Research Progress on the Pathogenesis of Circadian Rhythm Sleep-Wake Disorders

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Abstract. Circadian rhythm fluctuates within 24 hours, affecting many physiological processes and aspects of daily life, including eating behavior, regulation of sleep wake cycle and metabolic homeostasis. Circadian rhythm sleep-wake disorders (CRSWDs) refer to the inconsistency between the human body's circadian behavioral activities and the needs of social life. Common classifications classify it as Delayed sleep phase type (DSP), Advanced sleep phase type (ASP), Free-running type, and Irregular sleep-wake type. The potential pathogenesis of CRSWDs is closely related to human clock genes. Emens et al reported finding that N24H sleep-wake disorder is an important milestone in etiology. Light is the strongest inducement of circadian rhythm. CRSWDs may due to the long-term lack of light and other external timing factors, leading to circadian rhythm disorders and sleep homeostasis imbalance rather than being driven by a disorder of the central circadian clock. Regular exposure to strong light is often used to treat CRSWDs. This paper briefly introduces the historical background of understanding circadian rhythm, and then the common pathogenesis and mechanism of sleep wake disorder with different circadian rhythms and the corresponding treatment were discussed.

Keywords: Circadian rhythm, CRSWDs, pathogenesis, treatment.

1. Introduction

Under normal circumstances, the human body's circadian rhythm matches nature and society. This is controlled by the rhythm regulation system in the body and works together with external timing factors to maintain the body's sleep homeostasis.

Circadian rhythm sleep-wake disorders (CRSWDs) refer to the inconsistency between the human body's circadian behavioral activities and the needs of social life. Nowadays, the number of patients with CRSWDs is on the rise, like students reviewing before exams or workers with high work pressure, seriously affect the quality of life. The pathogenesis of CRSWDs may be related to changes in external stimuli. CRSWDs may be due to the long-term lack of light and other external timing factors, leading to circadian rhythm disorders and sleep homeostasis imbalance rather than being driven by a disorder of the central circadian clock [1,2].

This article will discuss the pathogenesis of CRSWDs in combination with homeostasis and the rhythm regulation mechanism, sleep, and analyze the main external factors that lead to various types of CRSWDs in the pathogenesis of CRSWDs. Provide reference for differential diagnosis of CRSWDs and to make recommendations for clear clinical conservative physical therapy of various CRSWDs, and to make recommendations for clear clinical conservative physical therapy of various CRSWDs.

2. Homeostasis and Circadian rhythm regulation mechanism

Homeostasis in the human body is mainly regulated by three axes of the endocrine system: the hypothalamic-pituitary-thyroid axis, the hypothalamic-pituitary-adrenal axis, and the hypothalamic-pituitary-gonadal axis.

The circadian rhythm is a biological rhythm that is slightly longer than 24 hours in the human body. It is regulated by external timing factors and is a regulatory mechanism that is almost synchronized with the circadian change. The external timing factors mainly include light, sports and so on. Homeostasis is the inherent state of the environment in an organism. Regarding the internal
regulation of circadian rhythms, there are substances inherent in the human body to maintain stable cycle.

Adenosine is a mediator that controls rhythm in mammals. Adenosine is produced by human cells and acts on the cardiovascular and cerebrovascular systems. Adenosine or Adenosine Receptor Deficiency Linked to Sleep Disorders in Alzheimer's Patients. Sustained wakefulness and exercise will accumulate adenosine in the body. Adenosine acts on receptors in the basal forebrain. The accumulation of adenosine drives the steady state of the internal environment to initiate the sleep-onset program. Adenosine is one of the ordinary macroscopic mediators. The most common antagonist of adenosine is caffeine. As caffeine is ingested into the human body, it prevents adenosine from binding to the receptor, so that the human body does not feel fatigue and sleepiness [3]. In recent years, the incidence of depression and affective disorders has continued to rise. Some studies have analyzed the effects of coffee and other substances on sleep disorders and personality disorders. The data results show that tobacco, alcohol, coffee, etc. are related to sleep disorders in patients with personality disorders. There are bidirectional correlations that promote each other [4]. Recent studies have found that the effect of adenosine on sleep may be achieved through glutamate neurons [5].

The pacemakers that control circadian rhythms are located symmetrically in the mammalian suprachiasmatic nucleus (SCN), on either side of the hypothalamus [6]. Under the action of external timing factors, taking illumination as an example, the illumination information is collected through the retina, and the external information is processed by the afferent nerve afferent central processing device—SCN, and the neuron responds. At the same time, the digestive system, endocrine system and genitourinary system of the human body will summarize the situation in the human body. After the integration of internal and external information, the secretion of various hormones, which are the mediators in the body, changes, thereby regulating the sleep and wakefulness of the human body. This is also the part about sleep factors in the maintenance of homeostasis in the human body.

Melatonin, a kind of hormone, is produced by the amygdala after the suprachiasmatic nucleus (SCN) of the diencephalon activates the rhythm regulation system. It acts on a variety of glands and hormones, which can inhibit the excitability of human sympathetic nerves and promote the sleep. Therefore, it is often used as a medicine to treat disorders of the biological clock to improve sleep quality, and patients with Alzheimer's disease [7]. Melatonin is an important circadian rhythm regulator that is regulated by a variety of factors, acts on cells throughout the body such as eyes, blood vessels, breast, liver, kidney, gastrointestinal tract and gonads. The pineal gland secretes melatonin, which acts on two receptors MT1 and MT2 in the suprachiasmatic nucleus of the human hypothalamus, reducing the body's alert state and promoting sleep. Thus, there is a change in light, which stimulates the SCN and melatonin to promote each other and guide the positive feedback regulation of sleep.

Melatonin is a member of the G protein-coupled receptor superfamily and is widely present in a variety of nervous system nuclei, such as the suprachiasmatic nucleus (SCN) of the diencephalon, hippocampus, cerebellar cortex, prefrontal lobe, basal ganglia, and ventral substantia nigra. Dorsal tegmental region, nucleus accumbens, etc. Melatonin-activated receptors mediate changes in intracellular messengers such as cAMP, cGMP, Ca2+, protein kinase C (PKC), and quinone reductase. There are three subtypes of melatonin receptors, MT1, MT2, and MT3. MT1 is highly concentrated in the SCN, thalamic nucleus and other parts, which can regulate sleep; MT2 is involved in circadian rhythm; MT3 has an unknown role. There are also circadian rhythms in the functions of the three receptors.

Orexin, a neurotransmitter, is important for maintaining long-term wakefulness. Impaired orexin production causes narcolepsy, which is characterized by prolonged sleepiness and irregular eye movement sleep. Recent trials have shown that the orexin receptor antagonist increases REM sleep and increases fear elimination rate [8]. Orexin-Related Drugs for Sleep-Wake Disorders is in a preclinical research program. The orexinergergic system is closely related to neurodegeneration in AD patients, but the current study cannot determine whether it is positively or negatively related [9].
Figure 1. Melatonin and the hypothalamic-pituitary-gonadal axis

Light stimulates the retina to produce electrophysiological impulses, which are transmitted from the afferent nervous system to the amygdala of the hypothalamus to inhibit the secretion of melatonin. Melatonin has the effect of inhibiting the hypothalamic-pituitary-gonadal axis and can promote the function of gonadal hormones; The hypothalamic-pituitary-gonadal axis controls the secretion of human sex hormones, the hypothalamus secretes gonadotropin-releasing hormone (GnRH), and GnRH promotes the pituitary to secrete luteinizing hormone (LH), follicle-stimulating hormone (FSH) and prolactin (PRL), lactation. The hormone acts on the mammary gland, promoting development and secretion of milk. LH and FSH act on the female ovary to promote the secretion of progesterone (P) and estradiol (E2); act on the male testis to promote the secretion of testosterone (T). Sex hormone negative feedback inhibits hypothalamic pituitary function. The hypothalamic-pituitary-gonadal axis is important for both sexual and physical development [3,7,8] (fig2).

Figure 2. SCN and the hypothalamic-pituitary-adrenal axis

The biological clock is divided into a central biological clock and a peripheral biological clock [10]. The central biological clock is located in the suprachiasmatic nucleus (SCN) of the hypothalamus. Light and dark information is transmitted from the retina to other brain regions to regulate body temperature, feeding and sleep. The surrounding organisms are located in various organ cells, and are regulated by the nerves (mainly autonomic nerves) of the central biological clock, and jointly maintain the body rhythm. The circadian clock system controls the rhythm of the hypothalamic-pituitary-adrenal axis. Small cell neurons in the paraventricular nucleus of the hypothalamus are stimulated to synthesize and release corticotropin-releasing hormone (CRH) and AVP, through the pituitary portal system in the median hypothalamic eminence, in the anterior pituitary, stimulate corticosteroid cells to release adrenocorticotropic Hormone (ACTH)[11], ACTH
reaches the adrenal cortex through the blood to promote the secretion of adrenal glucocorticoids, and negative feedback acts on the paraventricular nucleus and the adenohypophysis to inhibit CRH and ACTH. Glucocorticoids and their receptors (GR) are distributed in major systems in the body and are important substances to maintain the body's homeostasis [6,9] (fig2).

3. Sleep Homeostasis

Our sleep is made up of approximately 90 minutes sleep cycles with four stages each. Sleep homeostasis consists of two phases of REM and NON-REM, Co-regulation by circadian rhythms and homeostasis. Dreams with plot often appear in REM. REM sleep is an efficient stage of sleep, and previous studies Ephron and Carrington have shown that during REM sleep, when the cortex needs to be stimulated, people dream [12]. At the same time, surveys of elderly and infirm patients show that dreaming is good for mental health [13]. Therefore, this paper does not consider the negative effects of dreaming on sleep. Some neuroscientists working on adjusting sleep to improve work efficiency could focus on the discontinuous interactions of sleep stages, linking cortical tone and cortical efficiency. In addition, there is a close relationship between the cerebral cortex's need for sensory stimuli and REM sleep, but the specific mechanism of action remains to be analyzed in conjunction with the results of the persistently sharply reduced sensory input during REMs [12].

Electroencephalogram (EEG) is a commonly used clinical monitoring data to monitor sleep state, and may have significance in the differential diagnosis of depression and sleep-wake disorders. Recent studies have shown that awake EEG results are not affected by the degree of vigilance, and the exploratory basis for the association of depression severity and nocturnal REM sleep percentage with awake EEG power was not significantly correlated [14]. EEG slowing is predictive of idiopathic rapid eye movement sleep behavior disorder (iRBD) by predicting the occurrence of precursor α-synuclein degeneration [15]. EEG is more sensitive to circadian rhythm disturbance sleep-wake disturbance. Symptoms of non-24-hour sleep-wake rhythm disorder (N24SWD, a circadian rhythm sleep-wake disorder) often occur before the patient is diagnosed with depression, the development of the disease cannot be detected using brain waves.

4. Circadian rhythm sleep-wake disorders and their physiological mechanisms

According to the time of falling asleep, advanced sleep-wake type and delayed sleep-wake type are two typical classifications of circadian rhythm sleep-wake disorder. There are also Free-Running type and Irregular Sleep-Wake type [16].

4.1. Advanced Sleep Phase Disorder

Advanced sleep-wake types are more common in older adults, with an incidence of nearly 1% [16]. Sleep manifested as going to bed early at night and waking up early in the morning. It may be that the endogenous circadian rhythm is shortened due to the fact that the middle-aged and elderly people tend to go to bed early and get up early as their life patterns with increasing age. In addition, decreased retinal sensitivity to light is one of the pathogenic mechanisms.

4.2. Delayed Sleep Phase Disorder

Delayed sleep phase disorder is a common symptom in adolescents and is also a typical type of study [17]. The main clinical manifestation is that sleep delay is 2 hours or more later than the traditional clinical definition. Contrary to ASPD, the pathogenesis may be retinal hypersensitivity and endogenous circadian rhythm prolongation caused by exuberant hormone secretion during puberty. A recent article suggests that the melanopsin-dependent reduction in retinal phototransduction may be a novel pathogenesis for the development of DSWPD, normal-vision N24SWD as well [18]. Another studies suggest that abnormal sleep duration in patients with DSPD
does not affect sleep quality [19]. However, adolescents’ sleep hygiene still has an impact on their sleep quality[20]. It is recommended that adolescents pay attention to developing good sleep habits.

Secondary sleep disorders can be considered as a separate category of chronic insomnia, and the diagnosis of sleep-related hypoventilation should note that carbon dioxide partial pressure must be elevated. Medical personnel can follow the above methods when diagnosing young patients [21]. The blue light therapy can be tried, which can significantly improve the condition from a subjective point of view [22]. However, recent experiments have demonstrated that patients with DSWPD and N24SWD patients exhibit different delay mechanisms. Individuals with delayed DSWPD exhibit delayed sleep-wake time, while those with N24SWD exhibit progressive delays [18].

4.3. Free-Running Disorder

Free-Running Disorder is common in patients who are completely blind, the retinal-hypothalamic tract is damaged, and the human circadian rhythm has little or no correlation with the alternation of day and night. People with vision are rarely affected, and most of them co-occur with severe mental illness and delayed sleep-wake disorder [23]. The main pathogenesis of its occurrence is the inability to accept light stimulation.

4.4. Irregular Sleep-Wake Rhythm

Irregular sleep type is a pathological type that is common in patients with Alzheimer's disease. Sleep is divided into 3 or more periods, each within 4 hours. Severe pathological features are impaired or absent in Non-rapid eye movement(NREM) sleep. In addition, organic degenerative disease in the elderly is also an important pathogenesis. For example, AVP and VIP-like neurons were significantly reduced in the SCN [24], clock gene expression under the control of the pineal gland was impaired, and retinal-hypothalamic tracts were atrophied [25]. And older women experienced a more significant reduction in VIP [24]. The common sleep-wake disorders in the elderly are often closely related to psychological factors. Mental stress and sleep disorders promote each other, which indirectly promotes the aging process of the elderly [26]. Young people's shift work and jet lag can also cause this irregular sleep pattern, but the pathogenesis is simpler and short-term irregular sleep schedules patients can be cured with simple physical therapy, such as adjusting the time of light and the amount of exercise [16,27]. Although teenagers have stronger physical fitness, irregular sleepers can lead to changes in physical parameters and even depression [28]. Therefore, it is still recommended to adopt a regular life schedule and pay attention to sleep hygiene [29].

5. Pathophysiology—Analyzing CRSWDs’ pathogenesis from a Microscopic Perspective

Based on the cloning of animals and the Human Genome Project, the researchers found that the pathogenesis of CRSWDs is associated with mutations in ‘clock genes’ [17]. Recently, scholars have studied the genetic basis of CRSWDs. In 23 families in their experiments, they compared the genes of CRSWDs patients with normal genes at the molecular level, and found that the pathogenesis of CRSWDs is related to the deletion of genes, and the exact mechanism is related to the physiology and behavioral phenotypes, that is remain to be elaborated [6].

The pathogenesis of ASDP was analyzed from the genetic point of view. In an experiment that analyzed three high-risk American families of Nordic ancestry, it was found that the circadian rhythm (tau) of the high-risk patients was very short [30]. The gene is autosomal dominant and has a high probability of inheritance. The expression of hPr2 gene in one of the positive patients was obviously abnormal, and the study found that this gene is related to photoresetting [31], but not involved in the inheritance of ASDP. In a survey study of 410 middle-aged people, phase preference was measured with MEQ [32] (level 2), cytosine instead of threonine (C instead of T) at immediate 3, homozygous for the C allele at the hClock (Human Clock) gene fewer (CLOCK 3111 C/C, n = 28), the authors believe that the nocturnal factor on the MEQ is the main influencing factor. The link between hClock
and night may be reduced in DSPD patients. It has been suspected that DSPD may be directly caused by the hClock gene. Experiments with small samples have proved that the polymorphism of the Clock gene is of great significance in regulating the long-term periodic dimension of affective disorders [33]. It is not difficult to understand that DSDP often occurs in young people and is complicated by depression in young people[34].

6. **Common clinical misdiagnoses: Personality Disorders and CRSWDs**

There is this complementary relationship between sleep disorders and personality disorders. Circadian rhythm disorders are often misdiagnosed as personality disorders. Symptoms of some simple circadian sleep-wake disorders can be significantly improved with physical therapy [27], while misdiagnosed and incorrect medication can make the patient's condition worse. Commonly misdiagnosed disorders are unipolar and bipolar disorder, seasonal affective disorder, schizophrenia, and neurodegenerative disorders [26]. However, symptoms caused by antidepressants can be differential diagnosis with melatonin [6]. For the clinical diagnosis of children, more attention should be paid to the differential diagnosis of ADHD [35]. Depressed patients often seek tobaccoalcohol, etc. as short-term physical therapy, but these are not beneficial to the recovery of depressed patients [4].

7. **Differential Diagnosis and Treatment**

Sleep-wake disorders or circadian rhythm sleep-wake disorders in adults and children were diagnosed by a combination of clinical interviews and activity tests [6,27], which is a combination of medical history and dynamic monitoring. Actiology detection has great clinical significance. The subjects wore watch-style detectors on their wrists, which intelligently analyzed 7-14 days of sleep-wake data and came up with the results [36]. It should be noted that the subject should be of free movement, and the test is completed under the conditions.

The article THE AMERICAN SLEEP DISORDERS ASSOCIATION explains the detailed approach to the clinical treatment of sleep disorders [37]. In disease diagnosis, there is a relatively detailed analysis of visual cognition, behavior and its brainstem mechanism. It is necessary to combine the clinical diagnosis of tumors to distinguish children with ADHD and adults with behavioral abnormalities under the influence of alcohol [6]. Among them, ADHD and sleep-wake disorder in children are an issue worthy of further research. At present, Chiang, H. L et al. have discussed and found that the close relationship between the two is determined by ADHD classification and developmental dimensions [35]. The differential diagnosis of the disease requires clinicians to pay attention[38].

For the treatment of diagnosed patients, there are currently three clinically effective treatments, including phototherapy, melatonin therapy, and phototherapy combined with melatonin therapy and VB12 can be used as adjuvant therapy [6,17]. Artificial light (especially 2500~10000lux) is effective in improving sleep-wake rhythm and mood. For the treatment of blind people, the drug Tasimelteon can be selected when light stimulation is not acceptable. Recent studies have analyzed its mechanism of action [39]. The commonly used antidepressants in clinical treatment are benzodiazepine receptor agonists, which have less side effects than phenobarbiturates, but long-term dependence is still obvious. In case of overdose, flumazenil can be used for identification and rescue.

8. **Conclusion**

In terms of limited identification, misdiagnosis and health consequences, the impact of CRSWDs may be greater than estimated. A growing number of recent examples demonstrate that circadian rhythm disorders are not driven by central circadian rhythm system disorders. Long-term away from light, loss of free running ability, eventually lead to CRSWDs. Clinically, more attention should be paid to the differentiation between CRSWDs and other diseases. With the progress of clinical
research, further understanding the pathogenesis and different types of CRSWDs will help to provide information for more reasonable based treatment. A large number of further studies are still needed in the future, especially randomized controlled studies.

References