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Causes of circadian rhythm disorders and methods of their treatment

Damian Machaj Faculty of Medicine, Medical University of Wrocław, Wybrzeże L. Pasteura Street 1, 50-367 Wrocław Poland

Aleksandra Mazurek aleksandramazurek7@gmail.com Poznań University of Medical Sciences ul. A. Fredry 11, 61-701 Poznań, Poland

Katarzyna Cyboran katarzyna_cyboran@o2.pl Medical Faculty, Institute of Medical Sciences, Collegium Medicum, Oleska Street 48, 45-052 Opole Poland

Monika Kuc kuc.monika96@gmail.com ; Medical Faculty, Institute of Medical Sciences, Collegium Medicum, Oleska Street 48, 45-052 Opole Poland

Dominik Machaj Faculty of Medicine Medical University of Lublin Chodźki Street 19 20-093 Lublin Poland

ABSTRACT

The circadian rhythm is the main biological rhythm to which man is subject. During the day periods of activity and sleep, eating habits, body temperature, secretion of certain hormones and frequency of urination all change. In anatomical terms, the biological clock is located in the suprachiasmatic nuclei in the hypothalamus [3]. The most important factor in the circadian rhythm is sunlight. They are particularly vulnerable to disturbances of the circadian rhythm school students and shift workers, however, please note that phenomenon this can occur in anyone. The consequences of circadian rhythm disorders include: reduced work efficiency, reduced social contacts, mood disorders, depression, obesity or metabolic diseases [1].

Main causes and disturbances of the circadian rhythm is reduced exposure to natural sunlight [1, 2]. Studies have shown that the biological rhythm may be disturbed by: the aging process [3], incorrect concentration such hormones as melatonin and cortisol [4, 8-27], symptoms of various diseases such as schizophrenia and medications taken [6], extension of the circadian cycle [7, 28] and factors such asocial life, time spent using multimedia devices, putting off homework by the students late evening hours, decreased parental control, increased frequency

of anxiety disorders, non-compliance with the rules of sleep hygiene and consumption of caffeine-containing products [7, 28, 29, 30].

The treatment of circadian rhythm disorders is primarily based on the patient's adherence to the rules of sleep hygiene. The use of phototherapy is also an effective method. In case of the ineffectiveness of the above methods drug treatment may be considered. Melatonin is the drug of choice. In the case of treatment with melatonin, the correct time of administration is crucial and his dose. Pharmacotherapy with hypnotic drugs has a modest, short-term efficacy and should be used in last resort [7, 31].

KEY WORDS: circadian rhythm, activity, sleep

INTRODUCTION AND PURPOSE

The circadian rhythm is the main biological rhythm to which man is subject. Processes biochemical and physiological taking place in the human body are synchronized with each other and they occur in a specific order and frequency in the 24h day and night cycle [3, 4]. During this time, activity and sleep limits, eating habits, body temperature, secretion of certain hormones, and frequency of urination. Synchronization of vital functions with changes taking place in the environment is regulated by the biological clock insensitive to most disturbances, which is located in the suprachiasmatic nuclei in the hypothalamus. In the absence of signals from the environment, the clock biological it itself generates circadian rhythms with periods close to 24 hours [3]. The most important factor in the circadian rhythm is sunlight. However, technological and economic developments have significantly questioned this fact. The change in the social organization of life has led to discrepancies between the social and biological clock and consequently to disturbances in the circadian rhythm. This is mainly due to the presence of artificial light and reduced exposure to natural light. This leads to the occurrence of social jet lag (SJL). School students and shift workers are particularly exposed to the occurrence of SJL, however, please note that phenomenon this can occur in anyone. The consequences of circadian rhythm disorders include: reduced work efficiency, reduced social contacts, mood disorders, depression, obesity or metabolic diseases [1].

The aim of the study was to determine the main causes of circadian rhythm disturbances and methods of their treatment. Our research material includes publications in the PubMed, ResearchGate and Google Scholar databases. To find relevant publications searches were carried out using a combination of keywords such as: "biological rhythm", "jetlag", "circadian rhythm", "biological clock". The first step was to find relevant publications from the past 40 years. The second step was to review the publications found.

DESCRIPTION OF THE STATE OF KNOWLEDGE

In detail, the topic of the impact of changes in the circadian rhythm on the functioning of individuals was presented in the work by Kamila Kozaczka entitled „The influence of natural light on the functioning of shift workers in terms of activation, drowsiness and hedonic tone”. In her scientific work, the author describes a study dealing with the influence of working hours and exposure to natural light on the functioning of shift workers. In the study of the analysis covers: the effect of the change on the test results; the relationship between the level of activation and the hedonic tone; relationship between exposure to light and subjective

variables (activation, drowsiness, hedonic tone). Down assessment level at for somnolence the Stanford SSS Sleepiness Scale was used. In order to determine the hedonic tone, the SHAPS Scale of Feeling Pleasure was used. To measure activation level was used Adjectival Thayer Activation Scale AD-ACL. Seconds spent in natural light was calculated on the basis of the Outdoor Axis. The test group is 31 men being employee in institution Koksownia, Arcelor Mittal Poland in Krakow. Analysis of the results tests showed the existence of relationship between sleepiness and perceived anhedonia and the time of exposure to light during the morning and night shift. Noticed also importantly relationship between activation level and exposure time. The differences in the subjective well-being of an individual depending on the type of change turned out to be statistically insignificant [2].

The aging process plays a crucial role in disturbances in the biological clock. Similarly like the whole brain, the biological clock, which is part of the brain, also undergoes the process. As the years go by the number of neurons decreases, which the result is weakened functions biological clock. The consequences of aging are changes in sync with the environment and changes in the synchronization of the body's secondary, peripheral pacemakers. Biological rhythms healthy old organisms are correct, however have reduced amplitudes and often accelerated sleep-wake phases and body temperature, and marked lowered endogenous melatonin levels [3].

Abnormal rhythm of melatonin is another cause of disturbances in the circadian rhythm. In anatomical terms, the biological clock is the suprachiasmatic nucleus (nucleus suprachiasmaticus-SCN) whose neurons they influence the secretion of melatonin by the pineal gland through the fibers of the sympathetic part of the autonomic nervous system [4]. The secretion of melatonin takes place in an endogenous circadian rhythm regulated by the light cycle and darkness those. Under the influence of light stimuli, the secretion of melatonin decreases, which work slowed its level in blood. The concentration of melatonin in the blood begins to rise in the late evening and the highest values achieves between 2 am and 3 am, amounting to 80-150 pg / ml. In the following hours, the concentration of melatonin in the blood begins to decrease gently and before at dawn obtain slow values comparable to those observed throughout the day, that is 10-20 pg / ml. It has also been shown that the lifestyle does not affect the melatonin biosynthesis cycle in humans [4, 8]. The role of melatonin is "setting the biological clock", including the sleep-wake rhythm, but also changes in body temperature [4, 22, 23, 24]. Many studies have shown reduced nocturnal melatonin levels in blood in suffering people on sleep disturbance. This was especially true of the elderly. Lowered melatonin levels have also been observed in children and adults suffering from depression, in people addicted to alcohol, but also those suffering from schizophrenia or Alzheimer's disease. People suffering from breast, prostate, rectal, endometrial, cervical, lung, stomach and thyroid cancer also have a problem with too low melatonin levels. The administration of melatonin causes the normalization of biological rhythms in sleep disorders in the blind, shift workers and in people who change the zone temporal [4, 9, 10, 11, 12, 13]. However, the increased level of melatonin, which was observed in girls with anorexia nervosa, in women with hypothalamic amenorrhea, in hyperprolactinemia, and in men with hypogonadotropic hypogonadism, is also unfavorable. Currently there are three primary indications for the therapeutic use of melatonin. These are: sleep disorders, especially in the elderly, regulation of the sleep-wake rhythm in blind people and the elimination of disturbances resulting from the rapid change of time zones during the journey. Average doses used in therapy range from 1 to 5 mg, however, it should be remembered that both the dose and the duration of the treatment should be selected individually [4,14, 15, 16,17,18,19].

Another hormone whose abnormal concentration disturbs the circadian cycle is cortisol, commonly known as a "stress marker", as its concentration increases in stressful situations. Produced cortisol is mainly through the banded layer adrenal cortex, causes an increase in blood glucose, accelerates gluconeogenesis, decomposition fatty acids down ketone bodies and has an anti-inflammatory effect. The concentration of cortisol fluctuates daily, with the highest concentration of 150-250 ng/ml falling in the morning between 6:00 and 8:00, while the lowest is between 23:00 and 4:00 and is less than 50 ng/ml. The circadian rhythm of cortisol secretion is regulated by the central nervous system and is dependent on the time of sleep and wakefulness. In sharing cortisol characterizes high variability and this rhythm can be disturbed by mental stress, physical stress, shift work and various diseases. Within minutes of the onset of stress, the secretion of cortisol increases by increasing the secretion of hypothalamic CRH and pituitary ACTH [4.20, 21]. When the stress response is prolonged, it also disrupts the circadian secretion of cortisol [4.25]. Excess cortisol (especially in the evening and night hours) makes it difficult to fall asleep, which may lead to insomnia and, consequently, to disturbance of the human biological clock.

Agnieszka Adamczak-Ratajczak in the work entitled "Circadian rhythms of melatonin and cortisol in selected neurological diseases" described the study the purpose of which was determining the regularities or abnormalities of biological rhythms in patients diagnosed with Huntington's disease and ischemic stroke based on the circadian profile of melatonin and cortisol, as well as finding the usefulness of measuring melatonin and cortisol levels in the assessment of the severity of Huntington's disease. Huntington's disease patients were recruited for the study from the Neurology Clinic of the Medical University in Poznań, from patients admitted directly to the Neurology Clinic or referred to this Clinic by the European Huntington's Disease Network Poland from Poznań. Ultimately the application covered 8 patients aged 28-70 years, with various stages of the disease. Group comparative constituted 8 patients with ischemic stroke aged 52-84 years, in whom no pathological changes in the hypothalamus, where there is a pacemaker (SCN nucleus) for biological rhythms, were shown by computed tomography. Rwere recruited from the Impact Department of CM HCP in Poznań. Control group consisted of students of the Medical University of Poznań, aged 19 to 27, who were in an air-conditioned chamber during the study, where the lighting was controlled. To define the following tests were carried out on regularities or abnormalities in biological rhythms: 1) the material for research was collected at: 4:00 p.m., 6:00 p.m., 10:00 p.m., 24:00, 2:00, 4:00, 6:00, 10:00, 2) the peeled blood was centrifuged for 10 minutes at 3500 rpm and the serum obtained in this way was stored at -80 degrees Celsius, 3) Hormonal demands concerned determination of melatonin and cortisol levels using the enzyme immunoassay ELISA (Enzyme-Linked ImmunoSorbent Assay), a test kit produced by IBL Hamburg ELISA, 4) motor activity was assessed using the Oxford Actiwatch Plus recorder. Activity was measured from 16:00 to 10:00 am on the next day, and measurements were made every 30 seconds.

By analyzing biological rhythms, he determines amplitude, average level of oscillation, the so-called MESOR (midline estimating statistic of rhythm), period of oscillation and shift - acrophase. In the study, determine it parameters for the period of 18 h using the single cosinor method and the population mean cosinor for each study group. Thus, three parameters for melatonin and cortisol were obtained: MESOR, amplitude and phase shift. The obtained parameters were subjected to further statistical analysis in order to determine significant differences in the studied groups using the analysis of variance and the Kruskal-Wallis test. The analysis of the study results showed that disturbances in circadian rhythms in patients with ischemic stroke may be associated with inappropriate secretion of melatonin and cortisol.

The results of the study showed a statistically significantly lower melatonin concentration in patients with stroke compared to the control group, while the cortisol concentration in these patients is statistically significantly higher than in the control group. Also a link has been found between disruption of the suprachiasmatic nucleus in Huntington's disease patients and abnormal melatonin secretion. There was no statistically significantly lower melatonin concentration compared to the control group, while the melatonin phase was shifted depending on the stage of the disease. In people with Huntington's disease, not eit also has a statistically significantly higher concentration of cortisol compared to the control group [4].

In the test that showed the existence of a significant relationship between the concentration of melatonin and cortisol and the action of biological rhythms was an experiment conducted by Premkumar and colleagues on healthy scientists living in the Arctic. They were exposed to extreme weather conditions for over a year, and their biological rhythms were assessed on the basis of the concentration of melatonin and cortisol in the blood serum. Blood was collected for analysis 4x a day at 8.00, 15.00, 20.00 and 2.00 at night. Analysis of the results showed and that the circadian rhythm of cortisol was comparable in the polar summer and winter, while the daily melatonin secretion was higher during the polar winter and this increase was sustained throughout the day. It has influenced significantly for better quality of sleep in the winter [26].

In a 2014 study of biological rhythms, Videnovic and fellow-workers examined secretion of melatonin during the day in patients suffering from Parkinson's disease with excessive daytime sleepiness and no sleep disturbance. In patients without sleep disturbances there were no statistically significant differences in the daily melatonin secretion compared to the control group, while patients with Parkinson's disease and excessive daytime sleepiness had a statistically significantly reduced amplitude of melatonin concentration. The authors of the study concluded, that cause excessive daytime sleepiness in Parkinson's disease patients may be lowered melatonin levels [27].

When listing the causes of the circadian rhythm disturbances, it should be remembered that symptoms may contribute to the disturbance of the biological clock different diseases and medications taken. The purpose of the study described in the work entitled "Sleep and circadian rhythm disorders in schizophrenia" by Agnieszka Skowerska, Adam Wichniak and Michał Skalski was the assessment of the circadian rhythm of patients diagnosed with schizophrenia and the degree of improvement in their functioning and mental state in the period preceding discharge from the psychiatric day hospital, after a complete therapeutic process. The study was conducted at the Day Ward of the 3rd Psychiatric Clinic of the Institute of Psychiatry and Neurology in Warsaw. Research group consisted of 23 patients (14 women and 9 men aged 22 to 60) with a diagnosis of schizophrenia according to ICD-10, in whom functioning and mental state were assessed in the period preceding discharge from the ward. The control group consisted of 23 volunteers matched by age and sex to the research group. During the test, make and the following activities: 1) actigraphy was used to assess the duration of sleep, circadian rhythm of sleep and activity as well as the level of the patient's activity during the day; 2) sleep diary entries were made in which patients recorded the time of going to bed, waiting time for sleep, time of getting out of bed in the morning and estimated time of sleep; 3) standardized scales were used: sleep quality (Athenian Insomnia Scale - AIS), daytime sleepiness (Epworth Sleepiness Scale - ESS), akathisia (Barnes Akathisia Scale -BARS), general clinical condition and degree of improvement (CGI scale), patient activity on the therapeutic classes in the ward (Patient Functioning Questionnaire in the Day Ward), the presence and severity of psychopathological symptoms and depression in schizophrenia (PANSS scale, Calgary scale) and the severity of side effects (UKU scale). The

differences between the groups were assessed for statistical significance using analysis of variance (ANOVA). The relationships between the variables were verified using the Spearman correlation test. $P < 0.05$ was adopted as the level of statistical significance. Actigraphic examination showed that they were sick has schizophrenia they spent more time in bed and had longer sleep times than healthy people. It was found that the dominant factors contributing to the low activity of patients were negative symptoms of schizophrenia and the occurrence of side effects of drugs [6].

In work by Magda Kaczor and Michał Skalski entitled „Circadian rhythm disorders in adolescents - literature review " it was noted that with abnormal circadian rhythm they concern abnormal sleep times or the division of sleep into periods, but they do not affect the length and architecture of sleep. A negative impact of circadian rhythm disturbances on the functioning of the patient and his family has been observed. The causes of these disorders were divided into psychosocial and biological ones. Biological factors are the prolongation of the circadian cycle to 25 hours or more [7, 28]. Psychosocial factors include social life, time spent using multimedia devices, postponing homework until late at night, reducing parental control, but also reluctance to go to school, increasing the frequency of anxiety disorders, avoiding uncomfortable social contacts [7, 28, 29]. Another factor delaying the phase of falling asleep in among the youth is non-compliance with the rules of sleep hygiene. The average difference between going to bed during the week and over the weekend is 1-2 hours. Whereas weekend getting up is delayed on average by 3-4 hours compared to the rest of the week [7, 29]. The caffeine-containing products consumed by adolescents have a significant impact on delaying the falling asleep phase, which improves the quality of wakefulness [7, 30]. The basic method of treating circadian rhythm disorders is the implementation of sleep hygiene principles taking into account the type of the patient's disorder, comorbidities and perceptive abilities. The most important principles of sleep hygiene include: depriving the place of sleep of intense stimuli, constant sleep framework, avoiding caffeinated beverages after hours 15, moderate physical activity during the day, avoiding intense exercise 2-3 hours before going to bed, limiting the time before going to bed with devices emitting the blue light spectrum (tablets, smartphones, computers, TVs), eating breakfast rich in tryptophan and vitamin B6, exposure to light in the morning hours. The use of phototherapy is also an effective method, in order to accelerate the circadian cycle it is recommended to use phototherapy immediately after waking up, and to delay it, irradiation in the evening hours is used [7, 31]. The patient should also remember to respect the correct distance from the light source and always sit in front of the lamp with the whole face turned towards the light source, but without having to stare at the light [5]. In case of the ineffectiveness of the above methods drug treatment may be considered. Melatonin is the drug of choice [7, 31]. In the case of melatonin treatment, the correct time of administration is crucial. In DSWPD (delayed sleep-wake phase disorder) it must be many hours ahead of the planned sleep time. Correct dosage of melatonin is also important. In patients with CRSWD (circadian rhythm sleep-wake disorders) it is beneficial usually short-term (up to 6-12 weeks) use of higher doses, in neuropsychiatric disorders up to 10 mg/day. If, after this period, it is necessary to continue melatonin maintenance treatment, it should be significantly lower her dose up to 0.5–1 mg / d and discontinuation of treatment due to the possible inhibitory effect of melatonin on sex hormones [5]. Pharmacotherapy with hypnotic drugs has a modest, short-term efficacy and should be used in last resort [7, 31].

CONCLUSIONS

1. Disorders of the circadian rhythm negatively affect our health, well-being, professional and social life.
2. The main causes of disturbances of the circadian rhythm are: decreased exposure time to natural light, abnormal levels of hormones such as melatonin and cortisol, symptoms of various diseases such as schizophrenia and medications, and non-compliance with the rules of sleep hygiene.
3. The causes of the disorder the circadian rhythm divided into psychosocial and biological. Biological factors are the lengthening of the circadian cycle to 25 hours or more. To psychosocial factors we include: social life, time spent using multimedia devices, putting off homework by the students late evening hours, reduced parental control, reluctance to go to school, increased frequency of anxiety disorders, avoiding uncomfortable social contacts.
4. Treatment of the circadian rhythm disorders begins from the implementation of sleep hygiene rules. The use of phototherapy is also an effective method. In case of the ineffectiveness of the above methods drug treatment may be considered. Melatonin is the drug of choice.
5. Pharmacotherapy with hypnotic drugs has a modest, short-term efficacy and should be used in last resort.

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