

Advances in the study of corticoid and melatonin in circadian rhythm disorders of oncology patients

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Abstract. It has been increasingly common to be diagnosed with cancer in recent years. In addition to cancer itself, which torments the patient and impairs body functions, oncology patients may develop many complications, and sleep disorders are one of them. Sleep disorders that are found in tumor survivors including sleep related breathing disorders, sleep related movement disorders, parasomnias, central disorders of hypersomnolence, insomnia and circadian rhythm sleep-wake disorders (CRSWDs). It has been proved that tumors are the cause of sleep disorders, but the mechanism underlying them remains unknown. Therefore, the study of the mechanism of sleep disorders in oncology patients has become very popular among researchers today. A wide range of systemic tumors, including brain tumor, pancreatic cancer, colon cancer, lung cancer, renal tumor and so on have a mutation of RAS or MYC, which may cause circadian rhythm disorders through some changes on Clock genes in the body. This review will focus on whether different tumors follow the same mechanism causing circadian rhythm disorders. Whether Melatonin and Cognitive Behavioral Therapy (CBT) are efficient in treating post-cancer sleep disorders in clinical trials will also be introduced.

Keywords: Circadian Rhythm Disorders, Cancer, Corticoids, Melatonin, Oncogene, Treatment.

1. Introduction

According to the World Health Organization (WHO), cancer is one of the most common causes of death nowadays. However, fewer people smoke and medical science and technology are improved, so in fact, the population died of cancer from the 1990s to 2018 is continuously decreasing [1], which also means an increase in the number of oncology patients in survival phase. During cancer survival phase, patients often develop a range of complications, such as fatigue, sleep disturbances, pain and so on, due to cancer itself, psychological factors or treatment, which are not generally expected.

Sleep disorders are also very common problems in patients with cancer, and there are many factors that can cause sleep disorders. Sleep disorders have a bad impact on physical and mental health, and can even cause the aggravation of their own diseases. Sleep disorders are characterized by insufficient sleep, excessive sleep duration, or abnormal activity during sleep. There are six diagnostic features of major sleep disorders, which are insomnia, circadian rhythm disorder, sleep disordered breathing, narcolepsy/hypersomnia, abnormal sleep and restless leg syndrome/periodic limb movement disorder. These features can be very helpful in treating sleep disorders, especially in patients with cancer who have long struggled with the problem.

Some sleep disorders oncology patients commonly generates are insomnia/sleep-wake disturbances, breathing disorders (e.g. obstructive sleep apnea), circadian rhythm sleep-wake disturbances and sleep-related movement disorders (e.g. restless legs syndrome) [2]. Some researches show that therapy for cancer could be a possible cause of sleep disorders. For example, Pruritus caused by targeted anticancer therapy may also be a reason to sleep disturbance, though the mechanism remains unknown [3]. Adverse effects of some anticancer therapy can also contribute post-cancer sleep disorders, for example, Savard et al found that androgen deprivation therapy (ADT) and radiation therapy (RTH) can cause insomnia due to side effects such as hot flashes and night sweats [4]. In addition, Willis et al. have recently found that corticosteroid use was attributed as the

most significant factor leading to sleep disturbance in a clinic observation of brain tumor patients [5]. Although The prevalence of circadian rhythm disorders in cancer patients is not as high as insomnia, it is still very common to develop circadian rhythm disorders among cancer patients. Criteria that are recommended by physicians include actigraphy and biomarkers such as dim-light melatonin onset. Craniopharyngiomas are epithelial-derived neoplasms that occur exclusively in the region of the sella turcica and suprasellar cistern or in the third ventricle. Patients with craniopharyngiomas may present with pituitary hypofunction because of compression of the pituitary gland, pituitary stalk, or hypothalamus. In the following part of this review, whether some special kinds of tumors could lead to circadian rhythm disorders will be discussed.

The aim of this review is to overview the molecular mechanism under the development of cancer-related sleep disorders, and discuss developments in the treatment of sleep disorders in cancer patients. Cancer based inflammatory factor levels are always a popular topic of research, but the detailed mechanisms have not been studied thoroughly enough at present [6]. The positive effects of melatonin and Cognitive Behavioral Therapy (CBT) on circadian rhythm disorders based on clinical observation and the mechanism of action of the treatment component are also briefly described at the end of the article.

2. Potential Molecular Mechanisms of Corticoids and Melatonin in Oncology Patients with Circadian Rhythm Disorders

2.1. Corticoids

Cortisol rhythms have been shown to be inextricably linked to sleep. Most normal cortisol rhythms show low levels during the night, gradually increasing from the early morning, reaching a peak in the morning, and gradually decreasing during daytime [7]. As research progresses, more and more studies make the connection between cancer and circadian rhythms [8], including changes in pharmacokinetics and targeted responses in cancer due to altered circadian rhythms, and the impact of cancer on circadian rhythms which is described in the following details.

2.1.1 Synthetic Glucocorticoids

Synthetic glucocorticoids are widely used in the treatment of rheumatism, lung diseases, gastrointestinal diseases and skin diseases. In cancer, synthetic glucocorticoids are often used as anti-cancer drugs or for antiemetic purposes. Previous studies showed that the use of synthetic glucocorticoids [9], such as dexamethasone suppression test (DST), could disrupt circadian rhythms through affecting glucocorticoid receptor function and altering cortisol rhythms. In a recent study, Rao et al. found that long-term daily dosing of synthetic glucocorticoids could result in altered cortisol rhythms, and irregular dosing resulted in dysregulation of cortisol rhythms [10].

2.1.2 Tumor-related Corticoids

Some kinds of cancer, may cause ectopic adrenocorticotrophic hormone (ACTH) syndrome, which induces an abnormal level of corticoids. ACTH syndrome, also known as ectopic Cushing syndrome, is caused by an increase in cortisol levels due to the production of ACTH by cells outside the pituitary gland. Tumors that usually cause ACTH syndrome including lung cancer, pancreatic cancer, medullary thyroid cancer and thymic cancer [11]. A recent study has shown that cancer tends to affect the rhythm of cortisol in patients with adrenal incidentalomas [12]. About 30% of patients with adrenal incidentalomas have mild symptoms of autonomic cortisol hypersecretion [13]. In a meta-analysis of data, Debono et al. found that patients with autonomous cortisol secretion may have a disturbed cortisol rhythm (usually manifested as nocturnal excess) and that this phenomenon is likely to be related to IL-6, and that patients' cortisol rhythms tend to be improved after metyrapone administration [12]. But surprisingly, there tends to be no study of circadian rhythms in adrenal incidentalomas patients with autonomic cortisol hypersecretion. A recent study on breast cancer and cortisol tends to show a link, finding that a proportion of breast cancer patients have abnormal cortisol

levels at night, often accompanied by acute sleep disruption when cortisol peaks at night [14]. Similarly, some other patients with advanced cancer seem to have abnormal cortisol rhythms (flattened cortisol rhythms), and these factors have been used as predictors of carcinogenesis in some studies [15,16].

2.2. Melatonin

Another notable hormone is melatonin, because when it comes to sleep, many researches are about melatonin. It is known that, the secretion of melatonin is with circadian rhythmicity, regulated by the suprachiasmatic nucleus (SCN) [17]. Melatonin secretion is also related to light, temperature and other factors [25]. Researches show that, the same as corticoids, tumors may affect its secretion level.

The mechanism of the effect of cancer on melatonin rhythm has not been studied clearly yet, but a sleep-wake study in craniopharyngioma patients showed that there was a disappearance of the midnight melatonin peak, which often leads to sleep disorders in a proportion of craniopharyngioma patients, and that melatonin was independently associated with sleep duration after cortisol was modulated. In addition, it also causes symptoms such as daytime drowsiness and fatigue [20]. A recent study suggests that children and adolescents with brain tumor appear to have reduced melatonin production that affects circadian rhythms, leading to a reduced quality of life for patients [21]. In a study of patients using non-functioning pituitary macroadenomas (NFMA), Joustra et al. also found that patients frequently experienced abnormal melatonin secretion, leading to symptoms such as sleep disorders and daytime sleepiness [22]. Although the effect of cancer on melatonin is not fully understood, it has greater application in the treatment of cancer that will be covered in detail later in the article.

2.3. Oncogene Affecting Cortisol and Melatonin

MYC is an oncogene that causes cancer by removing cell cycle arrest and allowing cells to continue to growth [23]. MYC tends to be strictly regulated when the body is healthy, but it is highly expressed in most cancers that in humans [24]. In a recent study, Altman et al. found that MYC expression disrupts the circadian oscillatory rhythm of BMAL1 by upregulating REV-ERB α and REVERB β and that it also disrupts the circadian oscillatory rhythm of PER2 expression [25].

Similar to MYC, RAS is also heavily expressed in cancer. RAS is the most frequently mutated oncogene in human cancers and is composed of K-RAS, H-RAS and N-RAS [26]. In a novel study, overexpression of RAS was found to disrupt circadian rhythms in cancer patients by affecting the transcriptional expression of CLOCK/BMAL1, and activation or inhibition of the MAPK/RAS signalling pathway could affect the length of the rhythm [27].

It is interesting to note that MYC-induced or RAS-induced alterations in BMAL1 may also be associated with cortisol rhythms as well as melatonin rhythms. In a recent study on BMAL1 gene, crab-eating monkeys with BMAL1 knockout showed increased cortisol levels and decreased melatonin levels compared to the controlling group [28]. Similarly, another study showed disrupted melatonin rhythm in samples after knockout of the BMAL1 gene in Arbor Acre male broilers using CRISPR-Cas9 [29]. Although we still do not fully understand its effect on the body's circadian rhythm in vivo, scientists have some ideas to treat cancer and patients' circadian by targeting MYC [24]. A recent research has reported the development of therapies targeting KRAS and BRAF (a type of RAS) genes in rectal cancer [30].

In general, the mechanisms underlying cancer and circadian rhythms could probably be divided into two categories: direct effects and indirect effects. Cancers that directly affect circadian rhythms are those that cause loss in the expression rhythm of BMAL1 through the massive expression of MYC and RAS genes, thus leading to dysregulation of circadian rhythms in patients, as seen in most human cancers [25,27]. The indirect effect refers to the dysregulation of circadian hormones (e.g., cortisol and melatonin) in the body secreted by cancer leading to circadian rhythm disorders in patients. Examples include cancers that cause ACTH syndrome (e.g., pancreatic cancer, medullary thyroid cancer) and adrenal cancer that causes mild symptoms of autonomic cortisol hypersecretion.

Incidentalomas [11,31]. And there is another group of patients whose circadian rhythm disorders are caused by taking drugs related to cancer treatment (e.g. synthetic glucocorticoids) [10]. Figure 1 depicts, schematically, the complex interactions between circadian rhythm disorders and cancer above.

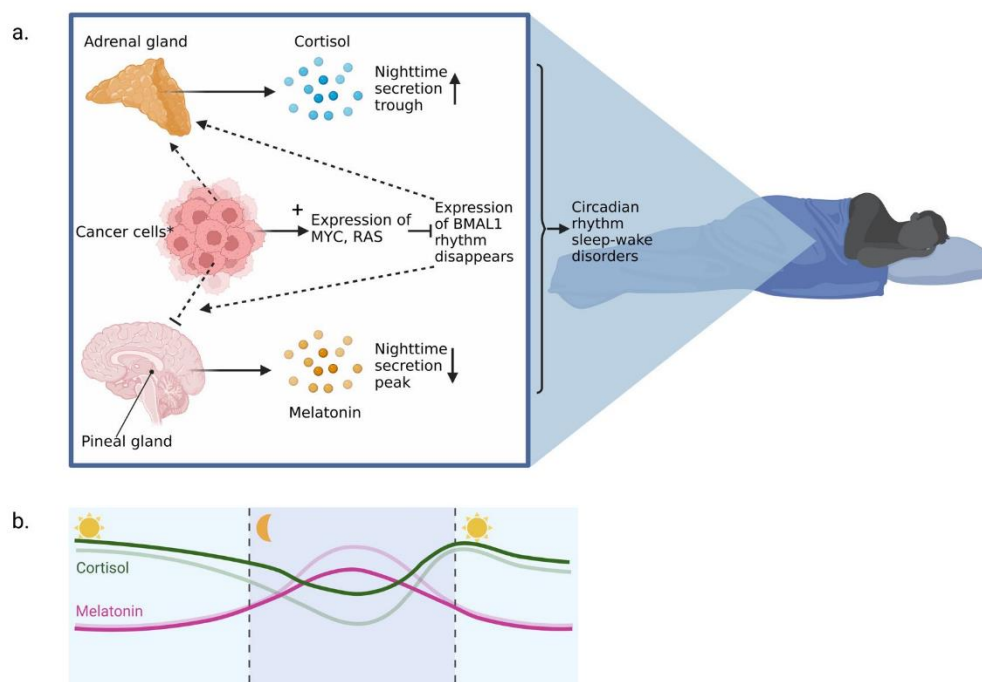


Fig 1. Schematic representation of the complex interactions between circadian rhythm disorders and cancer. The symbol “+” indicates stimulation while the up and down arrows represent an overall increase and decrease in levels, respectively. The solid line represents a clear mechanism of action and the dashed line represents an unclear mechanism of action. T-shaped head represents inhibition.

The symbol “*” represents a range of cancer which have MYC and/or RAS mutation including colon cancer, lung cancer, pancreatic cancer, bladder cancer, renal cancer, melanoma hematopoietic system tumor and neuroblastoma.

3. Treatment of Circadian Rhythm Sleep-wake Disorders in Oncology Patients

3.1. Melatonin

Melatonin is a hormone secreted by the pineal gland, whose main physiological function is to provide daily photoperiod information through a mechanism related to G protein linking membrane receptors MT1 and MT2 [32]. The main effect of melatonin is to regulate sleep and circadian rhythm, and this counteracting effect of circadian dysregulation has been shown to be beneficial for the clinical treatment of sleep disorders^[33]. The improvement in sleep quality may be related to synchronization of clock genes, as melatonin coordinates the sleep-wake cycle [34], and according to earlier studies, melatonin effects were found to control circadian rhythms in cancer patients [35]. One study showed that melatonin had a positive effect on depressive symptoms and sleep quality in cancer patients when melatonin was used after chemotherapy to treat symptoms such as sleep disorders and depression. At the end of treatment, changes in brain-derived neurotrophic factor (BDNF) and tropomyosin kinase B (Trk B) were inversely correlated with depressive symptoms and sleep quality. These findings suggest that melatonin has a neuroprotective effect that may offset adjuvant chemotherapy (ACBC) for cognitive function, adverse effects of sleep quality and depressive symptoms [36]. Another study showed that taking a certain amount of melatonin before going to bed can greatly improve sleep efficiency and reduce wakefulness after falling asleep after cancer treatment, which is very effective for cancer patients. Melatonin significantly improves sleep

efficiency after postoperative sleep initiation and reduces wakefulness during sleep, but has no effect on other objective sleep outcomes or subjective sleep quality (VAS and KSS) [37]. In general, the use of melatonin to treat sleep disorders after cancer treatment is very common, and melatonin may be absolutely dominant in the treatment of sleep disorders in cancer patients, but there are still a lot of questions to be asked, such as, whether the effects of melatonin may be related to the dose used, or whether the effects of melatonin may be different in different populations.

3.2. Cognitive Behavioral Therapy

Cognitive behavioral therapy (CBT) is considered as an effective treatment technique for insomnia^[38], but it is also available to circadian rhythm sleep-wake disorders. Cognitive behavioral therapy focuses on how behavior and perception affect sleep. Cognitive behavioral therapy can help address underlying behavioral difficulties by first identifying them and then changing sleep behaviors that are incompatible with good sleep. CBT can be used to retrain a new circadian rhythm when a person's circadian rhythm is disrupted, reducing sleep problems. Cognitive behavioral therapy works by changing people's thoughts and beliefs about sleep in order to improve their sleep problems. By setting up sleep expectations for themselves to give a certain psychological hint, this therapy helps patients with better sleep quality and effective improvement of sleep efficiency. CBT can help people reconnect with bedtime. These behaviors can also help people deal with circadian disruption and create a better sleep cycle [38]. Cognitive behavioral therapy includes behavioral components (stimulus control, sleep restriction, relaxation training), cognitive components (CT) and educational components (SH). Most CBT-I (Cognitive behavioral therapy for insomnia) interventions have at least three main components (sleep hygiene, stimulation control, and sleep restriction). Controlling these factors can achieve the treatment of sleep disorders. Cognitive behavior therapy is effective when patients use it face to face, but the effect seems to be more significant on the virtual network [39]. Although cognitive behavioral therapy has shown some efficacy in treating sleep disorders, the efficacy of CBT-I in cancer patients remains unclear. Therefore, more in-depth understanding and researches on cognitive behavioral therapy are needed.

4. Future Directions

As researches on the effects of cancer on sleep have progressed, how oncogenes such as MYC and RAS, which are heavily expressed in cancer, affect sleep in cancer patients have been largely elucidated [40], but researches on how targeting oncogenes that are related to circadian rhythms regulate patients' sleep status is at an early stage and more researchers' efforts are still needed. As mentioned above, there is a strong epidemiological link between cortisol or melatonin secretion and circadian rhythms in cancer patients, but this mechanism is still not well understood in current studies. Existing studies on melatonin have focused on its therapeutic effects on cancer, and the effects of cancer on melatonin secretion need to be further investigated. Moreover, further clinical and pharmacological studies are also needed to demonstrate how anticancer drugs causing circadian dysregulation.

Nowadays, a large number of cancer patients have problems with sleep disorders, which plague them. So, a lot of treatments have been developed. There are a large number of methods, some of which are effective in alleviating sleep disorders, but some are not. Even those that are effective may have only mild or moderate relief. So, our vision for the future of treatment on sleep disorders is to understand the mechanisms of sleep disorders or by improving existing treatments to achieve the expected effect. Treatment should have fewer side effects and be as cheap as possible. In the future, there may be more people with sleep disorders. Some methods may not be effective for patients with special conditions, so more studies and effective methods are needed to solve the problem of sleep disorders.

5. Conclusion

Sleep problems continue to plague tens of thousands of cancer patients. It has been shown that there is an interaction between tumors and sleep disorders. Cortisol and melatonin could affect circadian rhythms in turn, and then cause circadian rhythm disorders in cancer patients. Moreover, mutations in proto-oncogenes can lead to rhythm disruptions in clock genes, which in turn could lead to circadian rhythm disorders in patients. However, there is not much literature on tumors and circadian rhythm sleep-wake disorders, and thus the mechanisms involved are not very clear. Therefore, more lab researches on sleep rhythm disorders associated with tumors are needed. This will not only further improve the treatment plan for tumor patients with sleep disorders, but also prevent sleep problems in tumor patients at the root, thus facilitating their recovery.

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