Research Progress about Exploring the Impact of Jet Lag on Circadian Rhythms

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Abstract. Circadian rhythm, one of the fundamental laws of nature, plays an essential role in maintaining life processes. However, it is challenged by a modern situation known as jet lag. Jet lag brings disruption to circadian rhythm, breaking people's normal routine and causing troubles to people's lives. For the past few years, jet lag have been reported frequently. More researchers have realized the importance and complexity of jet lag. Jet lag can arise from travel crossing time zones as well as from shift works, impacting several aspects of life activity including metabolism, mental health, intestinal health et cetera. Beyond the macroscopical symptoms, microcosmic alterations are as important as the symptoms. Gene expression patterns can be varied by chronic jet lag even rewrote by the chronic jet lag and have long-term effects. Fortunately, several researches have revealed the possibility to lessen the influence of jet lag to fitness. Compared to the last century, people live in modern society have more optional methods to enjoy a much more comfortable life. Melatonin therapy and chronotherapy have been presented by scientists to settle the jet lag. But for the treatment of jet lag, there are still lots of details need to be considered.

Keywords: Jet lag, Circadian rhythm, metabolism, gene expression, potential treatment.

1. Introduction

Circadian rhythm is one of the most common phenomena on the Earth. The concept of the circadian rhythm was first be mentioned in 1940s. In modern society, more and more people would like to have international trips and cross time zones while some others have to experience shift work because of their occupational characteristics. Scientists named these conditions jet lag. The development of science and technology has created jet lag and jet lag is one of the important factors that cause the disruption of circadian rhythms which has brought great challenges to the health and quality of life of modern people. Under normal circumstances, human have a inner body clock which is close to 24 hours per day. When experiencing the jet lag, one of the most obvious difference towards to the normal days is the length of day which have changed. For example, when travel form western to eastern, the length of a traveler's day will be less than 24 hours because of crossing time zones. In shift workers, they experience a specific social jet lag. They do not cross the time zone, but their circadian clock does not fit the environment properly. For ordinary people, they go to work or study during the day and go to sleep at night. But for jet-lagged people, they usually have a disorder on their chronotype. They may feel sleepy during the days while awake during the night.

Meanwhile, because of the disorder, the environment will disrupt the sleep process and decrease the quality of sleep. Sleep is one of the most essential factors for human health, and the lack of sleep can cause a large amount of diseases [1]. Jet lag is quite different from the travel fatigue [2,3]. Paragliola, R. M. et al have shown that travelers who cross over 6 time zones will suffer much more serious jet lag than short-distance travelers [3]. Jet lag may cause different symptoms on different individuals. The most common symptoms contain insomnia and obesity. Behind these symptoms, jet lag has altered the metabolism level as well as gene expression pattern. For general public, their behavior is not only determined by their mind but also regulated by the environment. The circadian genes like CLOCK and BMAL will work in a specific pattern together with the environmental factors like sunlight to adjust the physical requirement. That is why people wake up in the morning and feel sleepy at night. But things have changed in jet-lagged individuals. The signals from the environment have conflict with the inner body pattern and bring a series of problems and develop into different symptoms. Troubles caused by jet lag make people annoyed and disposed. It is not easy for therapists to deal with these symptoms, but the modern technology still can seek for the opportunities to relief the symptoms.

2. Macroscopical changes causing by jet lag

Most mammals on the earth have their own circadian rhythm. Their bodies have a close to 24-hourbiotic clock. When suffering jet lag, the creature will experience a non-24-hour light dark cycle and lead to disorders to metabolism, mental health and so on. As one of the most complex organs, the gut has huge amounts of germs and plays an essential role in the inner environment. Matenchuk, B. A. et al have shown that after suffering jet lag, some species of bacteria in mice's intestinal canal will decrease while some others are on the contrary [1]. The variation in intestinal flora leads to obesity and intolerance of glucose. Furthermore, this situation can be delivered to another germ-free mouse by transplanting microbiota in the jet-lagged mouse's gut. What is more, Acosta, J. et al have exhibited that after building chronic 6-hour jet lag modeled male mice, the mice showed less interest on food reward and exhibited a higher level of anxiety and depression in an open field behavior test [4]. In summary, this study claimed that when mice are suffering from jet lag, they may have problems with their mental health, which can be performed like fewer immobility time.

This situation does not only occur in rodents, and other two studies have focused on human beings. Paragliola, R. M. et al invited 28 volunteers in good health in 2021[3]. All of the volunteers were not pregnant or taking contraceptive. They were traveling from Europe to North America during daylight saving time by direct flight. The researchers collected datas from these volunteers by providing a questionnaire and determining salivary cortisol level test. Then according to these data, they evaluated how serious the volunteers have suffered from jet lag. The questionnaire and the test reflected that compared to the period before traveling, jet lag made the volunteers' level of cortisol increase and only 2 volunteers haven't reported any symptoms. The other volunteers have suffered different levels of symptoms caused by jet lag and all of them have fatigue. Interestingly, the questionnaire results do not have pertinence with the cortisol level. Researchers have confirmed that over 5 time zones' travel do affect the rhythm of the cortisol. But considering the symptoms show no relationship between cortisol level and subjective feeling, the author supposes that there should be another theory which can explain what causes the difference between symptoms. Janse van Rensburg, D. C. et al paid attention on athletes who may cross time zones frequently in 2021[2]. According to the researchers, athletes from the National Hockey League (NHL) and Major League Baseball (MLB) travel more than 40,000 km every year, which means that athletes are excellent targets for the study of the affection of jet lag. Both two team of researchers consider that jet lag is similar to travel fatigue but they are different. Researchers did not provide results of the athlete study. Instead, they provide a methodology. In their opinion, level of melatonin and electroencephalogram can be applied to analyze the effect of the jet lag objectively. Due to the melatonin is one of the most important neural transmitters as well as hormone which is tightly related to sleep, changing of the melatonin level may cause jet lag happen and it may explain why human beings who suffer jet lag have a sleep disorder.

Since both study on human and mouse have reported mental symptoms after experiencing jet lag, Walker, W. H. II et al has discussed about this situation[5]. In this review, researchers not only consider about the jet lag causing by traveling but also pay attention to another type of jet lag which is causing by social life. The phenomenon called social jet lag is also named as shift work. In their review, they believe that jet lag may influence the quality of sleep by mood changes. Meanwhile, researchers claimed that travelers from west to east suffer more terrible effects of jet lag than travelers from east to west. In conclusion, these researchers do agree that the disruption of the circadian rhythm caused by jet lag does make the risk of having mental disease higher. But, they are not sure about the theory behind this situation. According to these articles, it is clear that jet lag can disturb circadian rhythm by interfering with the quality of sleep and vary the inner environment (such as intestinal flora) and the metabolism level (such as cortisol and melatonin). These macroscopical variations do occur in individuals who suffer jet lag no matter if they are rodents or human beings. An interesting fact is most of the studies focus on human beings have mentioned a questionnaire named Liverpool jet-lag questionnaire. In the author's opinion, this questionnaire should be a key for further study because a human has much more parameters than animals, directly research on human beings should receive a much more accurate conclusion about what jet lag does to the metabolism and mental health.

3. Microcosmic alteration when experiencing jet lag

Besides of the macroscopical changes, microcosmic changes are also an essential part of the explanation for why jet lag makes creature feel indisposed. For microcosmic alterations, gene expression is the most important section. Gene expression can affect circadian rhythm itself as well as causing symptoms like disorder of phenotype of sleep, fatigue and so on. As one of the most well-known gene, circadian locomotor output cycle kaput (CLOCK) and brain and muscle ARNT-like protein 1 (BMAL1) have mentioned many times in different articles about jet lag. Also in the Walker, W. H. II et al's article that mentioned perviously, light can be detected by retina and transmit the light information to the suprachiasmatic nucleus (SCN) where the master clock exists in. CLOCK and BMAL1 interaction with each other and form a complex [5]. With the help of other proteins and enzymes like PER, CRY, REV-ERB α , ROR α et cetera, they create a 24-hour-internal biotic clock. This system can work by itself and maintain a 24-hour-rhythm. It can also alter the environment like illumination intensity.

When suffering jet lag, the illumination intensity of rhythm does not fit the biotic clock and increase the potential of physiology and behavior dysregulation. Oneda, S. et al were aimed to the field of gene expression about jet lag [6]. They used male Institute for Cancer Research mice (ICR mice) as experimental animals and knock-in a PER2: LUCIFERASE (PER2: LUC) gene. They built a social jet lag model by providing a 6-hour delay of light dark cycle according to several previous studies. This delay would last for two days just like mimicking the weekends and the dark light cycle would go back to normal for five days and then this pattern cycled. In their studies, they claimed that 4 days after suffering the social jet lag, the expression of PER2: LUC was significantly delayed, and this delay cannot be affected by doing exercises. Furthermore, they provided a high-fat diet (HFD) to these mice which has already been proved to affect the circadian rhythm of mice. Interestingly, after providing HFD, the recovery of the social jet lag was better than normal diet. In addition, after combining HFD with exercise, the expression pattern of PER2: LUC was improved and showed no significant difference between the control group of HFD mice's livers and kidneys.

Oneda et al have shown that jet lag will make the expression pattern of PER2 alter, but PER2 is not the only gene which associated with circadian rhythm. Duong, H. A. et al showed that in liver cells, there existed many kinds of clock gene, such as Arntl, Csnk1d/e, Nr1d1/2 et cetera [7]. They focus on environmental circadian disruption (ECD) which includes jet lag, shift work and so on. In Chen, Y. et al's study, many circadian gene will change their rhythms when suffering jet lag[8]. Chen, Y. et al's study was matched to Duong et al 's study, they also realized this situation and investigated what the ECD did to reprogram the circadian genes' rhythms. In their research, they found that 4179 transcripts' rhythm have altered by ECD in liver cells which make the metabolism pathways changed, especially in the metabolism of fat and carbohydrate. This phenomenon will last more than one week even after the recovery of the ECD. Furthermore, they also showed the theory that could explain this alter. In their opinion, post-transcription and post-translation are two of the most important roles which cause this variation after suffering an ECD. Then the researchers have confirmed that post-transcription have bigger contribution to the circadian gene expression pattern. In conclusion, whether it's jet lag due to travel or social factors, the individuals who suffering jet lag do lead to a alternation to gene expression pattern. This change of the expression pattern has been confirmed that will occur in digestion system like gut and liver which can lead to a metabolism vary or certain disease as well as in the neural system. But, due to the complexity of human brain and society, there are still many questions need to be answered about what does jet lag affect the gene expression pattern in brain and whether this pattern can be reprogramed like liver cells in order to make the individual adapt to the jet lag.

4. Potential treatment for jet lag

Just like the previous studies showed before, jet lag will cause both mental suffering and physical disease. Chronic jet lag may break individual's sprite as well as bring some healthy problems. Since most of the time, jet lag is inevitable. It is difficult for modern people to avoid suffering jet lag, and finding a potential treatment to relief symptom causing by jet lag is necessary. Summing up the foregoing, one of the most obvious symptoms is fatigue, especially in the people who travel from west to east. Ordinarily, this kind of fatigue will lead to insomnia. Sun, S. Y. and Chen, G. H. mentioned that to treat sleep problems caused by confusion of sleep-awake rhythm which is consistent with the insomnia caused by jet lag in their article [9]. They regarded melatonin as a signal of darkness and claimed that providing exogenous melatonin can make patients's sleep cycle earlier without changing the sleep pattern. Combining the information provided in other articles in this review, providing a low dose of exogenous melatonin is more recommended by the researchers to relief the symptom of insomnia. However, melatonin treatment has a risk of addiction and increase dependency of melatonin. Unfortunately, besides the dependency problem, the security of melatonin treatment has not been fully confirmed and it is not recommended to be applied to pregnant and breastfeeding ladies.

Since it was previously stated there is a difference in the intensity of jet lag when traveling from east to west versus when traveling from west to east. In the author's opinion, traveler who travel from east to west will experience a more than 24-hour day while west to east traveler have the opposite situation. Applying chronotherapy should be a potential method to relief the jet lag. Lee, Y. et al emphasized how to apply chronotherapy to patients [10]. They suggest applying chrono-diet as a part of the therapy by restricting the period of time of taking food in order to correct the disordered circadian rhythm. The theory behind this method is linked to fixing the disruption of the intestinal flora and then fixing the disorder of metabolism. They have confirmed that mice which have a obesity induced by diet can correct the broken circadian rhythm of the gut microbiome activity. This approach corresponds to the previous article that mentioned that jet lag can cause intestinal flora disorder phenomenon and may be a potential direction for treating the gut disease caused by jet lag. Back to Sun and Chen's review, they also mentioned a treatment associated with chronotherapy. They suggest a much more direct approach by requiring individuals delay or advance their schedules of sleep for 3 hours every 2 to 5 days. This approach has not been fully proved in their article, but in the author's opinion, just like the previous study showed, a 3-hour jet lag is much more acceptable to individuals but there are still many obstacles to realizing this therapy.

Facing lack of sleepiness, modern people tend to choose to keep themselves awake rather than force themselves to sleep, which may lead to this therapy is not so effective. Another potential therapy is doing exercise. Oneda, S. et al shown previously, mice who suffering jet lag will have a better recovery if they do more exercise like running on a wheel [6]. Disappointingly, whether this approach can work in humans has not been accurately proven and need to have a further discussion. What is more, insomnia and obesity are not the only problems caused by jet lag. Zeng, H. et al showed another symptom will occur when suffering jet lag [11]. Researchers find that on chronic jet lagged mice, they have injury on their eyes, manifesting as an increase in the number of apoptotic cells and cytokines in the cornea which finally lead to a dry eye disease. Regarding that the symptom are caused by jet lag, researchers also

suggest a melatonin therapy and confirmed that after treating with melatonin, the situation of the damage to cornea was improved comparing to the control group. In conclusion, many researches about curing jet lag are based on curing the symptom like insomnia by using medication (such as melatonin) or macroscopic treatment (such as regular the schedule).Ultimately, these are treatments that treat the symptoms rather than the cause. It is hard for scientists nowadays to fix the problem causing by jet lag by altering the environment itself to make individual feel less suffering. Melatonin is not a panacea, and it is difficult to guarantee that melatonin do not have side effects and there still have obstacles for ordinary people who suffer jet lag to get melatonin and use it properly. There is still a long way to go.

5. Conclusion

In conclusion, jet lag makes a significant disruption to the circadian rhythm. Much evidence has exhibit that no matter what they are causing by travel across time zones or by shift works when suffering jet lag. Individual's metabolism level and gene expression pattern will be varied by the jet lag. At the metabolism level, jet lag will affect the inner environment of gut, varying the amount of intestinal flora and increasing the risk of obesity. Jet lagged individuals may also suffer a intolerance of glucose. In addition, jet lag can also modify the gene expression pattern compared to those with normal circadian rhythms. Jet lagged individuals' expression of most of the clock associated genes' pattern have been reprogrammed. This kind of variation occurs in multiple organs and systems. Notably, it is confirmed that the digestion system does have this alteration which explains why suffering jet lag is sometimes linked with symptoms related to the digestion system.

A substantial amount of research has been devoted to alleviating or even curing these symptoms. One of the most well-known approaches is the administration of exogenous melatonin to patients who suffer from insomnia, which is one of the most common symptoms of jet lag. Another group of researchers advocates chronotherapy to treat the symptoms associated with jet lag. Both potential therapeutic approaches have broad prospects, but for general population, there are still certain obstacles to apply these therapy. Moreover, the potential of addiction or tolerance to melatonin is still not be fully confirmed, which represent that there still have risk of applying melatonin therapy. Meanwhile, most of the treatments are essentially a palliative approach, but few articles have focused on solving jet lag more once and for all. Treating the symptoms of jet lag is still a long way off. For further study on jet lag, researches can be designed to explain how does the brain adapt to the changes in jet lag. Aiming to the neural circuits, synthetic regeneration et cetera. In parallel, for better treatment, researches can be designed to help human body itself to reprogram the gene patterns as well as demonstrate that melatonin is not addictive and lowering the operational and technical threshold for using melatonin for treatment.In summarize, the necessarily and the value of proceed with further study on jet lag, decoding the mystery of the jet lag can not only help people ease the suffering of jet lag but also help scientists understand the enigma of life.

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