep deprivation (SD) and caffeine (Caff) treatment on input pathways, the suprachiasmatic nuclei (SCN) and behavioural functions. The SD does not change the electroretinogram (ERG, left panel) (Schoonderwoerd et al., 2022). In the SCN (middle panel, van Diepen et al., 2014), SD reduces the amplitude of the circadian modulation of SCN neuronal activity (Deboer et al., 2007) and the light-induced increase in firing rate in SCN neurones (van Diepen et al., 2014). The latter can be reversed by Caff treatment (van Diepen et al., 2014). In humans, higher slow-wave activity (SWA) in the beginning of the night predicts a lower functional magnetic resonance imaging (fMRI) blood-oxygen-level-dependent (BOLD) response in an SCN encompassing region during task performance in the evening (Schmidt et al., 2009). On the output side, when analysing rest-activity behaviour (right, here of a night-active animal), SD in most cases, reduces light induced behavioural phase shifts (Burgess, 2010; Challet et al., 2001; Mistlberger et al., 1997; van Diepen et al., 2014). An exception to this was suggested to indicate a difference between diurnal and nocturnal animals (Jha et al., 2017). Caff treatment increases the phase-shift response to light particularly at the end of the active phase (Jha et al., 2017; Ruby et al., 2018). In addition, Caff seems to slow down the circadian clock (Burke et al., 2015; Oike et al., 2011; Ruby et al., 2018; van Diepen et al., 2014) in both diurnal and nocturnal animals. This is also the case in vitro (Burke et al., 2015; Oike et al., 2011) and mirrored in humans after acute Caff intake in the evening by a phase-delay of the dim-light melatonin onset (Burke et al., 2015) and during daily caffeine intake by a later bedtime when compared to placebo (Weibel et al., 2021)

Despite this clear influence of previous waking duration and adenosine on the phase-shifting capacity of the circadian clock, there are no data showing that expression of clock genes in the SCN changes under influence of sleep deprivation, but the data available are limited to one single circadian time point (Curie et al., 2015). This is supported by the finding that sleep deprivation alone hardly induces phase shifts of the circadian clock in rodents (Challet et al., 2001; Mistlberger et al., 2003; van Diepen et al., 2014). Also the amplitude of output markers of the circadian clock in humans, like melatonin release or core body temperature do not change under the influence of increased sleep pressure (e.g., Birchler-Pedross et al., 2009; Krauchi et al., 2006), but the sleep pressure induced may not be strong enough. Therefore, at the moment, the data indicate that the influence of increased adenosine on the central circadian pacemaker may be limited to clock input, the amplitude of part of the output, and the response to phase-shifting zeitgebers. On the other hand, adenosine may not influence the expression of core clock genes and the phase or period of the circadian clock. To investigate this further, sleep deprivation experiments in combination with clock gene expression in the SCN should be broadened to include different circadian time points. In addition, sleep deprivation experiments in humans should be extended to longer periods, measuring melatonin and body temperature, the typical "hands of the clock" measured in human subjects, to investigate this question further.

6 | DOES CAFFEINE INFLUENCE CIRCADIAN CLOCK FUNCTIONING?

As mentioned above, acute caffeine administration can increase the phase-shifting response to light in animals (Jha et al., 2017; Ruby et al., 2018). However, evidence on its potential to shift timing or change amplitude of the circadian clock *independently of light* is weak. In animals, timing of rest–activity after caffeine treatment did not differ from placebo during constant darkness (Jha et al., 2017). In humans, acute caffeine administration under dim-light delayed the dim-light melatonin onset (DLMO) (Burke et al., 2015). Melatonin levels (Wright et al., 2000; Wright, Badia, Myers, Plenzler, & Hakel, 1997) or the course of core body temperature (Wright, Badia, Myers, Plenzler, & Hakel, 1997) during 1 night of sleep deprivation were not significantly affected by acute evening caffeine treatment under dim-light conditions. To conclude, any pure circadian effects independent of light cannot be substantiated, as such studies need to be conducted in constant darkness, which is difficult in humans. Therefore, we cannot exclude thus far that the putative effects of caffeine observed under dim light in humans are still due to a caffeine-induced increase of the circadian response to light.

In real life, caffeine is usually consumed as a chronic stimulant. However, studies on the effects of chronic use of caffeine on circadian output markers are rare. Under chronic intake, the caffeine-

induced potentiation of photic phase delays in mice seems to be preserved (Ruby et al., 2018). Additionally, there is evidence that activity during the rest phase of the animals is reduced during chronic caffeine intake as compared to baseline (Ruby et al., 2018). This is in accordance with a study by Panagiotou et al. (2019), in which chronic caffeine increased the day-night amplitude of sleep and waking. The mice slept more and deeper, with increased EEG SWA and higher waking thresholds during the rest phase and were more awake and possibly more alert during their active phase. In humans, an indication for a stronger circadian wake- (but not sleep-) promoting signal during chronic intake was shown in a forced desynchrony protocol (Wyatt et al., 2004), in which participants underwent several cycles of roughly 28-h waking episodes in dim light, followed by ~14-h sleep episodes in darkness. During the biological night, sleep efficiency reached on average >90% in both the caffeine and the placebo group. During the biological day, sleep efficiency was reduced during chronic caffeine compared to placebo, specifically when sleep was scheduled at the end of the biological day when the circadian drive for wakefulness is at its maximum (i.e., during the so-called wake maintenance zone). This finding could, however, not be replicated in a protocol, in which the distance between caffeine intake and start of the wake maintenance zone was considerably longer, the sleep opportunity shorter, and in which circadian and sleep-homeostatic components could not be disentangled (Weibel et al., 2020). Interestingly, in contrast to the studies on acute caffeine intake mentioned earlier (Burke et al., 2015; Wright et al., 2000; Wright, Badia, Myers, Plenzler, & Hakel, 1997), neither Wyatt et al. (2004) nor Weibel et al. (2020) reported any significant changes in melatonin profiles during chronic caffeine intake. This may be due to an adaptation of the adenosine system or to a difference in the timing of intake or both.

In summary, there is currently no evidence supporting that caffeine per se (i.e., in the absence of any environmental light) affects the circadian clockwork. This is in accordance with case reports, in which caffeine treatment in the morning did not successfully entrain three totally blind patients (St Hilaire & Lockley, 2015). Caffeine effects on circadian timing under dim- or bright-light exposure need to be replicated and investigated under conditions of daily intake. Similarly, a potential strengthening of the circadian amplitude during chronic caffeine intake may open up possible routes for clinical applications, which aim to enhance circadian amplitude.

7 | GENETIC VARIATION IN THE ADENOSINERGIC SYSTEM AND SLEEP–WAKE PHENOTYPES

7.1 | Adenosine receptors

Adenosine is generally thought to contribute to sleep–wake regulation by binding to high-affinity A_1 and A_{2A} receptors, which are differently expressed in different brain areas and may play distinct roles in the regulation and the control of sleep. Surprisingly and apparently challenging the notion that A_1 binding sites contribute to sleep homeostasis, mice exhibiting constitutive and central nervous system specific, conditional ablation of A_1 receptors showed virtually unaltered sleep–wake behaviour and cognitive functions when studied under baseline sleep–wake conditions (Bjorness et al., 2009; Stenberg et al., 2003). Nevertheless, when the conditional knock-out animals were subjected to prolonged wakefulness, their working memory was impaired and they did not extend their sleep nor showed a normal rebound in EEG SWA in recovery sleep after the sleep deprivation (Bjorness et al., 2009). Similarly, early studies suggested that a constitutive knock-out of A_{2A} receptors may eliminate the homeostatic regulation of NREM sleep (Hayaishi et al., 2004). The findings of more recent work in genetically engineered mice, however, suggest a partly refined interpretation. More specifically, the chemogenetic or optogenetic activation of A_{2A} receptor expressing cells of the nucleus accumbens strongly induced slow-wave sleep, yet this intervention did not affect the sleep rebound after sleep deprivation (Oishi et al., 2017). There is a need for additional studies to clarify whether A_1 receptors contribute to the sleep homeostatic feedback signal and A_{2A} receptors provide sleep gating and modulate behavioural sleepiness without controlling sleep homeostasis as suggested on the basis of these insights from genetically modified mice (Lazarus et al., 2019).

In humans, no study has investigated the impact of functional variants of the A_1 receptor gene on the sleep EEG. With respect to the A_{2A} receptor gene (*ADORA2A*), the common variant rs5751876 was reported to modulate the EEG in both NREM and REM sleep. In a small case–control sample, EEG alpha activity (~7–10 Hz range) was invariably higher in C/C compared to T/T genotype carriers (Retey et al., 2005). More recent, larger studies confirmed this association (Tiechelmann et al., in preparation) and suggested that C-allele homozygotes exhibit increased time awake (as estimated from wrist actigraphy) and more frequent sleep complaints when compared to T-allele carriers (Erblang et al., 2021; Nova et al., 2012). In addition, when an array of eight genetic variants of *ADORA2A* was simultaneously considered, the rebound in EEG SWA in NREM sleep after sleep deprivation differed between two distinct haplotype groups, suggesting that in humans the functional state of A_{2A} receptors modulates the dynamics of sleep homeostasis (Landolt, 2012).

This conclusion was further corroborated by controlled pharmacogenetic studies, which specifically investigated adenosine-receptor-mediated processes. Among >4,300 respondents to a brief internet questionnaire about self-rated caffeine sensitivity and sleep, the level of habitual caffeine consumption was inversely associated with subjectively reduced sleep quality in caffeine-sensitive respondents, but not in caffeine-insensitive respondents (Retey et al., 2007). Intriguingly, the effects of double-blind administration of 2×200 mg of the stimulant on EEG markers of disturbed sleep confirmed the classification of self-rated caffeine sensitivity. Although the caffeine concentration in saliva did not differ, the stimulant induced sleep EEG characteristics of insomnia and attenuated the repercussions of prolonged wakefulness on psychomotor vigilance and the SWA rebound in recovery NREM sleep exclusively in C-allele carriers of the *ADORA2A* polymorphism rs5751876 (Bodenmann et al., 2012; Retey et al., 2007). Together, the convergent results of this series of

experiments suggest that genetic variants of *ADORA2A* alter the accumulation of homeostatically-regulated sleep propensity during prolonged wakefulness. Thus, in humans, the A_{2A} receptor may be part of the molecular machinery regulating sleep homeostasis.

7.2 | Adenosine formation and breakdown

Given that astrocytes are an important source of extracellular adenosine, astrocytes may also be a crucial component of sleep homeostatic signalling mechanisms. Indeed, mice carrying a conditional, dominant-negative form of the SNARE (dnSNARE) protein that controls adenosine release from activated astrocytes, demonstrated a sleep–wake phenotype that was remarkably reminiscent of conditional A_1 receptor knock-out animals (Bjorness et al., 2009; Halassa et al., 2009). The genetic construct eliminated the responses to A_1 receptor antagonists in vitro and in vivo, but conserved the actions of A_1 receptor agonists, which supports the notion that the genetic intervention eliminated the release of ATP by the astrocytes. Also the dnSNARE mice showed normal sleep at baseline but they lacked the SWA response to sleep deprivation (Halassa et al., 2009). In contrast to the A_1 receptor knock-outs, however, the dnSNARE mice did not show cognitive deficits associated with sleep loss. This study suggests that the sleep homeostatic feedback signal includes astrocyte-derived adenosine. The effects on sleep–wake regulation in mice with engineered mutations to reduce or enhance the expression of AdK, which is primarily expressed in astrocytes, are consistent with this hypothesis. They indicate that AdK could orchestrate signalling pathways involved in generating EEG oscillations that mark sleep–wake regulation (Palchykova et al., 2010).

As mentioned above, deamination of adenosine to inosine by ADA occurs primarily under conditions with elevated adenosine levels (Borea et al., 2018). In rodents, ADA is expressed in sleep–wake regulatory brain regions and exhibits region-specific diurnal variation of enzymatic activity (Chagoya de Sanchez et al., 1993; Okada et al., 2003). Pharmacological inhibition of ADA, elevated extracellular adenosine levels and prolonged the duration of slow-wave sleep (Radulovacki, 1985). In humans, the gene encoding ADA is naturally polymorphic. Functional experiments revealed that heterozygous carriers of a non-synonymous rs73598374 polymorphism of the *ADA* gene (referred to as G/A genotype) showed reduced breakdown of adenosine to inosine when compared to homozygous carriers of the major allele (G/G genotype). Independent data from different studies and laboratories confirmed that G/A allele carriers exhibited elevated EEG delta power in NREM sleep and enhanced activity in theta/alpha frequencies (~6–12 Hz range) in all behavioural states when compared to G/G allele carriers (Bachmann et al., 2012; Mazzotti et al., 2012; Retey et al., 2005). Interestingly, the difference in the NREM sleep EEG was most pronounced in the 0.75–1.5 Hz range and persisted in baseline and recovery nights after sleep deprivation (Bachmann et al., 2012). Similarly, waking EEG alpha (8–12 Hz) activity was invariably higher in G/A allele carriers than in G/G genotype individuals throughout 40 h of prolonged wakefulness (Bachmann et al., 2012). The genotype-related differences were not the consequence of different habitual sleep duration nor reflected an altered homeostatic response to sleep–wake history.

In contrast to the neurophysiological signals, self-rated sleepiness did not differ between the *ADA* genotypes when sleep pressure was low. However, after sleep deprivation the G/A allele carriers were sleepier than the G/G allele carriers (Bachmann et al., 2012; Reichert et al., 2014). These observations may be consistent with a primary role of ADA to clear elevated adenosine levels and suggest that functional genetic variation of *ADA* in humans contributes to individual variation in sleep-associated variables that reflect adaptive sleep homeostatic processes.

8 | POSSIBLE NOVEL APPROACHES TARGETING THE ADENOSINERGIC SYSTEM FOR CLINICAL APPLICATIONS

Although adenosine receptors have long been recognised as possible therapeutic targets for the pharmacological treatment of sleep disturbances (Chen et al., 2013; Jacobson & Gao, 2006), no approved drugs to ameliorate disturbed wakefulness and sleep by specifically targeting the adenosine neuromodulatory system are currently available (Borea et al., 2018). Nevertheless, methylxanthines such as caffeine, paraxanthine and theophylline are potent antagonists at adenosine receptors, whereas drugs such as dipyridamole may enhance the activation of adenosine receptors by reducing adenosine reuptake. In the following sections, we will review how pharmacological and physiological interventions affect wakefulness and sleep by presumably acting on the adenosinergic system and discuss potential targets in the adenosine neuromodulatory system to ameliorate sleep–wake and associated disorders.

8.1 | Hypersomnia disorders and excessive daytime sleepiness

In the doses commonly consumed from coffee and tea (~150–500 mg/day), acute caffeine intake promotes vigilance, attention and mood by blocking A_1 and A_{2A} receptors, particularly in conditions of insufficient sleep and increased sleepiness (Baur et al., 2020; Jarvis, 1993; Landolt et al., 2004; Lieberman et al., 2002; Penetar et al., 1993; Wyatt et al., 2004). Coffee and caffeine were among the earliest treatment recommendations for excessive daytime sleepiness in narcolepsy (Redlich, 1925). Although there are more potent medications available today, as long as the diagnosis is lacking, many patients with narcolepsy "self-medicate" with high amounts of caffeine to improve their alertness (Thorpy & Dauvilliers, 2015). Evidence from transgenic mice suggests that the alerting effects of caffeine are specifically mediated by antagonising A_{2A} receptors (Huang et al., 2005). Moreover, studies in rats revealed that the preferential A_{2A} (but also A_1) receptor antagonist, JNJ-40255293, dose-dependently enhanced wakefulness without affecting dopamine and noradrenaline release in

prefrontal cortex and striatum (Atack et al., 2014). Adenosine A_{2A} and dopamine D_2 receptors are co-localised on medium spiny neurones of the indirect pathway in the striatum (Lazarus et al., 2019). Activation of the excitatory A_{2A} binding sites of this pathway strongly induces sleep (Oishi et al., 2017), whereas a blockade of A_{2A} receptors on these cells enhances dopaminergic neurotransmission by functional A_{2A}-D_2 receptor antagonism (Figure 2). The A_{2A} receptor was thus proposed to provide a promising target as add-on treatment to ameliorate motor and non-motor symptoms such as fatigue in Parkinson's disease (Schwarzschild et al., 2006). In an attempt to test this hypothesis, caffeine (up to 400 mg/day) failed to reduce daytime sleepiness in a randomised controlled trial (RCT) in patients with Parkinson's disease (Postuma et al., 2012). However, the study did not control for caffeine consumption, sleep–wake history, nor common genetic variations in the A_{2A} receptor gene (*ADORA2A*). This is important, because the effects of caffeine depend on chronic caffeine intake, sleep pressure, as well as on polymorphisms of *ADORA2A* (see above). The prospective selection of study participants with predefined *ADORA2A* genotype is a powerful new paradigm to obtain reliable outcomes in clinical trials testing the responses to coffee, caffeine, and other adenosine receptor antagonists (Baur et al., 2020; Bodenmann et al., 2012; Chen & Cunha, 2020). Such studies may show that antagonists with more selective affinity for the A_{2A} receptor (e.g., istradefylline) have a more favourable safety profile to promote wakefulness when compared to high doses of caffeine or psychostimulants that can disturb sleep and cause anxiety and dependence.

8.2 | Insomnia and anxiety-related disorders

Disturbed sleep and increased anxiety are typically seen when large amounts of caffeine (>500 mg/day) are chronically ingested (Bonnet & Arand, 1992). Furthermore, it has long been noted that in sensitive people (e.g., patients with anxiety disorders) caffeine consumption (of 10 mg/kg) can cause symptoms of anxiety and panic attacks, which are related to the plasma caffeine levels (Charney et al., 1985). Moreover, healthy people with polymorphisms in the *ADORA2A* gene exhibit elevated risk of anxiety symptoms when consuming normal amounts of caffeine-containing products (Alsene et al., 2003). Given that *ADORA2A* polymorphisms also modulate subjective and objective effects of caffeine on sleep quality, sleep architecture and the sleep EEG, it may be that the adenosine system could contribute to the neurobiological mechanism linking disturbed sleep and anxiety/anxiety-related disorders (van Calker et al., 2019).

Indeed, independent of caffeine, insomnia often co-occurs with anxiety/anxiety-related disorders (Jansen et al., 2019) and functional genetic variants in adenosine receptors can predispose people to elevated trait anxiety and anxiety disorders (Geiger et al., 2016; Hohoff et al., 2010; Hohoff et al., 2014). Some of these polymorphisms may affect the functional connectivity in core brain networks that process and regulate emotions and sleep, including the cingulate cortex, insula, and amygdala. The functional connectivity within these networks is altered in certain patients with anxiety disorders and insomnia (Chellappa & Aeschbach, 2022). Notwithstanding, large genome-wide association studies failed to provide evidence for enriched variant adenosinergic genes in patients with insomnia (Jansen et al., 2019; Van Someren, 2021). Research is needed to elucidate whether such associations would emerge when homogenous disease subtypes or states are considered. In addition, similar to chronic caffeine consumption and constitutive genetic knock-out animal models, compensatory mechanisms may obscure the possible impact of functional gene variants on disease phenotypes.

Even though the accumulated evidence suggests that pharmacological activation of adenosine receptors may promote physiological sleep mechanisms, the use of adenosine receptor agonists for clinical applications in insomnia and other sleep–wake disorders faces important challenges. On one hand, available adenosine analogues hardly penetrate the blood–brain barrier. On the other hand, adenosine receptors are widely expressed in most tissues and organs and conventional adenosine analogues are likely to cause a variety of unwanted responses (e.g., adverse cardiovascular effects). Previous attempts to develop agonists that target adenosine receptors in tissue/organ specific manner have had limited success. Thus, the pharmacological enhancement of endogenous adenosine signalling, or the reduction of adenosine degradation may be more promising (Chen et al., 2013). One such possibility is the development of allosteric enhancers. These compounds lack agonistic activity per se but may amplify the action of endogenous ligands at their receptors by stabilising the ligand–receptor complex (Ferre et al., 2014). For example, benzodiazepines and Z-drugs are positive allosteric modulators of $GABA_A$ receptors. With respect to adenosine, a small, blood–brain-barrier-permeable positive allosteric modulator of A_{2A} receptors referred to as A_{2A}R PAM-1 was recently shown to promote slow-wave sleep in mice (Korkutata et al., 2019). This compound specifically enhanced A_{2A} receptor signalling in the brain, without causing the typical unwanted cardiovascular complications of conventional A_{2A} receptor agonists. Clinical studies are needed to determine whether allosteric enhancers of adenosinergic neurotransmission have the potential to ameliorate sleep quality and sleep efficiency in patients with insomnia and neuropsychiatric disorders.

8.3 | Restless legs syndrome

Restless legs syndrome (RLS) is frequently associated with insufficient iron availability in the brain (Manconi et al., 2021). Preclinical studies suggest that brain iron deficiency can cause a hypo-adenosinergic state and a disruption of the fine-tuned balance of adenosine-dopamine-glutamate neurotransmission in the striatum (Ferre et al., 2018). This evidence led to the recent hypothesis that pharmacologically increased extracellular adenosine concentrations may improve sensorimotor and sleep symptoms in RLS (Garcia-Borreguero et al., 2018). Consistent with this idea, blockade of adenosine reuptake by dipyridamole, a non-selective ENT1/ENT2 inhibitor clinically used as vasodilator and inhibitor of blood platelet aggregation, proved therapeutic efficacy in RLS by reducing periodic limb movements during

sleep, shortening sleep latency, increasing sleep efficiency, and enhancing the duration and proportion of slow-wave sleep (Garcia-Borreguero et al., 2021).

Also other blockers of adenosine reuptake may ameliorate RLS. Based on anecdotal evidence from patients and case reports, the consumption of recreational marijuana products can improve sensorimotor symptoms and the quality of sleep in RLS (Sullivan & Winkelman, 2020). The underlying mechanisms for these observations may be complex and have not been elucidated, and RCTs such as with dipyridamole are lacking. Nevertheless, it is interesting to note that one of the most abundant components in the native cannabis plant, cannabidiol, inhibits the ENT1 (Carrier et al., 2006). Together with the evidence outlined above, the data provide convergent support of a role for adenosine in RLS. Strategies that increase endogenous adenosine levels or specifically target adenosine receptors or nucleoside transporters may provide therapeutic benefits for patients with this neurological disorder. Future studies that elucidate whether the beneficial effects of dipyridamole and cannabidiol on RLS symptoms indeed reflect enhanced adenosinergic neurotransmission or another action of these non-selective compounds (e.g., (Friedman & Devinsky, 2015) are warranted.

8.4 | Depressive disorders

Depending on the severity of symptoms, 60%–90% of patients with a major depressive episode present with disturbed sleep (Argyropoulos et al., 2005). Notwithstanding, acute sleep deprivation - or "wake therapy" - improves depressive symptoms in ~60% of all patients (Wirz-Justice & Van den Hoofdakker, 1999). The antidepressant response of sleep deprivation is quantitatively similar to what can be achieved after several weeks of available standard treatments, including pharmaco-, psycho- and electroconvulsive therapies (Wu & Bunney, 1990). Unfortunately, the wakefulness-induced mood improvement is typically short-lived and followed by a relapse into the depressive state upon recovery sleep (Boland et al., 2017). This characteristic of sleep-deprivation therapy prohibits persistent remission. Nevertheless, the unique psychopathological switch-phenomenon of rapid onset and offset of depressive symptoms in relation to wakefulness and sleep represents a powerful paradigm to study the pathophysiology of depressed mood. Insights gained from such research may lead to more rapidly acting antidepressant treatments that are urgently needed.

Several models were proposed to explain the antidepressant response to sleep deprivation; a comprehensive review of the different theories is beyond the scope of this article. Within the conceptual framework of the "Two-Process" model, Borbély and Wirz-Justice hypothesised that depression is associated with a deficient build-up of homeostatic sleep propensity during wakefulness (Borbély & Wirz-Justice, 1982). Accordingly, after a normal duration of wakefulness sleep propensity would not reach the level attained by non-depressed individuals, resulting in "depression-like" sleep structure and reduced EEG SWA in NREM sleep. The model proposed that the deficient S-process in depressive patients is normalised by sleep deprivation. Although the underlying biochemical/molecular mechanisms are still elusive, the available findings confirm that increased process S is a core mechanism underlying the antidepressant efficacy of wake therapy (Dallaspezia & Benedetti, 2015).

Convergent lines of evidence indicate that adenosine could contribute to the neurobiological link between sleep and mood regulation and that depression and antidepressant interventions may alter adenosinergic signalling and purine metabolism in the brain. For example, polymorphisms in adenosine related genes, including the genes encoding ADA (rs6031682 and rs452159) and ENT3 (rs12256138), were associated with a lower risk of depression and disturbed sleep (Gass et al., 2010). While sex differences in adenosinergic mechanisms may be important (Gass et al., 2010; Pierling et al., 2021), female depressed patients who responded to the serotonin-reuptake inhibitor fluoxetine, also exhibited 30% lower brain ATP levels as quantified with magnetic resonance spectroscopy than treatment non-responders (Renshaw et al., 2001). Reduced adenosinergic signalling may thus predispose to depression, whereas increased adenosinergic signalling may elicit antidepressant efficacy.

These hypotheses were tested in a behavioural model of chronic despair in genetically engineered mice (Serchov et al., 2015). Although animal models of neuropsychiatric disorders have to be evaluated with caution, mice with conditionally enhanced A_1 receptor expression on forebrain neurones appeared to be protected against acute and chronic depressive-like behaviour. Conversely, genetically-induced A_1 receptor deficiency sensitised the animals to depressive-like behaviour and precluded the antidepressant-like response of sleep deprivation.

Recent findings in mice suggest that the immediate early gene Homer1a and metabotropic glutamate receptors of subtype 5 (mGluR5) may link sleep–wake related changes in A_1 receptor signalling to the antidepressant-like effects of sleep deprivation and antidepressant medications in mice (Holz et al., 2019; Serchov et al., 2015). These molecules are required for sleep–wake related changes in synaptic plasticity in vitro and the weakening of synapses during sleep in mice (de Vivo et al., 2017; Diering et al., 2017; Hu et al., 2010). More specifically, Homer1a is a core brain molecular correlate of sleep loss, responds to waking-induced increased extracellular adenosine levels, enhances mGluR5 signalling, and uncouples mGluR5 from the downstream signalling cascades during sleep (Holz et al., 2019; Maret et al., 2007; Martin et al., 2019). Consistent with the notion that Homer1a induction contributes to the antidepressant effect of sleep deprivation, specific knock-down of Homer1a in the medial prefrontal cortex (mPFC) enhanced depressive-like behaviour and prevented the antidepressant effects of A_1 receptor up-regulation, sleep deprivation, and different pharmacological interventions (Serchov et al., 2015). Subsequent studies in transgenic mice revealed that the antidepressant effect of sleep deprivation and Homer1a induction are mediated by mGluR5 in forebrain excitatory neuronws and depend on the synaptic expression and activity of glutamatergic α-amino-3-hydroxy-5-methyl-4- isoxazolepropionic acid (AMPA) receptors (Holz et al., 2019). Mice without functional mGluR5 exhibit

severe dysregulation of sleep–wake homeostasis, including lack of recovery sleep, and impaired behavioural adjustment after sleep deprivation (Holst et al., 2017).

Data in humans are consistent with these ideas derived from preclinical research. First, a combined genome-wide association, replication and neuroimaging study provided convergent evidence that the human gene *HOMER1* plays a role in the aetiology of major depression (Rietschel et al., 2010). The authors suggested that the *HOMER1* genetic variation affects depression by a dysregulation of cognitive and motivational processes. Furthermore, in healthy volunteers, the availability of mGluR5 correlates with changes in physiological and behavioural markers of sleep need after prolonged wakefulness and recovery sleep. Quantified with receptor-specific positron emission tomography, prolonged wakefulness increased the density of A_1 receptors (Elmenhorst et al., 2007). Furthermore, mGluR5 availability in the cerebral cortex correlated with NREM sleep "high delta" (2–4 Hz) activity in baseline and after sleep deprivation, as well as increased high delta power, elevated sleepiness, and involuntary sleep intrusions during waking after a night without sleep (Hefti et al., 2013; Holst et al., 2017). Importantly, the elevated availability of A_1 receptors and mGluR5 after sleep loss returned to baseline levels after recovery sleep (Elmenhorst et al., 2017; Weigend et al., 2019). Finally, the density of mGluR5 was reported to be reduced in depressed patients (Deschwanden et al., 2011). Future research may establish whether therapeutic sleep deprivation normalises mGluR5 density and whether changes in receptor expression are related to the antidepressant efficacy.

Taken together, based on the convergent preclinical and clinical findings outlined above, we hypothesise that sleep loss-induced changes in A_1 receptors (and mGluR5) could contribute to the neurochemical mechanisms underlying the rapid mood enhancing effect of sleep deprivation therapy. Interestingly, a recent meta-analysis of observational studies including almost 370,000 adults from the general population demonstrated that coffee and caffeine consumption was dose-dependently associated with decreased risk of depression (Wang et al., 2016). This study does not permit conclusions regarding the presence of a causal relationship between coffee/caffeine intake and depression nor the underlying mechanisms for the observed association. Future research is warranted, to investigate the roles of adenosine-modulated neurotransmission and its impact on homeostatic and circadian sleep–wake regulatory processes for the antidepressant efficacy of therapeutic sleep deprivation.

9 | CONCLUSIONS, OPEN QUESTIONS, RESEARCH AGENDA

From the available evidence it can be concluded that adenosine is probably involved in the adaptive homeostatic response to the prior duration of sleep and wakefulness, as its levels rise in the course of sleep deprivation and decrease during recovery sleep. Under conditions of prolonged waking, it is likely that adenosine is involved in inducing a subsequent increase in NREM sleep duration and NREM sleep EEG SWA. Whether adenosine is also involved in the regulation of the normal occurrence of the daily sleep–wake cycle is less certain and needs further investigation. The currently available data do not suggest the expected time course of daily changes in adenosine that would parallel the daily changes in NREM sleep EEG SWA, which is widely accepted as a physiological marker of sleep homeostasis. To obtain clearer insights, experiments are needed, which investigate the level of adenosine in different brain areas in parallel with simultaneous sleep recordings. Such experiments may shed light on the role of adenosine in tracking the need for sleep on a shorter time scale than the entire sleep–wake cycle. Given the fast kinetics of adenosine formation and breakdown, and the rapidly altered adenosine levels in response to changing vigilance states (Peng et al., 2020), adenosine may play a role in adaptive physiological processes at the transitions between wakefulness and sleep (Hubbard et al., 2020). For example, it remains to be investigated in detail whether such a role could underlie the caffeine-induced improvement of sleep inertia symptoms (Dornbierer et al., 2021; Van Dongen et al., 2001) and the beneficial effects of short naps on sleepiness that can be potentiated by caffeine intake (so-called "caffeine-naps") (Reyner & Horne, 1997). Finally, because polyphasic sleepers likely show less clear spontaneous changes in adenosine levels, it is important to understand how adenosine levels in the brain change in the course of the day in humans, as a mono-phasic sleeper. Innovative (metabolomics) approaches may be developed, to make such measurements possible in the future.

The effects of caffeine on the functioning of the circadian clock are intriguing. Caffeine seems to slow down the central circadian pacemaker, but, moreover, it also seems to increase the effect of light on the circadian clock. This opens up questions of possible applications of caffeine when it concerns light, as it suggests the effects of light treatment can be enhanced when it is combined with caffeine intake. It may also be possible to reduce the duration of jet lag with supplemental caffeine. As first evidence indicates reduced jet lag symptoms after caffeine intake (Beaumont et al., 2004), it appears promising to investigate the effects of a combined caffeine-light treatment on jet lag duration and strength.

When considering the possible range of applications for interventions targeting adenosinergic signalling as outlined in the previous section, it needs to be kept in mind that the adenosine system and, therefore, the effects of "adenosinergic" interventions on sleep and the circadian system probably adapt over time. This phenomenon has been observed in a range of caffeine studies, but the time course of such adaptations (and their reversibility) is not clear. It may depend on dosages, individual differences in metabolic processes, and differences in the adenosinergic system itself. It is critical to consider that adaptations do not only surface as tolerance, but present as reversed or qualitatively different with respect to the originally expected effect (Weibel et al., 2020; Weibel et al., 2021). Reduced activity during the rest phase (Ruby et al., 2018) or increased NREM sleep (Panagiotou et al., 2019) during chronic intake of caffeine may be such examples. An open question in this respect is whether seemingly paradoxical effects of caffeine, such as

those anecdotally reported in certain middle-aged individuals (Regestein, 1989), may reflect processes of adaptation.

Although sleep deprivation seems to be able to influence functioning of the circadian clock, it does neither seem to change the expression of clock genes in mice nor the amplitude of core clock outputs in humans (e.g., the amplitude of the melatonin secretion profile or the 24-h body temperature cycle). With respect to clock gene expression, up to now only one circadian time point was tested and clearly more experiments are needed to determine whether this effect depends on the time of day. In humans, it may be the case that a single night of sleep deprivation is not strong enough to influence core clock mechanisms and longer sleep deprivation protocols need to be tested.

In conclusion, many questions on the role of adenosine in sleep–wake regulation are still unanswered. For example, the study of chronic use of adenosine antagonists, like daily caffeine intake in a majority of people in Western society, has only recently started. The influence of adenosine and caffeine on the circadian clock is another area that only recently opened up. Concerning both these topics, many things are unclear and need further research. The detailed understanding of the complex relationships among adenosine, caffeine, and sleep may open up promising new treatment avenues. Thus, even after more than a century of active scientific research, new methodological approaches and experiments are warranted to fully elucidate the working mechanisms of adenosine in sleep–wake regulation.

CONFLICT OF INTEREST

All authors declare not having any conflicts of interest.

AUTHOR CONTRIBUTIONS

Carolin Franziska Reichert: conceptualisation, writing - original draft, writing - review and editing; Hans-Peter Landolt: conceptualisation, writing - original draft, writing - review and editing; Tom Deboer: conceptualisation, writing - original draft, writing - review and editing.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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How to cite this article: Reichert, C. F., Deboer, T., & Landolt, H.-P. (2022). Adenosine, caffeine, and sleep–wake regulation: state of the science and perspectives. *Journal of Sleep Research*, 1–21. https://doi.org/10.1111/jsr.13597