THE ROLE OF MELATONIN IN SLEEP DISORDERS

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Abstract:
Melatonin is the main hormone involved in the control of the sleep-wake cycle. It is easily synthesisable and can be taken orally, which has led to interest in its use as a treatment for insomnia. Moreover, as production of the hormone decreases as we get older, in inverse correlation with the frequency of poor sleep quality, it has been suggested that melatonin deficit is at least partly responsible for sleep disorders. Treating this age-related deficit would therefore come into sight to be a natural way of restoring sleep quality, which is lost as patients age. However, despite the undeniable theoretical appeal of this approach to insomnia, little scientific evidence is available that supports any benefit of this substitutive therapy.

Furthermore, the most suitable dose ranges and pharmaceutical preparations for melatonin administration are yet to be clearly defined.

Key words: sleep disorders, melatonin, advanced clinical studies.

Main part:

Melatonin is a hormone that our brain produces in response to darkness. It helps with the timing of your circadian rhythms (24-hour internal clock) and with sleep. Being exposed to light at night can block melatonin production. Research suggests that melatonin plays other important roles in the body beyond sleep. However, these effects are not fully understood. Melatonin dietary supplements can be made from animals or microorganisms, but most often they're made synthetically.[2]

Melatonin levels change throughout life. In humans, melatonin production begins at the age of 3-4 months. Levels gradually increase during childhood, peaking between 8 and 10 years of age. Melatonin synthesis decreases dramatically during puberty. After the age of 40-45, melatonin levels gradually decrease and by the age of 70 they represent barely 10% of the prepubescent level. In healthy individuals, melatonin is synthesized in response to darkness between 20:00 and 22:00, peaking between 00:00 and 03:00, regardless of sleep stage. After that, melatonin synthesis gradually decreases and remains very low during the day. Melatonin levels peak when body temperature is lowest. At night, peak plasma melatonin levels range from 100 to 200 pg/ml; The concentration ranges from 10 to 30 pg/ml during the day.[1]

Daylight exposure is the main factor in the regulation of melatonin secretion. Circadian synchronization initiates in the neonatal period due to changes in maternal melatonin levels. The effects of daylight depend on duration of exposure, sunlight intensity, and wavelength. The light spectrum is particularly important, since retinal ganglion cells contain melanopsin, a photoreceptor sensitive to blue light. Melanopsin plays an essential role in regulating the circadian rhythm.

Exposure to artificial light between 00:00 and 04:00 inhibits melatonin secretion. Morning light exposure causes a circadian phase advance, meaning that melatonin levels will peak earlier. Light exposure in the evening results in a phase delay. The phase response curve of melatonin concentrations in response to light exposure may be used in the treatment of circadian desynchrony.[1]

Melatonin mainly promotes sleep through its chronobiotic effects on the SCN (suprachiasmatic nucleus or nuclei). The hormone also has an effect on thermoregulatory and cardiovascular systems.

The circadian cycle is regulated by the SCN and synchronized to the light-dark cycle, and synchronizes other cycles in the body through melatonin synthesis. In turn, melatonin acts on the SCN, promoting resynchronization when environmental conditions change. Elevated blood

melatonin levels signal to tissues and organs that it is night-time, helping to regulate homeostasis.[1]

Melatonin resynchronises the circadian rhythm and the sleep-wake cycle, and also regulates the reproductive cycle. In animals with seasonal patterns of reproduction, pinealectomy has been revealed to suppress seasonal changes and synchronization with the annual cycle. However, these seasonal patterns reappear with the administration of exogenous melatonin. Melatonin is also involved in sexual maturation in humans: puberty is associated with a marked decrease in plasma melatonin levels. Pineal gland dysfunction may accelerate puberty, whereas melatonin hyperproduction may delay it.[1]

Melatonin reduces sleep onset latency to a greater extent in people with delayed sleep phase syndrome than in people with insomnia. The effects of melatonin on people with primary sleep disorders are mediated by a direct re-setting of the endogenous circadian pacemaker rather than via a direct action on somnogenic structures of the brain, given that individuals with delayed sleep phase syndrome are distinguished from individuals with insomnia by the presence of a circadian abnormality. It is also possible that melatonin may initially act on somnogenic structures of the brain to promote sleep; the reduction in sleep onset latency would decrease evening light exposure, which would in turn promote a phase-advance of the endogenous melatonin rhythm and a resetting of the endogenous clock.[3]

Recent studies have shown that dysregulation of sleep and circadian rhythms has long been established in several psychiatric and neurocognitive disorders. They confirm this finding consistently across disorders. In schizophrenia and neurocognitive disorders, melatonin secretion decreases due to the small volume of the pineal gland and increased calcification. On the other hand, melatonin dysregulation in bipolar disorder may be more dynamic and result from inhibition of light-sensitive melatonin and delayed melatonin secretion. In both cases, exogenous melatonin appears to be indicated to correct the dysfunction. However, very limited well-designed trials of melatonin to correct sleep and circadian rhythms exist in psychiatric disorders, and evidence of efficacy is limited to autism, attention deficit hyperactivity disorder (ADHD), and neurocognitive disorders. Overall, recent studies in psychiatric disorders suggest that melatonin may be effective in improving sleep parameters such as sleep onset latency, sleep efficiency, and sleep quality. A recent meta-analysis suggests that optimal dosing and timing of dosing may be important to maximize melatonin efficacy. The knowledge base is sufficient to recommend well-designed, larger studies with circadian parameters as inclusion and outcome criteria. Based on partially fragmented information, we suggest testing efficacy in disorders with neurocognitive etiopathology at later and higher doses, and affective and anxiety disorders at lower and earlier doses of melatonin. [6]

Disrupting the regular sleep schedule due to shift work or traveling across time zones can disturb the circadian rhythm and affect melatonin production. Shift workers may experience reduced melatonin production due to irregular light exposure patterns. Strategies like gradually

adjusting sleep patterns, optimizing light exposure during work shifts, and using melatonin supplements under medical guidance can help alleviate the negative effects of shift work and jet lag.[4]

Apart from supplements, certain lifestyle modifications can naturally enhance melatonin production and promote better sleep:

- Maintain a Consistent Sleep Schedule - Going to bed and waking up at the same time every day helps regulate the circadian rhythm and optimize melatonin production. Consistency in sleep patterns strengthens the body's internal clock and promotes better sleep quality;
- Create a Sleep-Friendly Environment - The sleep environment plays a crucial role in melatonin production and sleep quality. Keep the bedroom dark, quiet, and cool to promote the production of melatonin. Use blackout curtains, earplugs, or white noise machines if necessary;
- Limit Exposure to Blue Light - Minimize the use of electronic devices before bedtime and consider using blue light filters or amber-tinted glasses to reduce the impact of artificial light on melatonin production. Establishing a digital curfew at least an hour before bedtime can significantly improve sleep quality;
- Establish a Relaxation Routine - Engage in relaxing activities before bed, such as reading a book, taking a warm bath, practicing meditation or deep breathing exercises. This routine helps signal the body and mind that it's time to unwind and prepare for sleep; [4]

Melatonin therapy is an effective intervention for a range of sleeping disorders. A significant proportion of individuals living with complete blindness develop non-24-hour sleep-wake disorder as they are not able to synchronize with the environmental day-night cycle. Administration of immediate release, as well as modified release melatonin preparations, have shown considerable efficacy in treating this disorder. [5]

Insomnia is a common sleep disorder primarily observed in older people, particularly due to a reduction in melatonin production and secretion. Melatonin replacement therapies have been developed to replenish the deficiency of endogenous melatonin and treat such disorders. [5]

Clinical trials involving insomnia patients aged 55 years and above have shown that prolonged-release melatonin formulations can effectively reduce sleep onset latency and improve sleep quality, morning alertness, and overall quality of life. [5]

Children with autism spectrum disorder and other neurogenetic neurodevelopmental disorders also experience sleep disturbances. Recent evidence indicates that melatonin-based therapies, behavioral interventions, and parent education are the most effective approaches to mitigate sleep disturbances in these children. [5]

Prolonged-released melatonin formulations have proven efficacy in reducing systolic blood pressure at night in patients with nocturnal hypertension. Melatonin also has considerable efficacy in improving sleep quality and quantity in hypertensive patients with sleep disorders. Slow-release melatonin formulations have shown efficacy in improving sleep quality in AD (Alzheimer's disease) patients. AD patients treated with prolonged-release melatonin have shown significant improvement in cognitive functioning, such as memory and attention.[5]

Conclusion:

Melatonin plays a essential role in regulating sleep-wake cycle and ensuring healthy sleep patterns. Maintaining optimal melatonin levels is vital for a restful night's sleep and overall well-being. By understanding the factors that influence melatonin production and adopting healthy sleep habits, we can improve our sleep quality and wake up refreshed, ready to tackle the day ahead. Exogenously administered melatonin can potentially improve non-restorative sleep and circadian rhythm amplitudes and misalignments by reducing the activation of DMN. This mode of action of melatonin represents a promising investigational route for early intervention to promote healthy physical and mental aging.

References:

1. Melatonin in sleep disorders, DOI: 10.1016/j.nrleng.2018.08.004 J.J. Poza, M. Pujol, J.J. Ortega-Albás, O. Romero, on behalf of the Insomnia Study Group of the Spanish Sleep Society (SES) - https://www.elsevier.es/en-revista-neurologia-english-edition--495-avance-resumen-melatonin-in-sleep-disorders-S217358082030184X;
2. https://www.nccih.nih.gov/health/melatonin-what-you-need-to-know;
3. Melatonin for Treatment of Sleep Disorders: SummaryN Buscemi, B Vandermeer, R Pandya, N Hooton, L Tjosvold, L Hartling, G Baker, S Vohra, and T Klassen, 2004 - https://www.ncbi.nlm.nih.gov/books/NBK11941/;
4. https://nomoresnore.co.uk/2023/07/the-role-of-melatonin-in-sleep-regulation/;
5. https://www.news-medical.net/health/What-is-the-Role-of-Melatonin-in-Sleep-Regulation.aspx - What is the Role of Melatonin in Sleep Regulation? By Dr. Sanchari Sinha Dutta, Ph.D.Reviewed by Danielle Ellis, B.Sc.;
6. Role of Melatonin in the Management of Sleep and Circadian Disorders in the Context of Psychiatric Illness - 2022 Oct 13. Eunsoo Moon , Kyungwon Kim , Timo Partonen , Outi Linnaranta, DOI: 10.1007/s11920-022-01369-6https://pubmed.ncbi.nlm.nih.gov/36227449/;