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Sleep and circadian rhythms: the effects of ketamine, caffeine and anthracyclines

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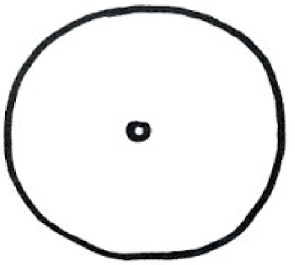
General Introduction



1. Circadian clock and sleep-wake regulation

1.1 The circadian timing system

The ancient Chinese medical book Huangdi Neijing (475-221 BC) includes circadian rhythms - physical, mental, and behavioral changes that follow a daily rhythm, a syzygial (lunar) rhythm, and a seasonal (annual) rhythm, creating a harmonious lifestyle between humans and our natural world. Ancient Chinese people thought that human rhythms are fundamental for good health, and thousands of years later this appears to be true.

The mammalian circadian clock is individually and collectively expressed by each of the ~20,000 cells of the master circadian clock, the suprachiasmatic nucleus (SCN), which is located in the hypothalamus, lateral to the third ventricle, above the optic chiasm [1]. The circadian rhythm generated is approximately 24 hours and mammals synchronize their circadian activity to the cycles of light and darkness originating from the rotation of the earth. Light information is sent directly from the retina to the SCN through the retinohypothalamic tract (RHT), which, through release of glutamate, activates neurons in the SCN [2]. Feeding and exercise can also act as zeitgebers to synchronize the central clocks [3,4]. For this, the SCN receives timing information of other brain regions via direct and indirect inputs, and sends its output, like hormonal and nervous signals, to synchronize the peripheral clocks and optimize physiology to the temporal changes in our environment [2].

Most outputs of the SCN are directed towards the hypothalamus, including the medial preoptic nucleus, dorsomedial hypothalamic nucleus, paraventricular nucleus, and dorsomedial hypothalamic nucleus [2]. The unique location of the hypothalamus allows it to directly connect to the cerebrospinal fluid, thus, the hypothalamus can convey information from the SCN in a neuroendocrine way, for example, pituitary/hypothalamus-pituitary-adrenal axis and pineal gland, and also send output via synaptic pathways to other brain areas, for example, the cortex, cerebellum or hippocampus (Figure 2, upper panel) [5,6]. The central circadian clock plays a crucial role in sleep-wake rhythm, rest-activity rhythm, thermogenesis, immunity and metabolism (Figure 1).

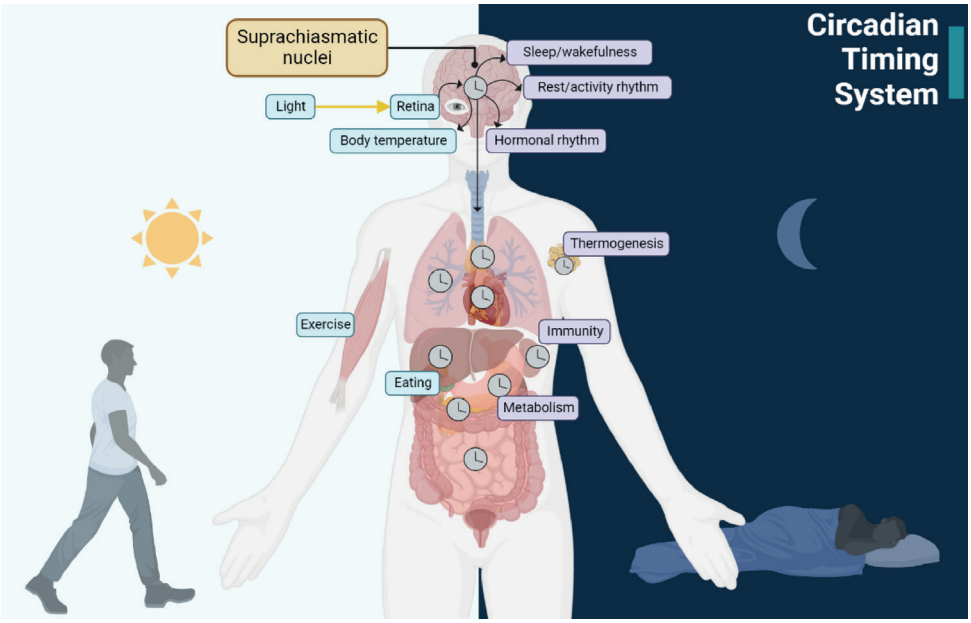


Figure 1. Schematic representation of the circadian timing system. The circadian timing system synchronizes clocks through the whole body and adapts the changes of the outside world. Created via BioRender.

The SCN is an evolutionarily conserved brain area. It generates daily electrical activity rhythms which can even be observed in brain slices, and in cultured slices (Figure 2, bottom right panel) [7]. Furthermore, SCN lesioning experiments in animals as well damage of the hypothalamus in humans show that animals and human lose their daily rest-active rhythm after such an event [8,9]. It is possible to restore circadian rhythms in SCN lesioned hamsters with SCN transplants that carry the rhythmic properties of the donor animal [10]. Thus, the SCN is considered to be the intrinsic endogenous pacemaker in the body. During the day, the neurons discharge action potential rate in the SCN is high and the resting membrane potential is more depolarized relative to the night. When SCN neurons discharge action potentials are at a lower rate and SCN neurons are most responsive to excitatory or depolarizing stimulation [11]. This kind of rhythmic firing of neurons across the 24-hour is regulated by an autoregulatory transcription-translation feedback loop (TTFL) of clock genes (Figure 2, bottom left panel) [12]. This TTFL comprises the interlocked activities of transcriptional activators (CLOCK and BMAL1) and repressors (PER and CRY). CLOCK and BMAL1 form a heterodimer that regulates the expression of clock-controlled genes as well as the repressor proteins encoded by Period and Cryptochrome. The PER/CRY heterodimer repressor complex,

in turn, inhibits CLOCK/BMAL1 activity at E-box target sequences on both clock-controlled genes and CLOCK/BMAL1 autoregulation [13]. The TTFL forms the basis for cellular rhythms in gene expression, intracellular Ca^{2+} levels, rate of action potentials, neurotransmitter release and electrical activity rhythms [13-15]. Light entrains the phase of these rhythms through release of glutamate by the RHT, which can set *Per* transcription levels and induce changes in SCN neuronal activity [2,16-18]. Multi-unit recordings reveal the synchronization of this activity across the SCN circuit [7]. In nocturnal animals, higher firing is associated with reduced locomotor activity, and decreased firing is observed during the active phase [19,20]. Diurnal rodents exhibit behavioral rhythms in the opposite phase, although the phase of clock gene and action potential rhythms are likely to be similar to that of nocturnal mammals (Figure 2, bottom right panel) [21,22].

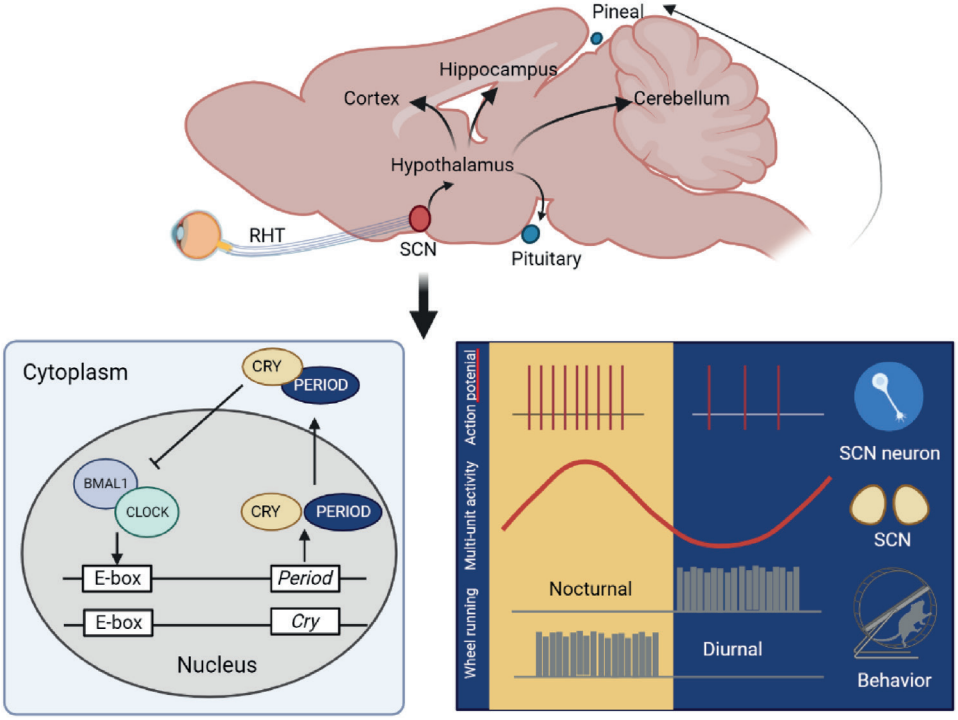


Figure 2. The suprachiasmatic nucleus is the central circadian pacemaker. Upper panel: Sagittal view of a rodent brain illustrating light input to the SCN via the RHT and output from the SCN to other brain areas. Bottom left (SCN neuron) panel is the simplified scheme of the molecular clock, the TTFL regulating the expression of clock genes and proteins that take around 24 h to complete a cycle. Bottom right panel is the representative rhythmic outputs from the SCN circuit. Adapted figure from Harvey et al., 2020 [23]. Created via BioRender.

1.2 Neurophysiology of sleep

Sleep sustains physical and cognitive performance, productivity, psychological health and well-being. Even mild sleep restriction over a few days negatively affect performance [24,25]. However, what exactly sleep is doing to our brain and body and the reason why we need sleep is still controversial in the research field. Sleep is a very complex physiological process involving the interaction of sleep-promoting and waking-promoting neural circuits. Most mammals have two different types of sleep: non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. The changes in cortical electroencephalogram (EEG) and muscular electromyogram (EMG) are generally used to distinguish different sleep and arousal states in mammals [26]. Frequency, amplitude and morphology are critical terms to characterize the EEG and EMG for different vigilance states.

NREM sleep, is characterized by high amplitude and low frequency waves, (0.5 Hz – 4.0 Hz) also called slow-waves. Surprisingly, almost half a century after the delta activity was first demonstrated by William Grey Walter in an isolated cortex in vivo in 1966, its mechanism of generation is still not fully understood [27]. Delta waves are generated within the thalamocortical network [28] and they are thought to represent the activity of synchronized cortical neurons [29,30]. However, delta waves are consistently observed in decorticated animals [31]. Other studies show that delta waves can also be observed in the isolated thalamus [32]. Moreover, also other brain areas may be involved in generating delta waves, as is shown by lesions of the anterior hypothalamus, preoptic region, and basal forebrain, all of which can abolish delta waves [33]. Although the body weight of rats (200 – 400 grams) and mice (20 - 35 grams) can be 10 times different, their EEG power spectrums are more or less the same compared with each other (Figure. 3). However different rodent species may still show subtle differences in their EEG is also shown in Figure 3, where the peak of the NREM power spectrum (left, blue) of mice have a peak of around 3 Hz, and the peak of the NREM power spectrum (right, blue) of rats have a peak that is near 1.5 Hz.

Eugene Aserinsky and Nathaniel Kleitman first discovered REM sleep [34]. They showed that rapid eye movements occur during “active” sleep in adult human and these sleep periods with rapid eye movements may be involved in dreaming [35]. Years later, using high quality REM sleep EEG/EMG recording showed low amplitude and high frequency bands of wake-like brain activity, but with the muscle tone reaching minimum level. Because of

this low amplitude and high frequency waves, REM sleep was termed active or paradoxical sleep in early studies. In rodents, REM sleep is rich in theta activity (6 – 9 Hz), as shown in Figure 3, both mice (peak around 8 Hz) and rats (peak around 7 Hz) had a similar REM sleep power spectrum pattern and theta peak frequency, which is generated by the hippocampus [36].

The daily NREM-REM sleep cycle duration is also different across the species, for example, REM sleep occurs in the rodent approximately every 10 – 15 min. However, REM sleep occurs every 90 – 120 min in humans [37]. The overall sleep architecture is different between rodents and humans. Humans show monophasic sleep which is restricted to the night, whereas rodents display polyphasic sleep over day and night [38]. The difference is considered to be related to the size of both body and brain across the different species. The functional role of REM sleep is unclear. After decades of research and studies, it is more evident that brain areas that generate REM sleep reside in the brainstem and hypothalamus [39]. Subgroups of neurons are activated during REM sleep, called REM-on neurons, and these neurons release neurotransmitters such as γ-Aminobutyric acid (GABA), acetylcholine, and glutamate [40]. Moreover, there is also a subgroup of neurons called REM-off cells, which release neurotransmitters like norepinephrine, epinephrine, serotonin, histamine, and GABA [40].

There is a relation between the cortical EEG and theta waves in the hippocampus during REM sleep. Some studies indicated that theta activity during REM sleep is essential for motor performance, learning and memory consolidation [41,42]. REM sleep deprivation in rodents and humans resulted in impaired formation of spatial or emotional memory [40,43]. Both animal and human studies showed increased theta activity during REM sleep following a learning or memory tasks. In mice, specifically inhibiting theta activity in the hippocampus during REM sleep impaired memory consolidation, indicating that theta activity is important in memory consolidation [42]. Another study showed that increased theta activity was associated with increased cerebral blood flow during REM sleep in humans [44]. This may further indicate an increased metabolic rate and increased the energy supply from the blood to the brain areas during REM sleep.

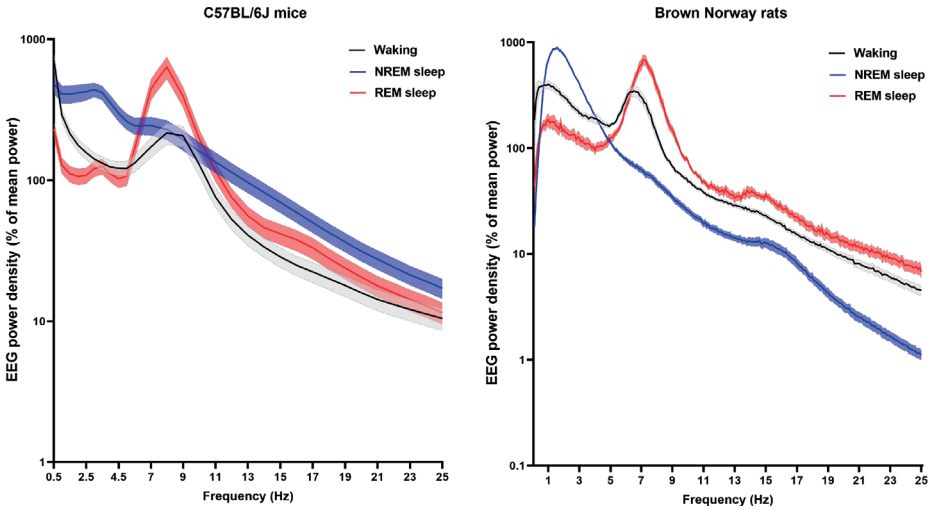


Figure.3 Spectral analysis of the EEG by a fast Fourier Transform routine. Left panel: A twenty four hours electroencephalographic power spectra in waking (black), NREM sleep (blue) and REM sleep (red) in C57BL/6J male mice under light-dark condition (n = 9). Right panel: A six hour electroencephalographic power spectra in waking (black), NREM sleep (blue) and REM sleep (red) in Brown Norway make rats under constant darkness condition (n = 8).

1.3 Homeostatic regulation of sleep

A balance of sleep and wakefulness exists, called sleep homeostasis. It means we tend to wake up when we sleep for a longer time, and when we stay awake for a longer time, the more sleepy we will feel. The sleepiness we feel is also called sleep propensity, or sleep pressure, which, in the two-process model of sleep regulation, increases during wakefulness and subsequently diminishes during sleep (Process S). This process S is thought to interact with signals received from the circadian clock (Process C) (Figure. 4). Both process C and S are influenced by external cues, like light and exercise. Slow wave activity (SWA) in the NREM sleep EEG is one of the best indicators for Process S. SWA in NREM sleep is increased with high sleep need, such as after sleep deprivation which is shown in the red line in Figure. 4 and decreased during sleep [26]. Homeostatic regulation of SWA has been demonstrated in a large number of rodents [26]. SWA is not only an indicator of Process S, but also critically important for the maintenance of sleep, brain plasticity, cognitive performance and memory [45-47].

The theories on the function of NREM sleep fall into three main categories: energy metabolism, neural plasticity, and cellular defense [48]. Sleep deprivation (SD) is often used as a mediator of sleep homeostasis and to investigate the function of sleep [49]. According to the metabolic theories on the function of sleep, the brain consumes energy during waking and restores energy in the subsequence sleep. Prolonged waking can induce an increase in adenosine. Adenosine is a ubiquitous nucleoside which serves as a building block for nucleic acids and energy storage molecules, enzyme's substrate and neuromodulator of cellular activity [50,51]. The adenosine theory states that during waking, due to neuronal activity-induced energy depletion, adenosine concentration in the brain increases, decreasing the neuronal activity of wake-active neurons and through this induces sleep [52]. Adenosine has therefore been proposed as a mediator of sleep homeostasis and a link between energy metabolism and sleep control.

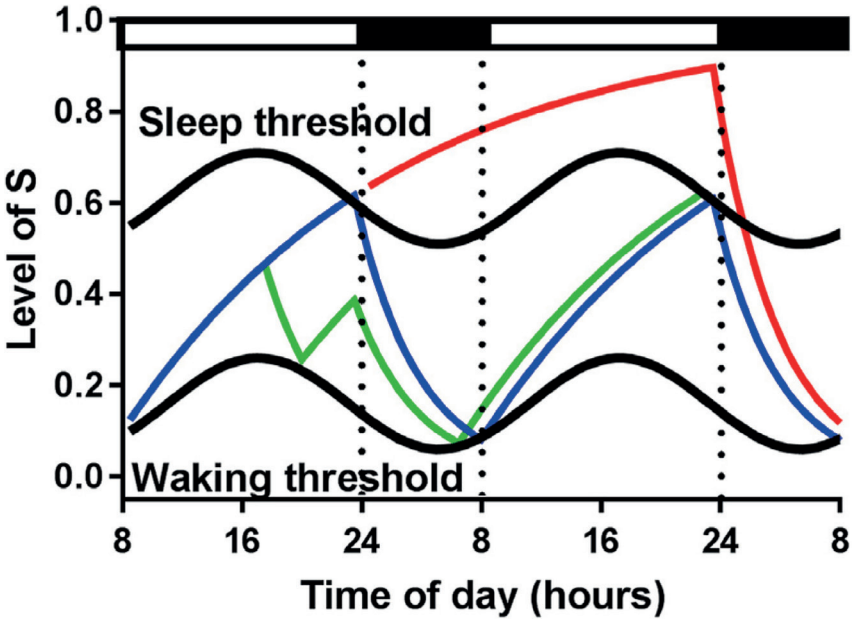


Figure 4. The two process model of sleep regulation. A simplified representation of the two process model of sleep regulation, similar to the version of the model in the initial publication (Borbely, 1982 [53]). The blue line represents the baseline condition with 8 hours of sleep and 16 hours of waking. The green line represents effects of 2-h nap and then a normal night sleep. The red line represents a 24-h sleep deprivation and followed by sleep. White and black bar represent the light and darkness. Figure adapted from Deboer 2018 [54]

2. Drugs influenced circadian clock and sleep-wake

2.1 Caffeine

As mentioned previously, adenosine may be an indicator of process S, and caffeine, which is found in coffee, tea and other types of food and beverages, is a non-selective adenosine receptor antagonist, is which widely used to induce wakefulness [55,56]. The pharmacokinetics of caffeine show a half-life of around 3 to 5 hours, and caffeine can induce waking, delay sleep onset and decrease slow-wave sleep [57]. Next to the effects on wakefulness, sleep and sleep homeostasis, caffeine is also known to improve alertness, mood, and cognitive performance, and counteract fatigue [58]. However, caffeine in doses of 5 cups of coffee or more induces anxiogenic symptoms in healthy adults and in some individuals it may induce panic disorders, and can lead to negative moods like anxiety and panic attacks [59]. Interestingly, these effects are absent when caffeine is given chronically. A recent study in mice compared the effect of acute and chronic administration of caffeine on day-night rhythm and sleep wake rhythm. Surprisingly, chronic caffeine did not induce wakefulness or disturbances of the sleep-wake cycle in contrast to acute caffeine administration. Instead, under chronic administration, it increases sleep during the rest phase and enhances sleep pressure in mice [60]. This suggests that acute and chronic caffeine influence sleep and sleep homeostasis differently.

Whether caffeine affects the circadian clock and further influences the circadian timing control of sleep is still debated. In rodent studies, increased sleep pressure by sleep deprivation can decrease the neuronal activity in the SCN, which suggests that the function of the clock can be modified by increased sleep pressure [61]. This may indicate that caffeine have an effect on the circadian clock. Acute caffeine administration can decrease homeostatic sleep pressure and increases SCN sensitivity of light in mice [62]. In humans, chronic caffeine consumption before bedtime delayed the melatonin rhythm by around 40 min, and chronic caffeine lengthened the period of circadian gene expression of human osteosarcoma U2OS cells [63].

2.2 Ketamine

Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist, applied mainly as anesthetic, which has attracted a lot of attention in the last two

decades because of the rapid antidepressant effect in depressive patients [64]. In Berman's study, a sub-anesthetic dose in depressed patients showed a rapid antidepressant effect within 40 minutes and this effect lasted for seven days after the first infusion [64]. Ketamine may therefore have the potential to develop into a novel antidepressant; however, the mechanism of the antidepressant effect is still unknown.

Ketamine has been used as a non-barbiturate anesthetic drug for a long time, and it was described as an ideal anesthetic for its rapid onset, short duration of action, rapid recovery, and safety [65-67]. In preclinical studies, anesthetic doses had no effect or even reduced glutamate in the medial prefrontal cortex, whereas in the sub-anesthetic dose, it increased the extracellular glutamate [68]. More and more evidence from both preclinical and clinical studies have linked major depressive disorder to a dysregulated glutamatergic system, and glutamate receptors are also viewed as potential targets for antidepressant [69-71]. Thus under the sub-anesthetic does, ketamine induced an acute glutamate surge which may lead to the observed rapid-antidepressant effect. When administered in a sub-anesthetic dose, ketamine blocks NMDA receptors on GABA interneurons, thereby reducing GABA release on principal neurons and, in turn, the increasing presynaptic release of glutamate. The function of NMDARs is tightly linked to α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs). AMPAR-mediated depolarization of the postsynaptic membrane is required for opening the NMDAR channel and removal of Mg^{2+} that blocks the channel pore; this is required for ketamine entry and blockade of the NMDAR channel (Figure 5, right) [72].

As referred to earlier, sleep quality is related to mood and mental health [25,73], and depressive disorders are associated with disrupted sleep and circadian rhythms [74,75]. Interestingly, SD in a subset of depressive patients is also known to induce a rapid antidepressant effect [76]. Thus, these antidepressant effects are suggested to work through sleep homeostatic mechanisms. Moreover, both SD and ketamine can increase SWA in NREM sleep and also the level of brain derived neurotrophic factor (BDNF), which are suggested to enhance the synaptic strength and plasticity [77,78]. Besides that, both SD and ketamine increase cortical excitability, and cortical excitability showed robust circadian dynamics [79]. Therefore, a rapid antidepressant effect may relate to the effects on sleep and the circadian clock. Understanding the rapid antidepressant effects of SD and ketamine from a sleep and chronobiology

perspective may contribute to exploiting the potential of these two treatments.

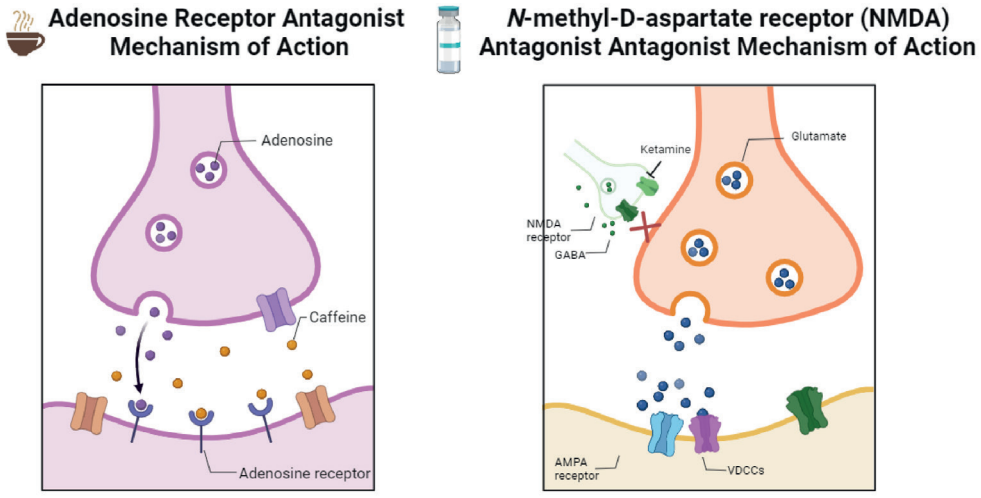


Figure 5. Action of caffeine and ketamine. *Left panel*: Proposed mechanism of caffeine's action, *Right panel*: Proposed mechanism of ketamine's antidepressant action. AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, GABA: γ-Aminobutyric acid, VDCCs: Voltage-gated calcium channels, created via BioRender.

3. Circadian clock, sleep and the relation with cancer related fatigue

3.1 Cancer related fatigue

Cancer-related fatigue (CRF) is a complex and debilitating side effect of unknown etiology, which affects more than 50% of cancer patients and cancer survivors [80,81]. CRF is defined as "a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning." [82]. Persistent CRF has a serious effect on the quality of life of these patients since they are too tired to go to work, socialize or even perform their normal daily activities. Many cancer patients report fatigue when they get diagnosed, and this number increases in incidence and severity during and after treatment with either chemotherapy (chemotherapy related fatigue), radiotherapy, hormone therapy, surgery, or combined therapy. One third of the patients still feel fatigued five years after the end of treatment [83]. Several hypotheses describe the possible mechanism

both from a preclinical and clinical perspective. These mechanisms involve the effects of both the diseases, and the side effects of the therapies on energy metabolism, central nervous system, inflammation, immune function, hypothalamic-pituitary (HPA) axis function, antioxidant metabolism, sleep, and the circadian clock (Figure. 6) [84-92].

Many anti-cancer drugs have been approved to treat cancer. Anthracyclines are one class of chemotherapy that has been widely used for over 60 years to treat different types of cancers. The mechanisms by which anthracyclines kill tumor cells are various, including inhibition of DNA replication and RNA transcription, free radical generation leading to DNA damage or lipid peroxidation, DNA alkylation, interference with DNA unwinding or DNA strand separation and helicase activity, causing double-strand breaks (DSBs) following the poisoning of topoisomerase II, and chromatin damage, mediated through histone eviction at selected sites in the genome [93,94]. Anthracyclines have toxic side effects on nontargeted tissues, which may contribute to fatigue symptoms over a more extended period [95,96].

Recent studies document that especially the treatment of cancer is associated with both immune stimulation and immunosuppression with increased concentrations of various cytokines including tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6) and interleukin 10 (IL-10) [97,98]. Immune stimulation, increasing circulating cytokines, can reach the brain through several pathways [99]. For example, circulating cytokines can cross the blood brain barrier to enter cerebrospinal fluid and interstitial fluid spaces of the brain and spinal cord, increasing microglia activation, which can produce pro-inflammatory cytokines and chemokines [100]. Consequently, it is possible that active microglia drive neuroinflammation and further influence the function of the brain. Peripherally administered interleukin-1 (IL-1) activates the HPA axis [101], and this may further influence hormonal levels like adrenocorticotropic hormone (ACTH) and corticosterone (CORT) [102]. When the peripheral cytokines transfer into the brain, IL-1, IL-6, TNF, and their family members may mimic leptin and, hence, target hypothalamic neuropeptides that regulate food intake and energy expenditure [103]. Pro-inflammatory cytokines, cardiotrophin-like cytokine (CLC), and acute infusion of CLC into the third ventricle inhibits locomotor activity in hamsters [104]. Furthermore, a variant of cytokines is correlated with sickness behaviors and fatigue in rodents and humans, which are also the proposed mechanism for CRF [105,106]. All these pieces of evidence indicate that peripheral cytokines

may play a role in developing fatigue.

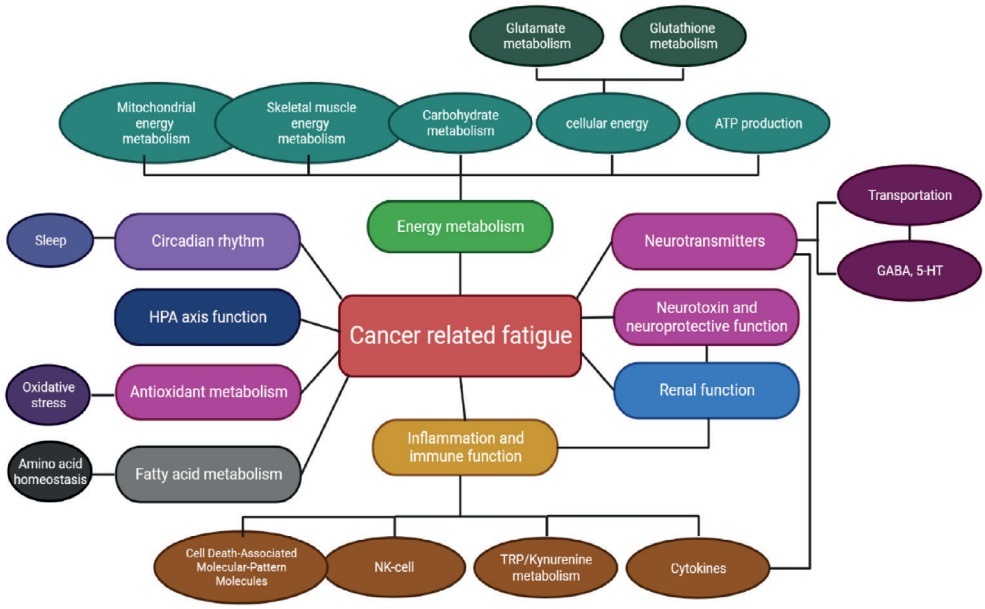


Figure.6 Possible relationships in cancer related fatigue. ATP: Adenosine triphosphate, HPA axis: hypothalamic-pituitary-adrenal axis, TRP: tryptophan, GABA: γ-Aminobutyric acid, 5- HT: serotonin. Created via BioRender.

3.2 Disruption of sleep

A common complaint of cancer patients is disrupted sleep [107]. Patients complain about poor quality of (subjective) sleep, difficulty staying asleep and insomnia during treatment and even months after the treatment [108-110]. Although we know that cancer related fatigue cannot be released after a good night of sleep or rest, a disrupted sleep-wake cycle may contribute to the fatigue experience of the patients [111]. Thus, normalizing the sleep-wake cycle of cancer patients, may help to reduce their fatigue level. However, a larger randomized trial of 219 breast cancer patients did not show any benefit of an individualized sleep therapy plan over the control intervention on fatigue [112]. Behavioral interventions aimed at improving sleep may be successful in their primary aim, but their effect on cancer-related fatigue is less obvious [113,114]. According to another study that reports sleep problems in around three thousand patients, instead of fatigue, sleep problems are more associated with pain and emotional distress [115]. The relationship between sleep and cancer related fatigue may therefore be more complicated.

3.3 Circadian disruption and cancer-related fatigue

Robust circadian rhythms are strongly associated with good health. Cancer and hospitalization can disrupt circadian rhythms [116]. One proposed underlying mechanism of CRF is disrupted circadian rhythm. Several studies used a wearable sensor to detect the subjects' activity, showing changes in daily rhythms. One study used the waist accelerometer which measured the daily activity, and further compared the daily activity before and after the first chemotherapy. This showed clear decreased activity after the chemotherapy, however, the changes in daily activity may be masked by the hospitalization [117]. Another study showed that the patients who wear the waist accelerometer show a dampened 24-h activity pattern compared with healthy subjects, and this dampened rhythm was associated with the level of fatigue, appetite and poor survival [118,119]. There is growing interest in HPA axis function and associated cortisol release in cancer survivors who have had fatigue complaints for years [120]. The daily cortisol rhythm is under strong control of the circadian clock. In healthy adults, a typical diurnal cortisol pattern is characterized by a high morning level that peaks about 30 min after awakening, followed by a decline over the course of the day with the lowest level achieved around midnight [121]. Breast cancer patients showed a dampened cortisol response compared with healthy subjects, and the decline in cortisol levels during the night is blunted in breast cancer patients [120,122]. However, it is not known whether these changes are the effects of fatigue or causal factors, for example, daily dysfunctioning.

Yet, these studies do not provide insight into the timing of the clock and the relation with fatigue. Animal models may provide more insights into the relationship among the circadian timing system, sleep-wake cycle and cancer related fatigue. Wheel running in rodent is voluntary, motivated behavior. Wheel running behavior is also a measure for accessing the circadian clock controlled behavior under continuous recording condition. Furthermore, wheel running is also viewed as a measurement of fatigue. In this case, with the animal fatigue model, it may be easier to answer the question : " Is fatigue a sleep problem, or clock problem, or both?".

Disruptions of normal circadian rhythms and sleep cycles are consequences of aging and can profoundly affect health. Accumulating evidence indicates that circadian and sleep disturbances are a risk for mood disorders and neurodegenerative conditions, and may actually drive pathogenesis early in

the course of these diseases [123-125].

In order to ensure normal functioning of the circadian clock, environmental time cues are quite important. Circadian misalignment occurs when the internal timing system runs out of synchrony with the behavioral cycle. One common example of circadian misalignment is shift work which misaligns the sleep-wake rhythm to the objective night. Shift work can result in disrupted sleep, impaired cognitive performance, fatigue, decreased alertness, impaired energy metabolism and inflammation (Figure. 7) [125-129]. Other types of misalignments include internal misalignments between the central and peripheral clocks. For example, research in animal models has demonstrated that altering the availability of food timing shifts the peripheral clock but not the central clock [130].

The rest-active rhythm is also a biomarker that reflects the robustness of the clock in patients. Interestingly, most cancer survivors benefit from daily exercise or routines [131,132]. These interventions probably help to maintain normal circadian rhythms in the body. Furthermore, cancer patients suffering from circadian disruptions have poor health outcomes compared to patients who have a robust daily activity rhythm [132,133]. Studies in rodents have added more evidence from different types of cancer, chemotherapy, radiotherapy and the consequences of circadian disruptions [134-137]. 5-fluorouracil affected rhythmicity of clock genes expression in the SCN and decreased locomotor activity during the dark phase under chronic treatment [138]. Clock mutant mice are more sensitive to the chemotherapy treatment with cyclophosphamide [139]. Recent advances identify disturbed clock gene expression and circadian rhythms to correlate with tumor development and tumor progression in mouse models [136,140,141]. These studies offer new insight into the interaction of previously unsuspected pathways with the circadian system besides cancer or treatments themselves. We can also begin to rationally develop new treatments for disorders affected by circadian disruptions.

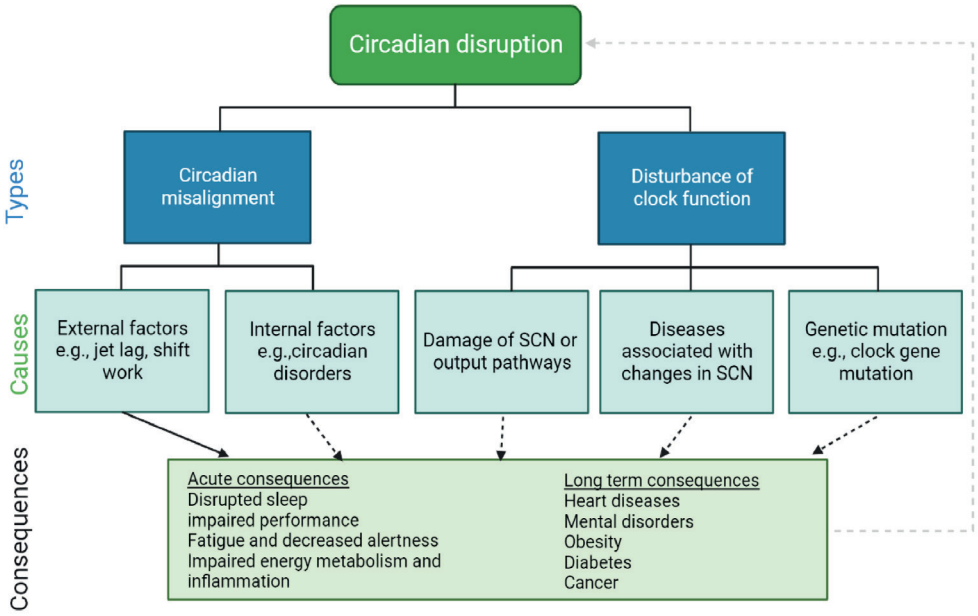


Figure 7. Schematic overview of different types of circadian disruptions, the causes and the consequences of health under acute and chronic situations. Acute and long-term consequences may send feedback and further disrupted the circadian clock. Modified from Rüger et al., 2011 [125].

Outline of this thesis

This research aims to understand how the circadian clock and sleep are influenced by different drugs, which include the most common CNS stimulant caffeine, ketamine, the newly proved anti-depressant drug, and anthracyclines, a widely used group of chemotherapeutic agents.

Caffeine is one the most widely used psychoactive stimulant across the world, it is known as a nonselective adenosine receptor antagonist, and it has been more than 60 years since adenosine has been discovered to be involved in sleep. However, most of the previous experiments have been performed under light-dark conditions and the entrainment of light has a massive effect on sleep-wake rhythm and is known to interact with caffeine. Thus, our question is how long the effect of acute caffeine lasts under constant dark conditions. **Chapter 2** describes the effect of acute administration of caffeine on sleep, sleep EEG and the circadian clock in Brown Norway rats.

As described in the introduction, mental health has a complex relationship with sleep, and the rapid-antidepressant effect of sleep deprivation is not well understood. Ketamine has a similar rapid anti-depressant effect and also changes sleep. Thus our hypothesis is that the rapid anti-depressant effect observed from both sleep deprivation and ketamine may have a similar effect on sleep and the sleep EEG. In **Chapter 3**, we investigate the relationship between the two treatments comparing the effect of sleep deprivation and low dose ketamine on sleep in Brown Norway rats.

The effect of chemotherapy on sleep and the circadian clock was investigated in **Chapter 4**. During chemotherapy, most patients complain about how tired or fatigued they feel both under the treatment and months to years after finalizing treatment. There are several hypotheses about the mechanisms of cancer-related fatigue, but there is still too much unknown about this particular type of tiredness. In this chapter, we want to investigate if CRF is a circadian problem, a sleep problem, or both. At the end of chapter 4, we conclude that it is a circadian problem, in which waking, rather than sleep is affected

Based on the conclusion in chapter 4, in **Chapter 5**, we performed a followed-up experiment that further investigated the effect on the neuronal activity of SCN and peri-SCN areas in the brain, rest-activity behavior, immune system responses and the effect on kidney and spleen, to establish where the circadian clock may be involved in CRF.

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