The research progress for the treatment of circadian rhythm disorder

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Abstract. With the development of The Times, more and more people need to work at night, which is different from the normal biological clock of life, the body's internal time and external environmental cues, resulting in the disturbance of circadian rhythm. Circadian rhythm disruptions are common to many people, and people can suffer from problems like chronic sleep deprivation or insomnia. Not only that, but over time it can lead to a variety of diseases that affect their lives and a greatly reduced sense of happiness. Recent research progress has suggested that patients with other medical conditions can also experience symptoms of circadian rhythm disruption. This suggests that the circadian rhythm disorder and the diseases are connected in two ways. Therefore, research that uses circadian rhythms to treat diseases by altering circadian rhythms will bring benefits to patients. In this review, the author first describes the relationship between circadian rhythm and specific diseases, such as hypertension, glucose metabolism, and immune system disorders, thus demonstrating a bidirectional relationship between circadian rhythm disturbance and many diseases. Then, three therapeutic methods of circadian rhythm disorder, namely light therapy, melatonin therapy and lifestyle change, are discussed, also mentions their combined use. The mechanism of action and therapeutic methods are introduced in detail, and the corresponding clinical data are given. Finally, based on the potential of circadian intervention, the future development possibilities are proposed.

Keywords: Circadian rhythm disruption, circadian-related diseases, light therapy, melatonin therapy.

1. Introduction

The body's internal functions and environmental regulation are controlled by the circadian rhythm system, so the optimal timing of physiological events is coordinated by these internal timers. The endogenous circadian rhythm has a cycle of about 24 hours and is reset precisely to 24 hours per day by exposure to alternating light and dark. However, with more and more people studying and working at night and the widespread use of electric lights, the line between day and night is increasingly blurred.

Circadian disorders have been linked to a variety of diseases, such as immune disorders and psychiatric disorders. These diseases affect a person's normal life very much, so it is necessary to find an effective treatment. There is a good idea to think that if only people could address the issue of circadian rhythm disruption, these diseases could also be cured. Some research supports the idea. The goal of treatment for circadian rhythm disorders is to reset the body's sleep-wake rhythm and align it with the external environment. The most common treatments are light therapy, medication and lifestyle changes. Often, doctors recommend a combination of these treatments. However, treatment options for everyone depend on the type and severity of the circadian rhythm disturbance.

Several researches have shown that ill-timed light is able to disrupt people's circadian rhythms, potentially causing further health effects. Instead, if people are exposed to light at certain times, it could be used as a treatment for circadian rhythm disturbances. In this therapy, it contains several parts, which contains SCN and whole mechanism. Melatonin therapy is one of the most common treatments, and drugs have been introduced in many countries. It is by far the safest treatment, has few side effects and is safe to use [1]. In this review, the author will illustrate the whole mechanism of light therapy and melatonin therapy to show how it works. There is also a familiar way to treat the disease, by limiting caffeine. This approach will not be the focus of this article.

This paper introduces three types of treatments for circadian rhythm disorders and their combined use, mainly focus on the light therapy and melatonin therapy. The mechanisms of each treatment will be elaborately described to provide an overview of treatment for patients with circadian rhythm disturbances.

2. The diseases related to circadian rhythm

There is evidence that this is a two-way relationship, as disruptions to circadian rhythms, which many diseases can disrupt, can increase disease severity. Circadian rhythm disturbances raise the likelihood of neurological, psychiatric, cardiovascular, metabolic, and immune diseases being expressed and developing [2]. In the latest study, high blood pressure was strongly linked to disrupted circadian rhythms. Endogenous rhythm influences blood pressure, as can be seen by changes in the circadian rhythm. During both sleep and wakefulness, disruptions in the circadian rhythm raise systolic and diastolic blood pressure. Long-term shift workers are more likely to have disturbed sleep patterns because of increased blood pressure after working at night. In addition, chronic sleep deprivation and shift work both increase the risk of high blood pressure [3]. Disruption of circadian rhythms can also cause metabolic disruption, which is involved in glucose metabolism. An endogenous circadian rhythm system controls glucose tolerance. If this system is disrupted, it causes structural sleep changes, which raise cortisol levels and lower insulin sensitivity [4]. In addition, studies have linked diabetes to circadian rhythm disruptions caused by shift work, and shift workers are at high risk for diabetes and obesity. This suggests that the greater the difference in bedtime, the greater the prevalence of disease, and that the difference between the body clock and the learning and working time can lead to metabolic disorders [2,3]. Disorder of circadian rhythms can lead to the development of mental illness, which can also cause it abnormalities. For people with mental illness, a poor circadian rhythm reflects the severity of the illness. Studies have found sleep-wake changes in patients with schizophrenia that are associated with delayed melatonin circadian rhythms, and patients also report sleep disorders, meaning that these patients have circadian rhythm disruptions [3]. Those result demonstrated that sleep patterns in people with mental disorders can break circadian rhythms and worsen their condition [3]. Circadian rhythm disruptions have also been linked to immune system disorders. One example of how the two are linked is COVID-19. Circadian disorders may increase the risk of infection, and while there is no definitive data on COVID-19, susceptibility appears to be affected by the time of the pathogen's infection [5]. The sickness seems to disturb circadian rhythms by upsetting typical rest and action rhythms after disease with the infection [5]. It is also hypothesized that infection may suppress melatonin rhythms and alter the timing of clock gene expression, leading to misalignment of expression of damaging inflammatory cytokines [2]. In addition, Alzheimer's disease and cancer are linked with disrupted circadian rhythms. Since circadian rhythm disorders are linked to many diseases, it is possible to fix the disorders and cure people of the diseases they have at the same time. So far, the treatments that have been developed are light therapy, melatonin therapy and lifestyle changes.

3. Light therapy

3.1. Background

In human's eyes, there are some cells related to the vision. Rods are for vision, Cones for color detection. And there is a cell called pRGCs that can regulate the circadian rhythm, if the light is pretty bright, this cell will start its function. Rod and cone cells can project and control the pRGCs' light response, according to studies conducted on mice, non-human primates, and humans. Rods can detect relatively dim light, cones can detect greater light, and melanopsin can measure prolonged periods of bright light thanks to this signal integration [6]. pRGCs is sensible to blue light, so when people use a long time on electronic devices, especially in the night, their circadian rhythm will be affected.

Light can animate and manage SCN cadence cycle and stage in accordance with the outside environment. The SCN is a tiny pair of wings in the hypothalamus that helps to establish and maintain the circadian rhythm by receiving signals from the eyes [7]. SCN can keep the whole body on an approximately 24 hours biological clock, however, light is required to prompt and reset the clock to let organisms to keep pace with outside time. Continue light in night may destroy circadian system, making it impossible for the body to distinguish between day and night. When people are exposed to light at the wrong time for too long, biological and behavioral rhythms become out of sync, which can have negative physical and psychological effects.

3.2. Mechanism

In vivo, pRGCs, which product melanopsin, receive light and activates the neurons in the retina and the neurons convert light particles to electrical signals [8]. The activation of the PLC pathway and the induction of G protein-coupled signaling cascades by melanopsin stimulation result in the opening of TRPCs, Ca^{2+} influx, and cell depolarization [8]. The input pathway of SCN is mainly dependent on single synaptic RHT, in which the main neurotransmitters are glutamic acid and aspartate. One of the main signals of light entrainment is glutamate binding to glutamatergic receptors, which causes an increase in intracellular Ca^{2+} concentration. In addition to mediating light Ca^{2+} influx to trigger synchronization of a variety of kinases, including PKA, MAPK and CaMK, PACAP that activate PAC1 receptors are also accountable [8]. The transcription of clock genes like PER1 is triggered by CREB phosphorylation, which binds to the promoter's cAMP response element. Furthermore, transcription factors including c-FOS and EGR1 participate in the control of the SCN clock by visual signals [8].

3.3. Treatment

A study was conducted on patients in intensive care units who are generally considered to have abnormal and fragmented night sleep. The researchers set up a cyclic lighting system in the ICU to support patients'circadian rhythms, exposing one group of patients to a cyclic lighting system and the other to a normal lighting system [9]. The results showed that patients in the room with the circulating lighting system had an advantage in the perception of brightness during the day [9]. The goal of the second stage is to describe the lighting experience of a room with a cyclic lighting system. Almost all are satisfied with the environment's cyclic lighting, which in conjunction with daylight and helps them regulate their circadian rhythm. This study could prove that light therapy is effective.

4. Melatonin therapy

4.1. Mechanism

The pineal gland's tryptophan-serotonin biosynthesis pathway converts serotonin into the indole hormone melatonin, and its concentration varies according to input from the circadian rhythm center of the brain [1]. Melatonin is a very important physiological sleep regulator. In animal species, the melatonin cycle is highest at night, no matter what kind of activity mode [10]. At night, signals from SCN cause the pineal gland to produce melatonin, which is then released into the third ventricle and into the bloodstream [11]. Tryptophan is converted to serotonin by the two enzymes [1]. In response to adrenergic neuronal input, 5-HT is acetylated by AA-NAT and then methylated by ASMT to form melatonin. It is possible that a location that governs melatonin synthesis is where the rate-limiting enzyme AA-NAT is located. Some people may decide to take melatonin supplements because they may not produce enough endogenous melatonin or because they are unable to do so. Melatonin supplements are relatively safe, do not form dependency, and the potential for abuse is low [1].

4.2. Treatment

Melatonin acts as a dark signal timing cue for various organs, including SCN themselves, and can regulate the 24-hour cycle of sleep-wake and neuroendocrine rhythms in the absence of light. Melatonin therapy is a reasonable method to treat N24HSWD in all blind people [11]. The physiological processes of circadian rhythm disturbance are thought to be related to the pacemaker, and they are related to the coupling of external signals or downstream synchronization mechanisms. A type of circadian rhythm disturbance known as DSPS is characterized by difficulty falling asleep and rising on time. Compared with normal people, patients with DSPS have delayed endogenous melatonin rhythm. There is compelling evidence that it is effective for DSPS patients. The approval of tasimelteon for blind people demonstrated good evidence for melatonin receptor agonists in clock phase reset-related conditions [11]. Melatonin taken orally can be absorbed rather quickly; it is typically prepared in tablets or capsules. The researchers involved found that oral melatonin peaked in plasma concentrations 41 minutes later, so for maximum effect, it should be taken about 40 minutes before trying to fall asleep [12]. To test the safety of exogenous melatonin, the researchers also studied neonates and older children. The children had acute or chronic clinical conditions that were treated with different doses of oral or intravenous melatonin. After three years, there was no difference in the adolescent development of children taking an average of 0.3 to 10mg/d compared with the observation of untreated children of the same age [13]. This could indicate that melatonin use does not affect children's development and could prove that melatonin is safe.

5. Limit caffeine

Many people suffer from the problem of not getting enough sleep, and they often use caffeine to help them active in the day. However, caffeine consumption can aggravate sleep problems by disrupting circadian rhythms. Caffeine stimulates A_{2A} receptors in the awake brain by antagonizing adenosine A_1[14]. Studies on humans and animals have demonstrated that adenosine regulates sleep and arousal. Adenosine receptor agonists generally advance rest. In general, caffeine can decrease sleep time and lowers the quality. Slow-wave sleep and EEG slow-wave movement generally decrease while first-stage wakefulness increases, establishing a dose-time-response relationship [14]. If people limit the caffeine intake, the problem of falling asleep can be solved.

In a double-blind and placebo-controlled study, scientists found that consuming a portion of caffeine identical to a twofold coffee three hours before routine sleep time created a setback for the melatonin circadian cadence in people of around 40 minutes, almost half the phase-delay response caused by three hours of nighttime bright light at the start of habitual bedtime [15]. It has been concluded that in vivo, caffeine consumption during the night delays the rhythm of melatonin, while in vitro, long-term caffeine consumption lengthens the circadian cycle of molecular oscillations [15]. One study examined the extent to which caffeine interferes with slow-wave sleep and delays circadian rhythms in adolescents. After six days of caffeine abatement and a fixed sleep-wake cycle, 18 male adolescents ingested 80 milligrams of caffeine and a placebo and underwent an EEG test four hours later. The investigation revealed that consuming caffeine reduced perceived sleepiness when compared to taking a placebo, indicating that caffeine interferes with the promotion of REM sleep, a crucial factor in subjective sleep quality. Although there was no appreciable difference in the amount of time spent sleeping overall, coffee ingestion had a longer REM sleep delay than a placebo [16]. Therefore, limiting caffeine intake can be very helpful in restoring normal circadian rhythms.

6. Combined use

In one study, a group of people took 1.5mg of melatonin a day, then 16 hours of lying in light for 8 days, and led to a 3 to 4-hour advance in endogenous melatonin and cortisol rhythms and a reallocation of sleep time. Notably, the accentuation was on the significance of melatonin's capacity to control rest timing, rather than its spellbinding quality [17]. It turns out that artificially boosting

nocturnal melatonin production over a few days, combined with dim light and lying position, appears to be a very efficient strategy for enhancing circadian rhythms. Combination therapy was better at promoting dim light and melatonin onset than just light therapy or melatonin, and although a single therapy had similar effects, the combination made significantly greater progress. Studies have evaluated the effectiveness of the combination therapy in healthy subjects who were provided with 3 hours of morning light and 5mg of melatonin 6 hours before their customary bedtime. The results found that 1 hour of light therapy and 3mg of melatonin at 16:00 produced a more significant phase forward shift than a single therapy [18]. In another experiment, researchers assessed circadian rhythm advance with and without green light treatment the following morning, on the premise of a sustained release of 3mg of melatonin the previous afternoon. The subjects were divided into four groups with only melatonin, only placebo, only light and melatonin plus light. For those with only melatonin or placebo, the capsules were taken at 16:00 on the first day; For the light-only group, light therapy was given between 7:00 and 8:00 the next day; For the combination group, melatonin was given at 16:00 on the first day, followed by light therapy between 6:00 and 7:00 on the second day. The circadian cycle was assessed by counting microlight melatonin starting with salivary melatonin [19]. The results prove that the combination of afternoon melatonin and morning light is additive, so it can be concluded that combined therapy has a better effect on the treatment of circadian rhythm disturbance.

7. Conclusion

Light therapy, melatonin therapy and caffeine restriction to regulate circadian rhythm disturbances can be effective treatments for some related disorders, and combined use can make the effect even more pronounced. But as far as the results go, there are still some problems with each treatment. Light therapy considers the intensity of light, the spectrum used and the duration, and melatonin therapy considers the dose and time of administration. Recent study suggests that short-wavelength light may be the best light for resetting the circadian clock, but there isn't any clear evidence to prove. Researchers still need to do more experiments to collect data on different factors. Until now, there has been little research into the adverse effects of combination therapy, and it is difficult to reach consistent conclusions about the effectiveness of treatment because everyone's situation is different, which shows the need for customized treatment. In addition, because there are different types of circadian rhythm disorders and different ages of patients, different scheme also should be considered according to the types and ages to maximize the effectiveness of treatment. So, there's still a lot to explore in terms of ways to treat circadian rhythm disorders.

References

[1] Vasey, C., et al., (2021). Circadian Rhythm Dysregulation and Restoration: The Role of Melatonin. Nutrients, 13 (10), 3480.

[2] Fishbein, A. B., et al., (2021). Circadian disruption and human health. Journal of Clinical Investigation, 131 (19).

[3] Hou, Y., et al., (2020). Association between circadian disruption and diseases: A narrative review. Life Sciences, 262, 118512.

[4] Gonnissen, H. K. J., et al., (2013). Sleep Architecture When Sleeping at an Unusual Circadian Time and Associations with Insulin Sensitivity. PLOS ONE, 8 (8), e72877.

[5] Vitale, J. A., et al., (2020). Is disruption of sleep quality a consequence of severe Covid-19 infection? A case-series examination. Chronobiology International, 37 (7), 1110 – 1114.

[6] Foster, R. G., et al., (2020). Circadian Photoentrainment in Mice and Humans. Biology, 9 (7), 180.

[7] Begemann, K., et al., (2020). Regulation and function of extra-SCN circadian oscillators in the brain. Acta Physiologica, 229 (1).

[8] Xie, Y., et al., (2019). New Insights into the Circadian Rhythm and Its Related Diseases. Frontiers in Physiology, 10.

[9] Engwall, M., et al., (2015). Lighting, sleep and circadian rhythm: An intervention study in the intensive care unit. Intensive and Critical Care Nursing, 31 (6), 325 – 335.

[10] Zhao, D., et al., (2019). Melatonin Synthesis and Function: Evolutionary History in Animals and Plants. Frontiers in Endocrinology, 10.

[11] Zisapel, N. (2018). New perspectives on the role of melatonin in human sleep, circadian rhythms and their regulation. British Journal of Pharmacology, 175 (16), 3190 – 3199.

[12] Zhdanova, I. V., et al., (2002). Melatonin promotes sleep in three species of diurnal nonhuman primates. Physiology & Behavior, 75 (4), 523 – 529.

[13] Cipolla-Neto, J., et al., (2018). Melatonin as a Hormone: New Physiological and Clinical Insights. Endocrine Reviews, 39 (6), 990 – 1028.

[14] Clark, I., et al., (2017). Coffee, caffeine, and sleep: A systematic review of epidemiological studies and randomized controlled trials. Sleep Medicine Reviews, 31, 70 – 78.

[15] Burke, T. M., et al., (2015). Effects of caffeine on the human circadian clock in vivo and in vitro. Science Translational Medicine, 7(305).

[16] Weibel, J., et al., (2021). Regular Caffeine Intake Delays REM Sleep Promotion and Attenuates Sleep Quality in Healthy Men. Journal of Biological Rhythms, 36 (4), 384 – 394.

[17] Pandi-Perumal, S. R., et al., (2008). The roles of melatonin and light in the pathophysiology and treatment of circadian rhythm sleep disorders. Nature Clinical Practice Neurology, 4 (8), 436 – 447.

[18] Cheng, D. C. Y., et al., (2021). The efficacy of combined bright light and melatonin therapies on sleep and circadian outcomes: A systematic review. Sleep Medicine Reviews, 58, 101491.

[19] Paul, M. A., et al., (2011). Phase advance with separate and combined melatonin and light treatment. Psychopharmacology, 214 (2), 515 – 523.