A Comprehensive Review of Chronobiological Challenges of the Sleep-Wake Cycle in Space: Implications for Long-Duration Space Missions and Translational Applications in Terrestrial Medicine

Md. Solaiman Hossain[1, 2], Tanoy Saha[1], Md. Ariful Islam[1], K M Ferdousul Haque[1], Md. Mirazul Islam[1], Md. Mahbubul Hoque[1] and Sumiya Sharmin Mou[3]

[1]Department of Pharmacy, School of Pharmaceutical Sciences, State University of Bangladesh, Kendua, Kanchan, Rupganj, Narayanganj-1461, Dhaka, Bangladesh
[2]Department of Clinical Pharmacy and Pharmacology, University of Dhaka, Dhaka-1000, Bangladesh
[3]Department of Pharmacy, University of Asia Pacific, Dhaka-1205, Bangladesh

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Abstract

Maintaining a healthy sleep-wake cycle is vital for the health and performance of astronauts on long-duration space missions. The unique session type induced by space environments (high levels of microgravity and the absence of a day-night cycle) disrupts physiological circadian rhythms and adversely affects health status primarily through sleep disturbances and cognitive impairments that lead to reduction in performance. This review discusses the chronicles made by the astronauts in the space like the reflection of sleep-wake cycle disturbances with their mechanisms and biological and psychological effects of the astronauts due to these disturbances. It also discusses current countermeasures such as manipulation of exposure to light, pharmacological interventions, exercise regimens and behavioral strategies to mitigate these effects. The review emphasizes the importance of personalized and multimodal approaches for enhancing astronaut health during missions. Moreover, space research has potential applications to terrestrial medicine, especially in the management of sleep disorders and circadian rhythm misalignment in non-astronaut populations.

Key words: Sleep-wake cycle, circadian rhythm, space medicine, light exposure, pharmacological interventions, chronobiology.

Introduction

The sleep-wake cycle (the circadian rhythm) is a core element of human physiology that coordinates numerous biological programs required for health and wellness. These mechanisms consist of sleep factor control, hormone release, metabolic function, and theory. The SCN in the hypothalamus controls the circadian rhythm by harmonizing the internal clock of the body with environmental stimuli, primarily the natural 24-hour cycle of light and dark (Van Drunen *et al.*, 2021). This synchronization, known as entrainment, allows organisms to prepare for daily oscillations in their environment, ultimately optimizing biological processes based on day-night rhythms (Häfker *et al.*, 2023).

This phenomenon, called entrainment, enables organisms to adapt to daily fluctuations in their environment, effectively fine-tuning biological processes to align with the day-night cycles. Space travel is often accompanied by unique challenges that affect circadian rhythms. Due to its artificial light cycle and fast orbit around Earth, the International Space Station (ISS) is a great setting to study how space exposure changes humans. Without

Corresponding author: Md. Solaiman Hossain; Email: solaiman.pharmacy@sub.edu.bd; Mobile: +8801521206536
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coordinated light-dark cycles, internal circadian rhythms fail to be entrained by external time cues (16 sunrises, and sunsets, each day).

Space microgravity uniquely affects physiological systems such as sleep architecture. Astronauts may experience disrupted sleep-wake cycles as a result (Kanas and Manzey, 2008). The misalignment of internal and external time cues serves to disrupt sleep-wake cycles (Baron and Reid, 2014), leading to decreases in sleep time, poor sleep quality and decreased alertness and mission performance. Circadian misalignment in space affects more than just sleeping difficulties. Studies show that humans in space experience circadian disruption and this leads to significant alterations in cognitive performance characterized by poor attention, increased reaction time and poorer decision-making ability which can threaten mission success (Desai *et al.*, 2022). Furthermore, the physiological consequences of prolonged sleep disturbance may include reduced immune function, greater susceptibility to sickness, and impaired physical performance, all of which are key variables in astronaut health during long-duration space missions (Whitmire *et al.*, 2016).

As we progress into human space exploration, the feasibility of long-duration missions to distant destinations like Mars, and beyond, deserves a more in-depth understanding of the mechanisms of circadian regulation in space. These missions could last months or even years and astronauts will be exposed to continuous circadian misalignment, adding additional stress to their biological systems. Consequently, the need for efficient countermeasures that lessen the consequences of sleep disturbance and circadian misalignment are essential, not only to safeguard astronaut health, but also to promote mission performance. (Duda *et al.*, 2021).

Significantly, the exploration of circadian cycles in space is one such field that yields findings with relevance outside of space medicine as well. Many of the issues that astronauts face in maintaining sleep and circadian stability are also seen in terrestrial populations. Shift workers, jet-laggers and people with seasonal affective disorder (SAD) all have their circadian rhythms greatly disturbed, resulting in comparable morbidities in the form of sleep deprivation, mood disorders and poor cognitive function. Understanding circadian rhythms in space may even allow for the development of new therapeutic measures that could be implemented in those earth-bound populations to improve their health and well-being, such as light therapy, pharmaceutical drugs, or behavior (Pandya, 2009).

The present contribution aims to explore this interplay of the sleep-wake cycle and circadian regulation during space travel. Specifically, it will explore the unique barriers faced by astronauts embarking on long-duration missions, the current countermeasures implemented to overcome these obstacles, and the potential of this research to inform strategies that improve and protect circadian health on earth. Knowing how spaceflight impacts circadian clocks and developing strategies to counteract these effects would lead to improvements in astronaut health and also translate to advancements in health care practice here on earth (Palomo *et al.*, 2021).

Methods and Materials

Data searching: Data related to the sleep-wake cycle, circadian rhythm disruptions and associated chronobiological challenges in space environments before 10 July, 2023 were retrieved from various online databases. Only articles published in English that met predetermined criteria were selected from PubMed, Google Scholar, Embase, Web of Science, and Cochrane Library. Data collection was conducted using the keywords: “Sleep-wake cycle,” “Circadian rhythm in space,” “Chronobiology in long-duration missions,” “Sleep disruption in spaceflight,” “Light exposure,” “Pharmacological interventions,” “Behavioral strategies,” “Exercise and circadian health,” “Sleep medicine,” and “Space exploration.” To identify any potentially missing articles, references from selected papers and review articles were also examined.

Eligibility criteria: Several criteria were applied to ensure the inclusion of relevant data from selected articles. Articles that did not meet these criteria were excluded from the study. Studies considered in the review adhered to the following eligibility criteria: (a) articles focused on circadian rhythm challenges, (b) articles addressing sleep-wake cycle disruptions during space missions, and (c) interventions aimed at managing circadian misalignment in space. Studies involving animal models, commentaries, editorials, and articles with insufficient data on space-related sleep-wake cycle challenges or potential terrestrial applications were excluded from the review.

Chronobiological disruptions during space missions and their impact on astronauts:

Space missions, especially long-duration missions pose unique chronobiological challenges with significant effects on astronaut health, performance and mission success. One big problem is disturbing the sleep-wake cycles of astronauts, which are influenced by their natural circadian rhythms. In zero-gravity situations, the lack of natural environmental cues such as the day-night cycle (of a planet) leads to major phase shifts between biological clocks and the external clock set by the artificial time structure of a space mission (Faerman *et al*., 2023). These chronobiological aberrations are exacerbated by the spacecraft that will never rotate to the other side of the planet, or the prolonged distances to planets like Mars that imposes considerable stress on crewmember physiological and mental health.

Circadian disruption in space sleep-wake cycles: The primary circadian concern for astronauts on space missions relates to the altered light-dark cycles they're subjected to. (This means that astronauts on the International Space Station (ISS), which travels at a much higher orbital speed, experience sixteen sunrises and sunsets in a single day.) These rapid cycles of light and dark are one reason it is difficult for astronauts to align their biological systems with the routine 24-hour day-night period of Earth (Palmer, 2002). This asymociacao between their internal clocks and the external rhythms leads to "circadian misalignment", yielding difficulties sleeping, reduced alertness, and impaired cognition (Naismith *et al*., 2013).

Planets, including Mars, add extra challenges to long-duration missions because their rotations open crew members up to the effects of prolonged exposure to day or night — in the case of Mars, 24.6 hours. This small shift from Earth Day and absence of natural light cues may strengthen difficulty in regulating sleep-wake cycles (Welsh, 2024). Astronauts on these kinds of missions will have to depend a lot on artificial light and black timing protocols to stay in tune with their internal clocks.

Sleep deprivation and cognitive impairments: Chronic circadian misalignment can have serious effects on astronaut performance. Sleep deprivation (or commonly caused by chronobiological misalignment), is associated with a range of cognitive deficits like impaired attention and memory and longer reaction times (Flynn-Evans *et al*., 2016). Such limitations are especially concerning in space missions, when astronauts must operate complicated systems, conduct scientific experiments, and make critical judgments in hostile situations.

Furthermore, as well as cognitive impairments, sleep deprivation has been shown to increase the risk of mood disorders such as irritability, anxiety and depression (Leach, 2016). These psychological effects may be magnified in the context of physical isolation and confinement in the space setting, creating a feedback loop whereby interrupted sleep increases psychological stress, which further disrupts sleep. The association between sleep deprivation and psychological distress is particularly alarming, as both traits may have an adverse effect on team performance, communication, and mission success (Litwiller *et al*., 2017).

Physiological consequences of circadian misalignment: Besides cognitive and psychological effects, circadian misalignment in space has several physiological effects. Perhaps the most striking effects are the disruption of hormonal patterns, particularly the regulation of melatonin, cortisol and a host of other hormones that are tightly entwined with the circadian clock. Melatonin, a hormone that regulates sleep, is naturally released in response to darkness, telling the body that it's time to sleep. In space, this suppression of melatonin secretion becomes more persistent, as astronauts are continuously exposed to artificial light (Strollo *et al.*, 2022).

Indeed, altered circadian cycles have been found to influence various metabolic processes, including reduced glucose metabolism and immune system regulation. Specifically, chronic circadian misalignment, isorsmal widespread occurrence on long duration missions can further exacerbate pre-disposed metabolic conditions that increase an astronaut's vulnerability to insulin resistance as one example (Buckey, 2006).

Additionally, the lack of alignment with the natural circadian rhythm can weaken the immune system, making astronauts more susceptible to infections, which is particularly problematic in the closed and sterile environment of a spacecraft (Mosa, 2018).

Interventions and countermeasures for chronobiological disruptions: Moreover, misalignment with normal circadian rhythm can potentially undermine immunity, increasing susceptibility to infections of astronauts, which is especially problematic within the sealed and sterile confines of a spacecraft (Mallis and DeRoshia, 2005). With potential serious consequences of circadian misalignment, various methods and therapies have been developed to minimize the adverse consequences of chronobiological disruptions during space flight. Light therapy is one of the most researched methods that can be used. Changing light intensity and timing allows astronauts to adjust their circadian cycles to the proper sleep versus wake schedule (Munmun and Witt-Enderby, 2021). On the ISS, for instance, blue light is exploited during wake times to enhance alertness, whilst red light is employed during sleep windows to minimize interference with melatonin production. Other candidates as possible countermeasures are pharmacological therapies as melatonin supplements or sleep aids, which may modulate sleep-wake cycles (Morrison *et al.*, 2022).

The potential yet overused value of this therapeutics despite the promising potential of these therapeutics, attention must be paid so that chronic consumption does not yield less than desirable side effects or dependence. Exercise is likewise a critical countermeasure to mitigate the negative physiological outcome of space travel - *i.e.*, muscular atrophy and cardiovascular hardships. Also, exercise has been shown to help regulate circadian rhythms, improve sleep quality, and mitigate some of the negative effects of sleep deprivation (Zwart *et al.*, 2021).

Beyond these therapies, research is currently underway to explore the potential of customized sleep-wake schedules that would match astronauts' individual chronotypes and performance needs of astronauts. This may enable more individualized and effective means of circadian entrainment during prolonged missions (Johnston *et al.*, 2019).

Chronobiological implications of long-duration space missions:

It's also a complex scientific problem to solve, especially given long-duration missions that are being planned for Mars or prolonged stays aboard the International Space Station (ISS), which present a unique set of chronobiological challenges for humans. Circadian rhythm regulation is affected significantly at longer set times of stayed in altered environments, where microgravity, artificial lighting, and constant bright-dark cycles might have persisted. Such disturbances can deal a blow to astronaut health and performance during missions. Gaining a better understanding of the chronobiological consequences of long-duration space travel is essential to develop countermeasures to prevent these risks and ensure the well-being of the astronauts (Guo *et al*., 2014).

Circadian misalignment and sleep deprivation in extended missions: One of the most frequent chronobiological challenges caused by long-duration missions is a lack of circadian alignment. As mentioned earlier, ISS orbits earth in 90 minutes which makes them experience 16 sunrises and sunsets in 1 day. On the longer voyages to Mars, the problem is vastly more complex, because astronauts will find themselves in darkness or light for long stretches depending on their location in relation to the planet's rotation. This disturbance of the natural 24-hour cycle can lead to significant circadian misalignment, leading to disruptions in sleep-wake cycles (Albornoz-Miranda *et al.*, 2023).

Astronauts face dire consequences related to long-term circadian misalignment. More sleep deprivation due to circadian misalignment is a well-known problem for spaceflight that can lead to both acute and chronic cognitive performance deficits. These are diminished attention, slower responses, memory deficits, and difficulty performing complex tasks (Garbarino *et al.*, 2021). Such cognitive impairments can be particularly hazardous during space missions, where astronauts are required to work in high-risk conditions that demand critical decision-making and knowledge of their surroundings.

Moreover, accumulation of "*sleep debt*" due to limited hours of sleep in longitudinal missions can further increase the burden on physical health. Long-standing sleep misadventures were found to be associated with weakened immunological processes, higher susceptibility to sickness and negative impact on metabolic system (Thornton and Bonato, 2017). Insufficient rest can also affect physical recuperation, leaving astronauts vulnerable to fatigue, muscle atrophy and cardiovascular ailments (Jiang *et al.*, 2022).

Impact of artificial lighting on circadian rhythms: Artificial light is an indispensable strategy used in the space industry to simulate day-night cycles and control the circadian physiology of astronauts. During long-duration missions, however, the application of artificial illumination brings about distinct challenges. Lighting systems on spacecraft and in habitats are designed to recreate the light-dark cycles of the Earth. These systems can use bright white or blue light during "daytime" to increase alertness and cognitive performance and can use red or amber light during "nighttime" to reduce wakefulness. But artificial light cannot recreate the full range or intensity of the whole spectrum known from light on Earth; especially when it comes to generating strong circadian entrainment (Guo *et al.*, 2014).

In addition, the high frequency of light and dark changes on a mission, especially on a vessel like the International Space Station, throws off astronauts' circadian cycles. In fact, on ISS, the 90-minute intervals between sunrise and sunset lead the astronauts to be frequently exposed to light and disrupt their natural circadian cycle. Sleep deprivation has been associated with inadequate exposure to the appropriate spectrum of light, at also the right time of day, which leads to circadian misalignment (Rahman *et al.*, 2022).

Longer missions to Mars, with longer days and nights, will require even more dynamic artificial lighting systems. Long days, which expose a crew to too much light, will make it hard to fall asleep during the "night" phase, while a long night will lead to disrupted awareness during the hours they should be awake. After all, astronauts on such missions may face a number of issues, including misalignment with Earth-based time zones and the difficulty to synchronize their circadian rhythms with that of the Martian day (Walker II *et al.*, 2021).

Psychological and physiological effects of long-term circadian disruption: Long-duration space flights may induce long-term alterations in circadian rhythms, which can lead to adverse psychological as well as physiological consequences. Consistent circadian misalignment however has been linked to mood disorders (like irritability, depression, and anxiety) and sleep disorders (Pagel and Choukèr, 2016). The psychological effects of isolation and confinement in the space environment can exacerbate these issues, creating a feedback loop where disrupted sleep produces mood anomalies, which lead to further sleep disruption. Physiologically, the absence of a stable circadian rhythm can disrupt hormonal regulation, including the secretion of melatonin, cortisol and other circadian-controlled hormones. These hormonal imbalances can affect various bodily functions, including immune function, metabolism and stress responses. For example, insufficient sleep and circadian misalignment have been associated with altered glucose metabolism, which can increase the risk of developing insulin resistance (Capri *et al*., 2023).

Furthermore, disrupting the normal circadian cycle can have an impact on muscle mass maintenance and cardiovascular health, both of which are already compromised by microgravity environment of space (Dose *et al.*, 2023).

Strategies for mitigating chronobiological disruptions: There are a number of methods under development to reduce the adverse impact of circadian misapprehension on long-duration space missions. This can involve optimizing light patterns, pharmaceutical therapies (*e.g.*, melatonin supplementation) and exercise and behavioral interventions. This, for instance, is one way intense light exposure several times throughout the mission can help modify circadian cycles and facilitate sleep. Dim light or red light exposure in the hours before sleep, by contrast, may help maintain sleep duration and quality (Guo *et al.*, 2014).

In conclusion, astronauts could use appropriate lighting condition and sleep-wake cycle aided by judicious use of sleep aids like melatonin. But their use of medicinal remedies must be carefully monitored as sleep medication has long-termoral impact such a dependence or side effects. Sleep deprivation is also overcome with a countermeasure of exercise because exercise also regulates circadian rhythms and sleep quality and helps amortize a portion of the negative physiological spaceflight effects (Song *et al*., 2023).

Finally, personalized chronobiological treatment interventions based on individual sleep preferences and activity levels, as well as mission needs, may also support astronaut good sleep and health maintenance. Wearable technological advances that are able to detect ongoing circadian cycles (in real-time) may potentially help astronauts adapt light exposure and sleep protocols to their internal clocks (Rahman *et al.*, 2022).

Countermeasures and interventions to mitigate chronobiological disruptions:

Disruption of the sleep-wake cycles of astronauts during space missions is a major obstacle and robust countermeasures are needed to promote health and cognition levels. Such disruptions may have lasting physiological, psychological and cognitive consequences, warranting effective countermeasures for circadian rhythm management. A combination of light exposure regulation, pharmacological therapies, behavioral measures, and exercise regimens have all been developed to mitigate these effects and keep astronauts healthy for long-term missions, such as those to Mars.

Light exposure and chronotherapy: However, light is clearly the most useful external cue for circadian rhythm entrainment, and space agencies have already invested heavily in light modification technology. Lower timelines of light conveyance schedules are being adapted in flat to enable astronauts to be boxed in on biological clocks where sunrises and sunsets are frequent. Sallinen *et al.* 2008 showed that being exposed to bright light early in the sleep period reset the circadian clock and enhanced sleep and alertness. Astronauts use blue light to push phase in when they require adaptation to new working hours because blue light has strong phase advancing capabilities (Shattuck *et al.*, 2021). This is important for performance during space missions, since quick transitions from light to dark can disrupt the ability to sleep and perform well.

Others suggest a more personalized approach to light exposure. The specific cycles employed can be adjusted to an astronaut's preferences for sleep and wake time, hence bettering their circadian alignment and quality of sleep. Long duration missions to Mars pose specific challenges that require intelligent methods to align people's endogenous circadian rhythms with the cycle of the planet (Cheng *et al.*, 2021). Using tailored light has the potential to help mitigate the adverse effects associated with circadian misalignment including irritability and fatigue, which both have mental and physical health implications (Mulvin, 2018).

Pharmacological interventions: Although light treatment will be crucial, there are also pharmaceutical approaches to promote sleep and maintain circadian synchronization during spaceflight. Melatonin, in particular, has been widely studied for use as a sleep aid. Melatonin helps astronauts to phase shift their circadian cycles with the mission schedule and it leads to the onset and improvement of sleep quality. Melatonin supplements taken before bedtime had the ability to reduce sleep latency and increase deep sleep - the most important phase of sleep when cognitive recuperation and overall health occurs. (Mulvin, 2018).

But melatonin is not a cure-all. Individual chronotypes, light exposure, and environmental factors can influence the efficiency of its suppression, leading to differences in melatonin response in astronauts (Shattuck *et al*., 2021). For this purpose, it needs precise dosing and timing of melatonin release to work as effectively as possible without affecting performance at work during the day hours. Other pharmaceutical therapies, such as sedatives and benzodiazepines, have been investigated to treat sleep disturbances, yet their use in space remains controversial due to potential cognitive and performance impairments (Mantle *et al.*, 2020).

Exercise as a countermeasure: Circadian misalignment can also be prevented by exercise. Exercise can enhance sleep quality, modulate circadian rhythms, and increase cognitive function. The effects of microgravity require astronauts on the International Space Station to exercise every day to maintain cardiovascular health, muscle mass, and bone density during extended missions. Exercise has added benefits, such as enhancing sleep quality and reducing the effects of stress (Moosavi *et al.*, 2021). Especially moderate-intensity aerobic exercise has been shown to enhance both sleep and mood, which are fundamental for astronaut health on long-duration missions. Resistance training and high-intensity exercise too were found to improve sleep, eliminating anxiety and improving overall physiological balance. *(*Alnawwar *et al.*, 2023).

Behavioral and cognitive interventions: Along with physical countermeasures, behavioral interventions play a major role in minimizing the adverse outcomes of circadian disruptions. Incorporating cognitive behavioral treatment for insomnia (CBT-I) that has been designed for use in space, CBT-I addresses common problems in space, including poor sleep hygiene and high sleep stress (Bean *et al.*, 2021). Such interventions help astronauts alter their habits and attitudes about sleep, especially around sleep regularity, and can lead to sleep that is more consistent and restful. Mindfulness meditation and progressive muscle relaxation have also been utilized to alleviate stress and improve sleep quality (Rusch *et al.*, 2019). These interventions can be vital - especially due to the isolation and confinement faced by astronauts - in alleviating the psychological toll of missions in space.

Multimodal countermeasures: As the research shows, combining different countermeasures is probably the way to go. Such multi-faceted approaches incorporating light treatment, exercise and pharmacological-based interventions may offer even more holistic solutions to spatial circadian misalignment (Ahmed *et al.*, 2024). For instance, light exposure combined with individually-tailored sleep schedules and melatonin can promote the regulation of sleep cycles, while also facilitating alertness for critical mission operations. Additionally, note that regular physical exercise, in conjunction with targeted behavioral treatments, such as CBT-I, could promote long-term benefits for astronaut health (Cheng *et al.*, 2021).

Future space exploration missions, such those to Mars, will benefit greatly from understanding how to combine countermeasures using multimodal techniques, which are now being investigated. Developing tailored and adaptive countermeasures to enhance astronaut health is crucial for long-duration missions as space agencies push the bounds of discovery.

Conclusion

Space missions can disrupt the body's sleep-wake cycle, which significantly affects astronaut health and performance, especially on long-duration missions such as those to Mars. Circadian misalignment due to microgravity and irregular light cycles in space leads to sleep deprivation and cognitive impairment. These disorders require effective countermeasures, including light exposure regulation, pharmaceutical therapies, exercise and behavioral techniques. Tailored approaches to these interventions will be more effective, resulting in the promotion of the astronaut's well-being and mission success. Moreover, non-terrestrial research insights are highly relevant to solving sleep disorders and diverse circadian rhythm dysregulations on earth, including those suffering among shift workers and similar conditions.

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