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

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General Discussion

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This thesis consists of two parts. The overall theme is the study of pharmacological treatments and their effects on sleep and the circadian clock. The first part, consisting of **chapter 2** and **3**, focuses on the long-term effects of caffeine, ketamine and sleep deprivation (SD) on vigilance states, electroencephalogram (EEG) power density spectra and locomotor activity under constant dark conditions. For this first part, we asked two questions: 1. How long do the effects of the treatments last?; 2. What are the similarities and differences in the effects of SD and ketamine on sleep and the EEG? This latter question is of interest because both treatments are known for their rapid antidepressant effect. The second part, **chapters 4** and **5**, explores the mechanism of cancer related fatigue (CRF) induced by chemotherapy. Here are three questions we tried to answer: 1. Is CRF a clock problem or a sleep problem? 2. How does neuronal activity in the suprachiasmatic nucleus (SCN) respond to chemotherapy? 3. As a follow up question, we investigated the alignment between activity of the central clock versus the brain, and the bodily function and behavior.

1 Drugs that influenced sleep

1.1 Acute caffeine had a long lasting effect on REM sleep and neuronal activity of the hypothalamus

Caffeine is a commonly used central nervous system (CNS) stimulant which is known to increase waking and alertness. Most studies report only short-term effects of caffeine administration. However, the effect of caffeine may last longer, particularly under conditions of low light levels or constant darkness. In **chapter 2**, we investigated the long-term effect of acute caffeine administration on sleep, EEG power spectrum and neuronal activity of peduncular part of the lateral hypothalamus (PLH).

After treatment with caffeine, we found that waking was increased and sleep was delayed, on the first day after treatment, which is the normal and well-known response to caffeine. However, we also observed that the amount of activity in the peduncular part of the lateral hypothalamus (PLH) and the amount of REM sleep was still reduced on the second day. Research on the acute effect of caffeine (100mg, a dose that is at the lower limit of the effective dose range) at bedtime in human has shown prolonged sleep latency

and decreased sleep pressure [1]. The dosage in our study, which is equal to 3 – 4 mg/kg in human (around 200 - 300 mg), is considered to be a medium to a high dose of caffeine. Studies in humans showed that higher doses (400 mg) further prolong sleep latency, decrease total sleep time, sleep efficiency and reduce the amount of SWS and REM sleep [2]. More recent research in adolescents showed that a single dose of 80 mg caffeine (content in 250 ml of energy drink) is also enough to induce alertness at a subjective level and slightly reduced SWS [3]. Consistent with the notion of the arousal effect of acute caffeine in humans, animal studies give more insights into the changes in adenosine receptors, neurotransmitters and brain activity [4-6]. It was shown that caffeine mediates its effect by an antagonistic action on adenosine receptors [7].

Adenosine is thought to increase extracellularly after prolonged waking, and has been proposed as an indicator of the need to sleep. During the spontaneous sleep-wake cycles, extracellular adenosine levels to increase during waking and decrease during sleep in several brain regions [8]. Moreover, microdialysis studies in rats revealed that adenosine level increased by more than 200% in the basal forebrain after a 6 hour sleep deprivation (SD) [9]. In a recent study, Peng et al. first designed a genetically encoded G protein–coupled receptor (GPCR)–activation-based (GRAB) sensor for adenosine ($GRAB_{Ado}$). This sensor was expressed in the basal forebrain and the fluorescence was measured by fiber photometry [10]. With the high temporal resolution of this adenosine sensor, a higher concentration of extracellular adenosine during REM sleep was found, even higher than compared with waking [10]. This may indicate that the REM sleep state is more sensitive to adenosine antagonists, like for example, caffeine, than previously thought, which may have led to the prolonged influence of caffeine or caffeine metabolites on REM sleep in our study.

Interestingly, when caffeine was taken daily, the changes in waking which we observed in acute administration in both animals and humans were not visible [11,12]. Studies in human showed that SWA in NREM sleep during night was not different after nine successive days of chronic caffeine consumption (3 x 150 mg, daily) compared with a placebo. Moreover, chronic caffeine did not change the sleep structure in these healthy subjects [12]. Thus, caffeine intake might differently affect the homeostasis of sleep when taken in an acute and chronic manner.

In acute caffeine experiments, it is well documented that caffeine not only has an effect on sleep, but also on the circadian clock [7]. The SCN is sensitive to caffeine in both humans and rodents, suggesting there is a pathway where adenosine and its receptors are involved in influencing the SCN network [13-16].

In our results, caffeine caused an increase in neuronal activity in the PLH. It has been demonstrated that systemically administered caffeine induced c-Fos expression in several brain areas, including the cortex and hypothalamus, that control energy homeostasis [17]. Caffeine activated the orexin neurons in the lateral hypothalamus (LH) in rats [18]. There is also evidence indicating that injection of orexin A into the rostral LH of rats induces running independently of feeding behavior [19]. This may indicate that caffeine can increase activity in the LH and may be active by the orexin neurons, which may be in line with our finding of increased REM sleep and increased neuronal activity in the PLH after acute administered caffeine.

1.2 Similarities between ketamine and sleep deprivation on sleep, differences in waking

Disrupted sleep is more likely to increase the risk of developing mental illness, like anxiety and depression [20]. In the *diagnostic and statistical manual of mental disorders-IV-TR*, both insomnia and hypersomnia are common symptoms of depression, indicating that sleep disruption is common in depression [21,22]. The implication is that disrupted sleep can be a symptom or consequence of mental problems and is suggestive for a bi-directional link between sleep and mental health. Sleep deprivation (SD) and low dosages of ketamine are two rapid-acting antidepressant treatment strategies. In **chapter 3** of this thesis, the effect of both ketamine and sleep deprivation on sleep and EEG power density were compared.

Although both treatments are rapidly acting anti-depressant treatments that also influence sleep and the sleep EEG [23,24], there are not many studies comparing the two treatments on these effects [25]. In chapter 3, we compared these two treatments in the same animal model, and determined the similarities and differences in their effect on sleep and waking and the EEG power spectrum. The sleep-wake changes after SD and ketamine were in line with what was known from previous studies. In our study, however, we show that the EEG power spectrum of waking immediately after ketamine

is different compared to during SD, which suggests that SD and ketamine induce two different qualities of waking. Further, we analyzed the subsequent NREM and REM sleep power spectrum and noticed that both ketamine and SD increase slow wave activity in the NREM sleep EEG, which suggests that both treatments had a similar effect on sleep homeostatic processes in the recovery period after the initial waking period. Although ketamine induced hypoactivity, the waking EEG was not different compared with saline during waking after sleep onset. This may indicate that the active waking induced by ketamine only lasts for 2-3 hours; after which the waking power spectrum is less influenced by ketamine. When we compared the waking and NREM sleep power spectrum, we noticed that the peak frequency is faster after SD than the baseline condition and ketamine treatment, this may suggest that the cortex is activated differently during the recovery period after SD compared to ketamine. In contrast to the strong acute sleep disturbance, ketamine administration and SD were not associated with long-term changes in sleep-wake architecture, however, both SD and ketamine were associated with long-term changes in EEG power density, especially in the NREM and REM sleep EEG. The common actions of SD and ketamine on sleep consist of an acute increase in NREM sleep SWA and a reduction in REM sleep. With the similar features of these two rapid antidepressants, it may help to target these similarities to develop new treatments against depression.

2. Is cancer related fatigue a clock problem? Or a sleep problem?

Cancer related fatigue is a debilitating side effect of cancer and cancer treatments. However, the mechanism underlying cancer-related fatigue is unclear. In **Chapter 4** we investigated how sleep and clock controlled behavior changes under chemotherapy induced fatigue. Furthermore, **chapter 5** is a follow-up study that further investigates the effect of chemotherapy on the master clock and peripheral circadian activity in the brain and body.

Fatigue is a common and distressing symptom reported by cancer patients before, during, and after cancer treatments, and it has negative effects on the quality of life [26-29]. Chemotherapy is nonspecific, thus it not only eliminates tumor cells, but also damages normal cells and tissue and is known to cause side effects through that. Cytotoxics, including but not limited to doxorubicin, etoposide, 5-fluorouracil and paclitaxel cause fatigue symptoms both in human and mouse models [30-35]. Different types of chemotherapy

also had different side effects, even if they came from the same drug family. Furthermore, patients who received dose-dense or standard-dose taxane treatments presented no significant difference in fatigue scores, indicating that fatigue severity changed significantly over time with different chemotherapy treatment types [36,37]. Sleep problems are commonly mentioned in patients with cancer, and CRF may influence sleep efficiency, maintaining sleep and waking [38,39]. In chapter 4, we applied three different anthracycline cancer drugs to investigate the effects on circadian controlled wheel running activity and the sleep-wake cycle in a fatigue model. Wheel running activity is not only a voluntary behavior but also a circadian controlled behavior. Therefore, it can be applied as a measure for both fatigue and daily circadian rhythms in mice. Voluntary running, compared with forced activity like treadmill running, is a naturally occurring and spontaneous behavior in rodents, more related to the level of fatigue of the animal [40]. The fatigue-like behavior induced by doxorubicin showed similar symptoms as found in cancer patients in their daily activity (Figure 1) whereas the other treatments (aclarubicin and etoposide) did not induce these long-term symptoms. To our surprise, the sleep-wake cycle was not disrupted and the EEG power spectrum was not differing substantially from the baseline condition in the chemo-induced fatigue mice. This may indicate that objective sleep is less disrupted in a chemotherapy induced fatigue model, and suggests that there may be an association between impaired circadian rhythms and fatigue severity. We found that as the animal showed fatigue symptoms, their circadian rhythms became less strong. Compared with sleep problems reported by the patients and studied in animal models, this is one of the few studies investigating the relationship between CRF and circadian rhythm, but, the fatigue symptoms may be more complex in cancer patients and survivors.

It is generally accepted that fatigue is related to the loss of muscle mass, but research has found that fatigue like symptom, such as decreased wheel-running distance is not correlated with muscle contractile properties or motor coordination, indicating that fatigue is more associated with behavioral activity motivation rather than muscle dysfunction [32,37,41].

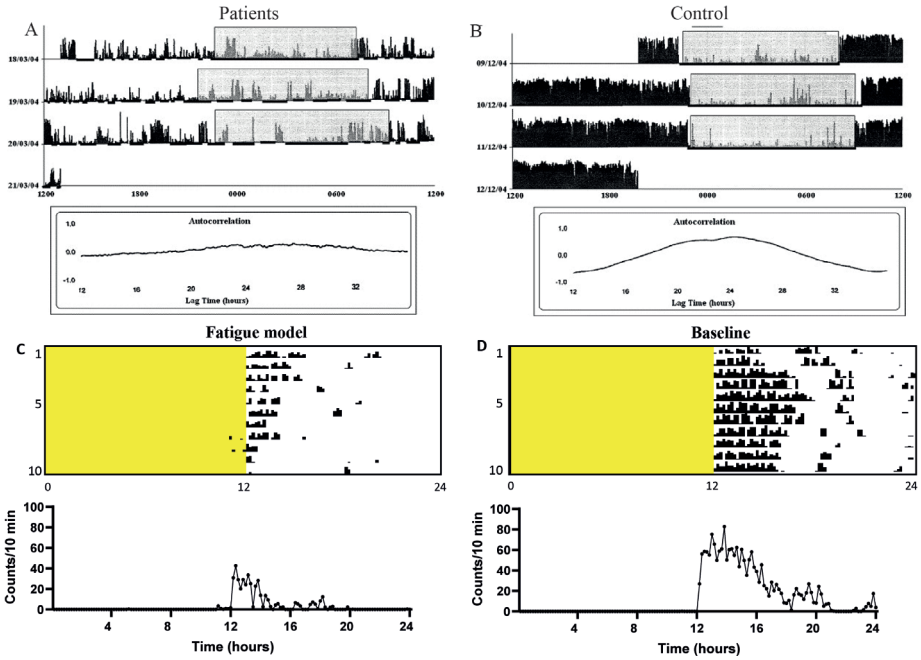

Figure 1. The actogram of patients and animal models. A. B are the representative actograms of cancer patients and healthy control. Grey block indicated the sleep period. Adapted from Fernandes et al., 2006 [43]. C. D are the representative actograms after chemotherapy and the baseline recording of the same animal. The lower panels are the average of 10 days running activity, data was sampled in a 10 min bin size. Yellow indicated the light phase.

Chemotherapy induced fatigue also depends on the type of cytotoxic drugs patients receive. In our study, we tested three different cytotoxins, aclarubicin, doxorubicin and etoposide. Only the mice treated with doxorubicin showed clear fatigue like symptoms both during treatment and after treatment. One previous study found that female C57Bl/6J mice displayed significantly reduced wheel running activity under repeated etoposide administration, and etoposide may induce CRF by increasing interleukin-6 concentration in serum [31]. In our study, we did notice that the mice treated with etoposide showed a slower recovery of wheel running activity after the etoposide compared to aclarubicin, but we did not find the chronic fatigue phenotype like after doxorubicin. Aclarubicin treatment did not induce fatigue like symptoms in our animal model. It was also reported that patients who received combinations of cyclophosphamide, fluorouracil, doxorubicin experienced more severe fatigue than those who received only paclitaxel in breast cancer patients [42]. Despite that these cytotoxics belong to the same drug family as those used in our study, they still induced different levels of fatigue both in our animal

model as well as in cancer patients.

In summary, in chapter 4 we used an animal model which can mimic the pathological features (decreased voluntary activity) of chemotherapy induced CRF. This allowed us to test the side effects of different cytotoxics from the same drug family. CRF appeared strongly dependent on the type of chemotherapy, and hopefully this knowledge will lead to an additional criterium for selecting cancer drugs for treatment. This would strongly contribute to the quality of life for (ex-) patients.

2.2 Cancer related fatigue and internal misalignment

The results we obtained in chapter 4 indicated that CRF is related to a disrupted circadian clock. In chapter 5, to understand how doxorubicin disrupts the clock and clock controlled running behaviors, we set up a follow-up study, to explore the neuronal activity of both SCN and peri-SCN brain areas before and after the doxorubicin treatment.

There is recent evidence showing that cancer and cancer treatment may influence the central circadian clock [44,45]. One study used the PER2::LUC rhythms in SCN slices and adrenal glands after paclitaxel and showed that paclitaxel shortened SCN slice circadian rhythms, increased the amplitude of adrenal gland oscillations in PER2::luciferase cultures, and increased the concentration of pro-inflammatory cytokines and chemokines released from the SCN [46]. However, in a brain slice, without all the inputs to and outputs from of the SCN, it is challenging, if not impossible, to predict the full consequences for the *in vivo* condition.

Thus, we applied multi-unit activity (MUA) recordings in the SCN and in the peri-SCN areas (hypothalamus areas, surrounding SCN), which allowed us to measure the neuronal activity in both brain areas. To our surprise, the SCN maintained its normal neuronal 24-hour rhythm in the mice that showed fatigue like symptoms. We further checked the MUA recording of the peri-SCN, and we observed a disrupted circadian rhythm in the electrical discharge of the neurons. Therefore, the data showed that the clock is still ticking normally but that the output of the SCN is disturbed after the doxorubicin treatment. Together, this new evidence, highlights that the rhythm of the SCN remained strong in mice with CRF but shows a reduced synchronization with the peripheral brain areas. We proposed that the cause of fatigue-like symptoms

originate from a reduced output of the circadian clock with consequently a reduced waking promoting effect (Figure.2)

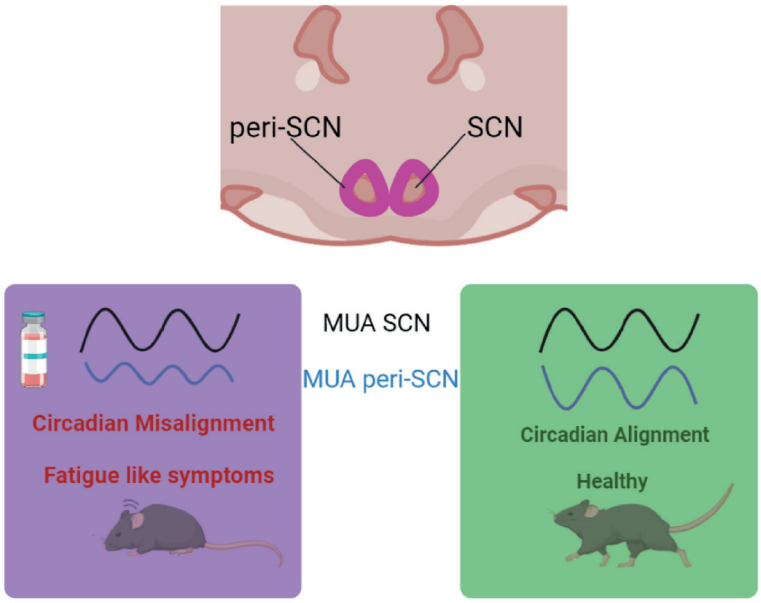

Figure 2. Internal misalignment and cancer related fatigue

2.3 What is the origin of the reduced signaling capability by the SCN?

The running wheel data showed that the 24 h rhythmic behavior was much more disrupted after doxorubicin treatment compared with the baseline condition in the same mouse, but to our surprise, the SCN maintained its 24 hour neuronal activity. One recent study hypothesized that the central clock is disrupted in CRF mice [46]. Here our study showed that even though the mice show disrupted circadian behavior, its 24-h rhythmic electrical activity in the SCN was intact. Partial lesions of the SCN in squirrel monkeys, even though only 20% of the SCN remained, still showed persisting rhythmicity in body temperature (Tb) [47]. Similar findings were obtained in male Long-Evans rats after partial SCN lesion [48]. The resilience of circadian timekeeping of the SCN, demonstrated by these findings may be a unique neurophysiological property of the SCN. Besides the evidence shown by the lesion studies, also in several animal disease models, the SCN clock still functions even though the behavior is arhythmic. In the mouse models of fragile X syndromes, the *Fmr1* knock-out and *Fmr1/Fxr2* double knock-out mice still showed rhythmic SCN

activity in *in vitro* electrophysiology recording which indicated that the output is affected [49]. Similarly, a mouse model of Huntington's disease replicates the disrupted behavioral rhythm of the human disease, but the *Per2* rhythm within SCN does not seem to be affected in the BACHD (expressing the entire human huntingtin gene with 97 mixed CAA–CAG repeats) transgenic mouse model [50]. Interestingly, in SCN brain slices of animals treated with paclitaxel, a commonly used chemotherapy in clinical, the *Per2* rhythm was intact even though the mice showed disrupted behavioral rhythm and fatigue symptoms after treatment [46]. Likewise, in aging mice, the behavioral activity and rhythmicity is reduced, despite normal electrical rhythmicity in the SCN [51]. These studies suggest that circadian timing control in the SCN might be maintained under particular disease states, including CRF.

Behavioral activity rhythms are driven by the SCN, but vice versa, activity itself feeds back to the SCN electrical activity [52]. Behavioral activity maintains a phase-locked relation to the activity of SCN neurons in anti-phase in nocturnal animals. The fatigued mice showed a reduction in this phase locking meaning that the SCN rhythm is only loosely coupled to behavior. Intriguingly, the peak time of peri-SCN area neuronal activity was changed, indicating that the circadian timing was disrupted in these peri-SCN areas after doxorubicin treatment. This change was in phase with the changes in the peak time of the rest-activity behavioral rhythm. The peri-SCN areas were not able to generate robust circadian rhythms under DD condition, which indicates that the circadian timing system is weak in doxorubicin induced fatigue mouse model.

3. Concluding remarks and future Perspectives

In the first part of this thesis, we observed a long-lasting effect of caffeine on REM sleep and theta activity in REM sleep, not previously observed. We obtained these results under constant dark conditions, which may be important, considering the interactive effects of light and caffeine on sleep and the circadian clock. In future research, it may be important to consider lighting levels when investigating the effects of caffeine in humans and rodents. Moreover, since this long-term effect of caffeine was observed, the time between different treatments in the case of caffeine should maybe also be longer in future experiments.

SD is a widely documented rapid antidepressant treatment, but SD alone has

only a transient effects on mood. However, the effect can be sustained by treating the patient with selective serotonin reuptake inhibitors and circadian related interventions that include a phase advance of the sleep-wake cycle and bright light therapy [53]. Ketamine raised attention these last two decades because of its rapid antidepressant effect. Hence, considering the similar fast effects, comparing SD and ketamine may actually give us more insight into the mechanism of the antidepressant effect of both. In chapter 3 we showed that both the acute effect and long-lasting effect share similarities in the sleep EEG power spectrums of both, and that differences between the two are mainly found in waking. Moreover, from the similarities we observed in our study, we may be able to explain the rapid antidepressant effect on different levels, such as sleep homeostasis, and glutamatergic mechanism [53]. Although the neurophysiology mechanisms involved in rapid antidepressants, and how chronobiological and sleep interventions improve the rapid antidepressant effect, are still unknown, inducing these shared effects on sleep and chronobiological variables may be beneficial for the patients.

With regard to chemotherapy and the circadian clock, our study only showed differential effect of cytotoxic effects on chronic fatigue. Doxorubicin, a frequently used drug in the clinic had major effects whereas aclarubicin had only minor effects on fatigue like symptoms. Although we did not find any changes in sleep-wake rhythm a few weeks after the treatment, there are some studies that showed disrupted sleep after chemotherapy [34]. This may, however, be related to disturbance in the communication of the circadian clock with the rest of the brain, as we showed in Chapter 5. Future studies should examine both the acute and chronic effects of these treatments in mice, to see whether the same mechanisms driving the acute response to the chemotherapy are also responsible for the long-term fatigue in the CRF mouse model and to see whether these effects can be prohibited.

A strong circadian clock that is able to signal its rhythm to the rest of the body may be essential in preventing cancer related fatigue. This is supported by the notion that patients with a robust 24-h rhythm have a higher survival outcome than those who suffer from these disruptions [54,55]. Based on the results we obtained from our animal model, we hope to raise awareness of circadian disturbances among the patients who get doxorubicin treatment. These patients may need interventions to boost their circadian rhythms during and after chemotherapy. Interventions aimed at maintaining circadian alignment with the light/dark cycle, may include exercise to boost the circadian

amplitude. Also, increased exposure to natural light or light treatment could be promoted, engaging in out-of-bed activities, scheduled food intake, and minimizing napping in the daytime, minimal light, noise and disruptions maintaining regular bedtime routines [56,57]. The response to chemotherapy may also vary with the time of day, which has led to timing of treatment, or chronochemotherapy, as a means to improve the therapeutic efficacy of cancer treatment while limiting toxicity and side effects [58] [59]. CRF is a major consequence of cytotoxic doxorubicin treatment. This serious debilitating effect can probably be prevented by better selection and/or development of the drug.

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