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

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Summary

The circadian timing system is highly integrated with the sleep-wake regulation system. This thesis focuses on how different pharmacological treatments influence the sleep regulation system and the circadian timing rhythm in two murine models. In the first animal model, which is presented in Chapter 2 and 3, we implanted EEG/EMG electrodes in freely moving Brown Norway rats. We chose this rat strain because it is pigmented and therefore a more representative model than the more mainstream rat strains which are usually albino rats. This study aimed to investigate the effect of caffeine, sleep deprivation and ketamine on sleep and circadian-controlled activity under constant darkness. In the second animal model, which is presented in Chapter 4 and 5, we implanted EEG/EMG or Multi-unit electrodes in chemotherapy-induced fatigue mice. This study aimed to investigate the effect of anthracycline cancer drugs on sleep, wheel running behavior, and brain neuronal activity.

In **Chapter 1**, we review the circadian timing system and physiology of sleep. The first section focuses on neuronal anatomy, physiology and the genetic bases of the circadian timing system. This is followed by a description of the neurophysiology and homeostatic regulation of sleep and the pharmacological regulation of sleep-wake function. Finally, the possible mechanism of cancer related fatigue and the relation among fatigue, sleep-wake and the circadian rhythm are discussed.

In **Chapter 2**, we studied the effects of acute caffeine administration on sleep-wake regulation and the neuronal activity in the peduncular part of the lateral hypothalamus. Most studies investigate the effect of caffeine for 24 hours but not long enough. We therefore investigated after effects of acute caffeine for two days. We found that acute administration of caffeine led to a decrease in REM sleep lasting for approximately two days. In addition, in vivo electrophysiology recordings of the peduncular part of the lateral hypothalamus showed increased neuronal activity that also lasted for two days, particularly in NREM sleep. This is evidence that caffeine influenced sleep-wake regulation substantially longer than thought until now.

In **Chapter 3**, we compared the similarity and differences between sleep deprivation and acute ketamine administration on sleep, EEG power spectrum and locomotor activity. Sleep deprivation and ketamine administration are the

few therapies that can have a rapid antidepressant effect in depressed patients. Most of the studies ignored the overlapping effects of these two therapies on sleep and circadian rhythm. The common actions of sleep deprivation and ketamine subsequently on sleep consist of an acute increase in NREM sleep SWA and a reduction in REM sleep. Although both sleep deprivation and ketamine initially keep the animals awake. Our detailed analysis show that the mechanisms of waking inducting effect is probably different and therefore not related to antidepressant effect. Therefore, we hypothesis that reducing REM sleep and increasing SWA can be part of the mechanism of the antidepressant effect.

The second animal model in this thesis we used is cancer-related fatigue mouse model. We use the C57BL/6J mouse which is commonly used in the circadian, sleep, and pharmacology field. Cancer related fatigue is a devastating side effect of cancer, cancer treatments, or both. In **Chapter 4**, we investigated three different anthracycline cancer drugs on wheel running behavior, sleep architecture and EEG power density spectrum before and after chemotherapy. Mice treated with doxorubicin, which combines both DNA- and chromatin damage activity, results in increased fatigue symptoms in tumor-free mice. In contrast, treatment with aclarubicin or etoposide which use only one of the two mechanisms failed to induce long-term fatigue, suggesting that the development of this devastating side effect is probably the result of combined DNA- and chromatin damage activity. In addition, we observed that fatigue was not the result of changes in sleep duration. We conclude that fatigue symptoms are more associated with a disrupted circadian rhythm, hinting at a deficit in SCN clock.

To further explore to what extent chemotherapy influences the circadian clock, in **Chapter 5** we examined the neuronal activity of the SCN master clock, and the peri-SCN areas located in the hypothalamus in the doxorubicin induced fatigue mouse model. Similar to what we observed in the mouse model in chapter 4, the doxorubicin treated mice showed decreased wheel running activity, decreased strength of the circadian clock, lower day-to-day stability and increased fragmentation of the rest/activity cycle. Next we investigated whether the behavior phenotype was caused by a disrupted rhythm produced by the SCN, or alternatively, by a reduced capacity of the SCN to impose the circadian rhythm, on other brain areas. We found that the doxorubicin treated mice still showed robust rhythmic SCN neuronal activity. However, the relative timing of peri-SCN areas activity and behavior was

affected by the doxorubicin treatment. This indicates that the disruption in circadian behavior is caused by the internal misalignment between the master circadian clock and the periphery.

The studies in this thesis contribute to understanding the effect of caffeine, ketamine, sleep deprivation and anthracycline in sleep-wake regulation and the circadian timing system. All the results from this thesis and future perspectives were discussed in **Chapter 6.** We are able to see how disruption of sleep and the circadian clock adversely affect health and may contribute to many diseases in modern society. In this thesis, these studies provide a better understanding of these drugs influence the circadian timing system and sleep - wake regulation and maybe new treatment approaches for antidepressant therapy and cancer related fatigue.