IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 23, Issue 5 Ser. 9 (May. 2024), PP 28-34
www.iosrjournals.org

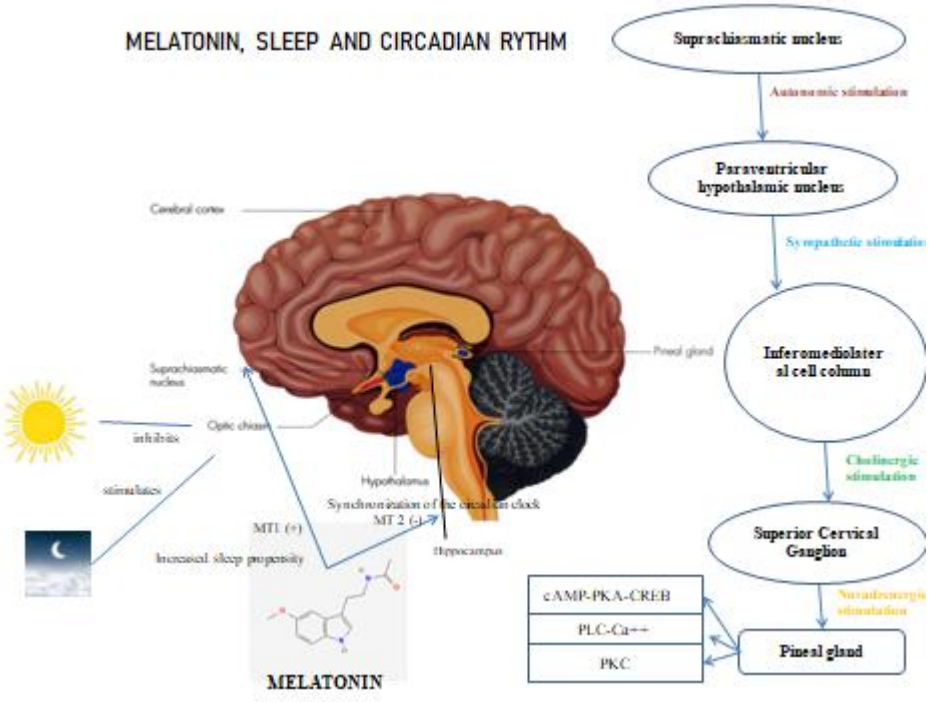
Melatonin Supplementation: A Promising Approach To Sleep Disorders

Sabarni Mandal
Ugc Net Jrf

Aditi Munmun Sengupta
International Member Of American College Of Physicians(Macp), Associate Member Of Royal College Of Physicians, Edinburgh(Uk),Harvard Medical School, Department Of Continuing Medical Education, Post Graduate Association Member(Usa),

Abstract
Sleep is a fundamental physiological process essential for overall health and well-being. The regulation of the sleep-wake cycle involves intricate interactions between endogenous biological rhythms and environmental cues. Melatonin, a hormone synthesized and released primarily by the pineal gland, plays a critical role in orchestrating the timing and quality of sleep. Its secretion is tightly regulated by the circadian system, with levels peaking during the night and declining during the day. Clinical studies have demonstrated that exogenous melatonin can improve sleep quality, reduce sleep onset latency, and mitigate symptoms associated with disrupted sleep patterns, such as jet lag and shift work. Melatonin supplementation represents a valuable adjunctive approach to managing sleep disorders, particularly when integrated with behavioural and lifestyle interventions aimed at promoting overall sleep health. Further research is needed to elucidate melatonin's mechanisms of action, long-term safety profile, and efficacy across different patient populations.
Key Words: *Sleep, Melatonin, Circadian system, Sleep disorder*

Graphical Abstract



Date of Submission: 14-05-2024 Date of Acceptance: 24-05-2024

I. Introduction

Our daily well-being relies heavily on the biological clock, which regulates our sleep patterns and primes us for upcoming activities through an anticipatory increase in heart rate, glucose, and cortisol levels[1]. Within mammals, including humans, the circadian system operates in a hierarchical manner, with a central pacemaker situated in the suprachiasmatic nucleus (SCN) of the hypothalamus, orchestrating our sleep-wake cycle as the most prominent circadian rhythm. The sleep-wake cycle, governed by a neurochemical process involving sleep-promoting and arousal centres in the brain, is the most overt circadian rhythm [2]. Melatonin's influence on sleep primarily stems from its chronobiological effects, impacting the initiation, quality, and timing of sleep rather than its overall duration, believed to occur through its hypothermic effect and involvement in thermoregulation [3]. Melatonin, predominantly secreted by the pineal gland and released into the bloodstream exclusively at night following the circadian rhythm, is attributed to regulating sleep patterns [4]. Melatonin levels fluctuate throughout life. In humans, production begins at 3-4 months of age, increasing progressively during childhood and peaking between 8 and 10 years. However, synthesis dramatically decreases during puberty. By age 40-45, levels progressively decline, representing only about 10% of prepubertal levels by age 70 [5]. Acting as a synchronizer by providing information on the light/dark cycle, melatonin stabilizes and reinforces circadian rhythms and maintains their mutual phase relationship [6]. Various studies suggest feedback from the pineal gland to the SCN and neurobehavioral variables involved in regulating the sleep-wake cycle, potentially promoting sleep by inhibiting SCN wake-promoting activity [7]. Sleep disorders encompass a wide range of dysfunctions involving sleep, including difficulty falling asleep, poor sleep quality, early waking, circadian rhythm disorders, parasomnias, sleep-related movement disorders, and sleep-related breathing disorders (SBDs) [8]. Melatonin supplementation has been proven to be a safe and effective method for improving sleep onset latency, duration, and quality.

Sleep And Its Stages

The classic definition of sleep primarily relies on observable physiological characteristics observed in mammals, including decreased body movement and electromyographic activity, reduced responsiveness to external stimuli, closed eyes, diminished breathing rates, and altered body position, as well as changes in brain wave architecture detected through polysomnography [9]. The sleep cycle is regulated by the circadian rhythm, which is governed by the suprachiasmatic nucleus (SCN) of the hypothalamus. GABAergic sleep-promoting nuclei are distributed across the brainstem, lateral hypothalamus, and preoptic area [10]. Additionally, the circadian rhythm controls the nighttime release of hormones such as adrenocorticotropic hormone (ACTH), prolactin, melatonin, and norepinephrine (NE) [11].

Sleep serves several crucial functions [12]:

- Energy conservation: Sleep minimizes oxygen consumption and energy expenditure, allowing for the accumulation of adenosine triphosphates (ATPs) in the brain. It also influences overall body growth by facilitating the release of essential hormones like growth hormones
- Enhanced memory and immune function: Quality sleep has been linked to improvements in memory consolidation, bolstering the immune system, and promoting overall life survival
- Glymphatic function: During sleep, there's an enhanced convective flow from the brain to circulation, facilitating the removal of soluble neurotoxic waste products like β-amyloids. This drainage system is primarily active during sleep

Stages and mechanism

Sleep is categorized into five stages: wake, N1, N2, N3, and REM. The N1 to N3 stages constitute non-rapid eye movement (NREM) sleep, with each stage progressively leading to deeper sleep [13].

During the wake stage, characterized by either open or closed eyes, brain activity shifts from beta waves during wakefulness with open eyes to alpha waves as individuals become drowsy and close their eyes [14].

Approximately 75% of sleep is spent in NREM stages, with most of that time in the N2 stage. NREM sleep is distinguished by slow, high-voltage EEG patterns, along with reduced heart rate and blood pressure [15]. Various physiological functions including immune response, development, and cognition, influence the regulation of NREM and REM sleep by modulating vigilance states in specific brain regions and networks [16].GABAergic neurons in the ventrolateralpreoptic nucleus (VLPO) of the lateral hypothalamus play a significant role in promotion of NREMS [17].

REM sleep, associated with dreaming, initiates approximately 90 minutes after sleep onset, with each REM cycle increasing in duration throughout the night. The first REM cycle typically lasts around 10 minutes, while the final cycle may extend up to an hour [18]. Research indicates that REM sleep is essential for proper neural development in neonates, a concept termed the ontogenetic REM sleep hypothesis [19]. Physiological

characteristics of REM sleep include fast-frequency, low-amplitude cortical EEG patterns, hippocampal theta rhythmicity, muscle atonia, PGO waves, and rapid eye movements [20]. The reciprocal interaction model proposes that REM sleep is regulated by the interplay of cholinergic, glutamatergic, and monoaminergic brainstem nuclei [21].

Melatonin

Melatonin, also known as N-acetyl-5-methoxytryptamine, is a widely distributed molecule in nature, present in nearly all living organisms. Its primary synthesis occurs within pinealocytes from the amino acid tryptophan, which undergoes hydroxylation (by tryptophan-5-hydroxylase) to form 5-hydroxytryptophan, followed by decarboxylation (by 5-hydroxytryptophan decarboxylase) to produce serotonin [22]. Subsequently, serotonin is converted into melatonin through a two-step process: first acetylated to N-acetylserotonin by arylalkylamine-N-acetyltransferase and then methylated to melatonin by acetylserotonin-O-methyltransferase [23].

Regulation of melatonin

The synthesis and release of melatonin are regulated by the suprachiasmatic nuclei (SCN) through a multisynaptic pathway involving the sympathetic nervous system. Specifically, a subset of SCN neurons projects directly to the dorsal parvocellular neurons in the autonomic subdivision of the paraventricular hypothalamic nucleus (PVH). These PVH neurons then send glutamatergic projections to the sympathetic preganglionic neurons in the intermediolateral (IML) cell column of the upper thoracic spinal cord. Subsequently, the IML neurons connect via a cholinergic projection to the superior cervical ganglion (SCG), and the SCG postganglionic sympathetic neurons send a noradrenergic projection to the pineal gland [24]. Norepinephrine released by the sympathetic terminals interacts with classical beta and alpha noradrenergic receptors on the membrane of pinealocytes, activating the cAMP-PKA-CREB and PLC-Ca++-PKC pathways, which in turn initiate melatonin synthesis [25].

Melatonin release in humans normally begins shortly after sundown, peaks in the middle of the night (between 2 and 4 a.m.), and gradually reduces throughout the later half of the night [26]. Light plays a dual role in regulating pineal melatonin production: light-dark cycles synchronize the rhythm by entraining the circadian pacemaker, while acute light exposure at night rapidly inhibits serotonin N-acetyltransferase (SNAT) activity, thereby halting melatonin production [27]. The alternation between light and darkness acts as a synchronizer of this rhythm, determining the timing of its peak and decline. Consequently, pineal activity and melatonin synthesis and release are heightened during the night (or darkness) and suppressed, sometimes to undetectable levels, during the day (or under exposure to bright light). Some suggest that the pineal gland, primarily through melatonin, functions as a "tranquilizing organ" to maintain homeostatic equilibrium and serves as a general synchronizer, stabilizer, and moderator. Melatonin itself is often referred to as the "hormone of darkness"

In mammals, the suprachiasmatic nucleus (SCN) governs the circadian rhythm, and disruptions to the SCN can disrupt the circadian pattern of melatonin release. This rhythm is primarily synchronized with the light-dark cycle [28]. Although the master clock is housed in the SCN of the brain, most cells in the body have a working clock. Certain genes are directly regulated by these cellular clocks via clock proteins at the transcriptional level, whereas others are controlled by cascades of circadian transcription factors or neural stimulation. The SCN is responsible for regulating sleep, wakefulness, and other physiological and behavioural cycles [29]. There exists a close interaction between circadian rhythms—such as body temperature, blood pressure, immune and hormonal rhythms—and the sleep-wake cycle, which collectively optimize internal temporal order [30].

Comprising three main components, the circadian system orchestrates these rhythms: the central and peripheral circadian clocks (the central pacemaker and the peripheral oscillators), the input pathway, and the output pathway [31]. The circadian rhythm, a biological cycle lasting approximately 25 hours, governs various physiological processes such as body temperature, feeding, motor activity, and sleep. While these rhythms are endogenous, they adjust to the local environment. The primary factor influencing their synchronization is the light-dark cycle, although other factors such as eating patterns, regular exercise, sleep habits, and social contact also play a role. Melatonin secretion acts as an indicator of this clock's status, responding to signals from the suprachiasmatic nuclei. The timing of the melatonin rhythm reflects the phase of the internal clock relative to external clock time.

Melatonin receptors

Melatonin functions through its own receptors, namely MT1 and MT2, which belong to the G protein-linked receptor family [32]. These receptors, existing as dimers, can form MT1/MT1 and MT2/MT2 homodimers, as well as MT1/MT2 heterodimers, each with distinct responses to melatonin. Additionally, MT1 receptors can form dimers with the GPR50 protein, influencing MT1 response indirectly. Both MT1 and MT2

receptors play roles in mood regulation [33]. Melatonin's impact on sleep is thought to stem from mechanisms involving increased sleep propensity through enhanced circadian clock oscillations via MT1 receptors and synchronization of the circadian clock via MT2 receptors [34]. Melatonin exhibits contrasting effects on GABA-A receptors in specific brain regions, potentiating these receptors in the suprachiasmatic nucleus (SCN) via MT1 receptors while inhibiting them in the hippocampus via MT2 receptors [35].Melatonin's GABA-A effects in the SCN may contribute to its sleep-promoting effects, whilst its anti-GABAergic impact may explain why amnesia is not induced [36].

Melatonin onset appears to serve as the hormonal cue for the increase in blood flow in distal skin regions, promoting heat loss, which is a key physiological predictor for the rapid onset of sleep [37]. This rise in endogenous melatonin levels in the evening initiates the entire thermoregulatory cascade, leading to a decrease in heat production and an increase in heat loss, ultimately resulting in a decrease in core body temperature [38].

Interaction between exogenous melatonin and the melatoninergic system Exogenous melatonin mirrors the physiological effects observed during endogenous melatonin secretion in the evening. Its effectiveness is most pronounced when endogenous levels are low during the biological day, exerting time-dependent soporific effects. This has been validated through measures such as electroencephalographic theta activity during wakefulness [39]

In experimental models, acute exposure to high concentrations of melatonin induces desensitization and internalization of MT1 and MT2 receptors. Immediate-release melatonin administration leads to acute exposure of these receptors to elevated ligand concentrations, resulting in parallel increases in receptor desensitization and internalization. Consequently, higher melatonin doses may be less effective than those achieving physiological concentrations similar to those in the suprachiasmatic nucleus (SCN). Immediate-release melatonin, administered orally, reaches peak concentrations within minutes, inducing a hypnotic effect. However, it is rapidly metabolized and eliminated within 3-4 hours, leading to a decline in melatonin levels at a time when physiological secretion peaks are inhibited. Prolonged-release melatonin, with slower and sustained absorption, delays and reduces peak concentration magnitude, maintaining stable melatonin levels for 8-10 hours and replicating the physiological secretion curve [31]

Numerous studies have confirmed the sedative and sleep-inducing effects of supplemental melatonin, although there is variability in reported side effects. Melatonin appears to be safe within the studied population, doses, and timeframes, with nausea, headache, dizziness, and drowsiness being the most commonly reported adverse effects [40]

Pathological conditions affecting sleep rhythm and role of melatonin

Substances with therapeutic potential for circadian disorders of the sleep-wake cycle or insomnia fall into two categories: chronobiotics and hypnotics. Chronobiotics, such as melatonin, have the ability to induce phase shifts and entrain the circadian clock, thereby increasing sleep propensity at desired times [41]

Circadian rhythm sleep disorder

A circadian rhythm sleep disorder is a chronic condition in which a person's circadian cycle of sleep and wakefulness is out of sync with normal environmental rhythms. Electric illumination delays sleep onset, shortens sleep duration, and appears to disrupt the circadian timing system's alignment with the natural light/dark cycle [42].Several circadian sleep disorders have been identified, including delayed sleep phase syndrome (DSPS), advanced sleep phase syndrome (ASPS), irregular sleep-wake patterns, and non-24-hour sleep-wake syndrome in blind and sighted people [43].Endogenous melatonin rhythms in delayed sleep phase syndrome (DSPS) are delayed as compared to those in healthy people [44].In studies, melatonin was given orally at a dose of 5 mg once daily for 28-30 days. In one study, melatonin was given to all patients in the evening (22:00 h) [45]. According to the athlete's chronotype, exercise causes a phase advancement of the melatonin rhythm, restoring its acrophase. The rising phase of the plasma melatonin rhythm was delayed by 1.1 hours without exercise [46].

Insomnia

Defined as persistent difficulty with sleep initiation, consolidation, and maintenance, insomnia is linked to abnormal circadian clocks [47]. Melatonin's chronobiotic properties make it a key treatment for various sleep conditions associated with circadian disruptions [48].Melatonin improves sleep onset latency and increases total sleep duration in adults with or without insomnia; however, it is unclear whether these improvements are clinically relevant [49].As people age, their ability to sleep declines, and the prevalence of sleep problems gradually rises. During middle age, the sleep architecture begins to change, resulting in a significant decline in non-rapid eye movement (NREM)-slow wave sleep, whereas the amount of rapid eye movement (REM) sleep decreases just little. Thus, decreased melatonin secretion may play a role in the pathophysiology of insomnia [50].The apparent association between growing age, decreasing melatonin

synthesis, and increasing insomnia prevalence has led to the'melatonin replacement' theory, which indicates that refilling the shortage in the endogenous sleep-regulating hormone can enhance sleep [51].Melatonin and its agonists are useful in the treatment of insomnia because they activate the MT1 and MT2 melatonin receptors. Comai et al. demonstrated that MT1 and MT2 receptors play distinct functions in sleep by investigating knockout mice of each [52].Beta-blockers inhibit natural nighttime melatonin release, which could explain the reported sleeplessness adverse effect. Melatonin administration significantly enhanced total sleep time, improved sleep efficiency, and shortened the sleep onset delay to Stage 2 [53].Wade et al. (2007) conducted a trial that included a 2-week single-blind, placebo run-in period followed by a 3-week double-blind treatment period with PR-melatonin or placebo, one tablet per day, two hours before bedtime. It concluded that PR-melatonin results in significant and clinically important improvements in sleep quality, morning alertness, sleep onset latency, and quality of life in primary insomnia patients aged 55 years or older [54].

Sleep Breathing Disorder

Sleep Breathing Disorders (SBDs) involve abnormalities in respiration during sleep, including obstructive sleep apnea (OSA), central sleep apnea, sleep-related hypoventilation disorders, and sleep-related hypoxemia disorders [47]. Melatonin has showed potential in animal and human trials for reducing complications associated with SBDs. In sleep apnea animal models, melatonin inhibits the normal increase in glucose levels caused by intermittent hypoxia [55]Additionally, melatonin protects against cardiac hypertrophy induced by chronic intermittent hypoxia by modulating autophagy through the 5′ adenosine monophosphate-activated protein kinase pathway [56].

Parasomnias

Parasomnias are classified according to the stage of sleep in which they occur (REM or NREM). Parasomnias are aberrant sleep-related complex movements, behaviours, emotions, perceptions, dreams, and autonomic nervous system activity that cause physical injury, sleep disruption, bad health impacts, and negative psychosocial repercussions [47].Parasomnias are characterized by abnormal behaviors, movements, emotions, and perceptions during sleep. REM sleep behavior disorder (RBD), for instance, involves dream enactment, often leading to violent or injurious behaviors during REM sleep. It is strongly associated with synucleinopathy and neurodegeneration [57]. A small pilot trial demonstrated that nightly administration of 3 mg melatonin significantly reduced REM sleep without atonia and improved clinical symptoms of RBD [58].

Jet lag disorder

Jet lag disorder arises from rapid travel across multiple time zones, leading to desynchronization of sleep and circadian rhythms. Common symptoms include sleep disturbances, anxiety, gastrointestinal issues, and menstrual irregularities in women [59]. . Melatonin administration follows a phase response curve, with morning intake causing a delay and evening intake causing an advance in circadian rhythms [60]. Combining morning light exposure with afternoon melatonin treatment has been shown to significantly advance circadian rhythms with minimal side effects [61].

II. Conclusion

Sleep is a fundamental physiological process that plays a crucial role in maintaining overall health and well-being. It is essential for cognitive function, emotional regulation, immune function, metabolism, and overall physiological homeostasis. However, disruptions in sleep patterns, whether due to lifestyle factors, medical conditions, or environmental influences, can have significant negative effects on both physical and mental health.

Melatonin, often referred to as the "hormone of darkness," is a key regulator of the sleep-wake cycle. It is primarily synthesized and released by the pineal gland in response to signals from the suprachiasmatic nucleus (SCN), the body's internal clock. Melatonin levels typically rise in the evening, signaling the onset of darkness and promoting the transition to sleep. Throughout the night, melatonin levels remain elevated, helping to maintain sleep and regulate the sleep architecture. As morning approaches and light levels increase, melatonin levels decline, signaling the body to awaken.

In addition to its role in regulating the sleep-wake cycle, melatonin also possesses antioxidant, anti-inflammatory, and immune-modulating properties. This multifaceted hormone has been studied extensively for its potential therapeutic effects in various sleep disorders, including insomnia, circadian rhythm sleep disorders, sleep breathing disorders, and parasomnias.

Melatonin supplementation has emerged as a promising intervention for individuals struggling with sleep disturbances. Exogenous melatonin can help regulate the sleep-wake cycle, improve sleep quality, reduce sleep onset latency, and alleviate symptoms associated with jet lag and shift work. Moreover, melatonin has been shown to have a favorable safety profile, with minimal side effects reported in clinical trials.

However, it is essential to consider individual differences in response to melatonin supplementation, as well as potential interactions with other medications and health conditions. Furthermore, the optimal dosage and timing of melatonin supplementation may vary depending on the specific sleep disorder and individual factors such as age, circadian rhythm, and underlying health status.

Overall, while melatonin supplementation shows promise as a therapeutic intervention for sleep disorders, further research is needed to fully understand its mechanisms of action, optimal dosing regimens, long-term safety, and efficacy in different patient populations. Additionally, integrating behavioral and lifestyle modifications, such as maintaining a consistent sleep schedule, minimizing exposure to artificial light at night, and practicing relaxation techniques, can complement melatonin supplementation and promote overall sleep health.

Reference

[1] Buijs Rm, Van Eden Cg, Goncharuk Vd, Kalsbeek A. The Biological Clock Tunes The Organs Of The Body: Timing By Hormones And The Autonomic Nervous System. J Endocrinol 2003; 177 (1): 17- 26.

[2] Saper Cb, Scammell Te, Lu J (2005). Hypothalamic Regulation Of Sleep And Circadian Rhythms. Nature 437: 1257–1263

[3] Sleep And Melatonin Mehmet Özsan, 1st International Conference On Modern And Advanced Research , July 29-31, 2023, Turkey

[4] Geoffroy Pa, Etain B, Franchi Ja, Et Al. Melatonin And Melatonin Agonists As Adjunctive Treatments In Bipolar Disorders. Curr Pharm Des. 2015;21:3352–3358.

[5] Xie Z, Chen F, Li Wa, Geng X, Li C, Meng X, Et Al. A Review Of Sleep Disorders And Melatonin. Neurol Res. 2017;39:559—65

[6] Claustrat B, Brun J, Chazot G. The Basic Physiology And Pathophysiology Of Melatonin. Sleep Med Rev 2005;9:11–24

[7] Czeisler Ca, Buxton Om, Khalsa Sbs. The Human Circadian Timing System And Sleep-Wake Regulation. In: Kryger Mh, Roth T, Dement Wc, Editors. Principles And Practice Of Sleep Medicine. 4th Edition. Philadelphia: Elsevier Saunders; 2005. P. 375–94

[8] Amihaesei Ic, Mungiu Oc. Main Neuroendocrine Features And Therapy In Primary Sleep Troubles. Rev Med Chirsoc Med Nat Iasi. 2012;116:862–866

[9] Zielinski, Mark R., James T. Mckenna, And Robert W. Mccarley. 2017. "Functions And Mechanisms Of Sleep." Aims Neuroscience 3 (1): 67-104.

[10] Schwartz Md, Kilduff Ts. The Neurobiology Of Sleep And Wakefulness. Psychiatrclin North Am. 2015 Dec;38(4):615-44.

[11] Zajac A, Skowronek-Bała B, Wesołowska E, Kaciński M. [Sleep Paroxysmal Events In Children In Video/Polysomnography]. Przegllek. 2010;67(9):762-9

[12] Sleep And Health—An Introduction Sheilja Singh , Namratayadav , Sanket Jain International Journal Of Head And Neck Surgery (2019): 10.5005/Jp-Journals-10001-1361

[13] Malik J, Lo Yl, Wu Ht. Sleep-Wake Classification Via Quantifying Heart Rate Variability By Convolutional Neural Network. Physiol Meas. 2018 Aug 20;39(8):085004

[14] Varga B, Gergely A, Galambos Á, Kis A. Heart Rate And Heart Rate Variability During Sleep In Family Dogs (Canisfamiliaris). Moderate Effect Of Pre-Sleep Emotions. Animals (Basel). 2018 Jul 02;8(7)

[15] Siegel Jm. Do All Animals Sleep? Trends Neurosci. 2008; 31:208–213.

[16] Murillo-Rodríguez E, Arias-Carrión O, Sanguino-Rodríguez K, González-Arias M, Haro R. Mechanisms Of Sleep-Wake Cycle Modulation. Cns Neuroldisord Drug Targets. 2009 Aug;8(4):245-53

[17] Sherin Je, Shiromani Pj, Mccarley Rw, Et Al. Activation Of Ventrolateralpreoptic Neurons During Sleep. Science. 1996; 271:216–219.

[18] Della Monica C, Johnsen S, Atzori G, Groeger Ja, Dijk Dj. Rapid Eye Movement Sleep, Sleep Continuity And Slow Wave Sleep As Predictors Of Cognition, Mood, And Subjective Sleep Quality In Healthy Men And Women, Aged 20-84 Years. Front Psychiatry. 2018;9:255

[19] Frank Mg, Heller Hc. The Ontogeny Of Mammalian Sleep: A Reappraisal Of Alternative Hypotheses. J Sleep Res. 2003; 12:25–34

[20] Jouvet M. Research On The Neural Structures And Responsible Mechanisms In Different Phases Of Physiological Sleep. Arch Ital Biol. 1962; 100:125–206

[21] Hobson Ja, Mccarley Rw, Wyzinski Pw. Sleep Cycle Oscillation: Reciprocal Discharge By Two Brainstem Neuronal Groups. Science. 1975; 189:55–58

[22] Axelrod J., Weissbach H. Enzymatic O-Methylation Of N-Acetylserotonin To Melatonin. Science. 1960;131:1312

[23] Simonneaux V., Ribelayga C. Generation Of The Melatonin Endocrine Message In Mammals: A Review Of The Complex Regulation Of Melatonin Synthesis By Norepinephrine, Peptides, And Other Pineal Transmitters. Pharmacol. Rev. 2003;55:325–395.

[24] Claustrat B, Brun J, Chazot G. The Basic Physiology And Pathophysiology Of Melatonin. Sleep Med Rev 2005;9:11–24.

[25] Kappers Ja. The Development, Topographical Relations And Innervation Of The Epiphysis Cerebri In The Albino Rat. Z Zellforschmikrosk Anat. 1960;52:163-215

[26] Brzezinski A. Melatonin In Humans. N. Engl. J. Med. 1997;336(3):186–195

[27] Gastel Ja, Roseboom Ph, Rinaldi Pa, Weller Jl, Klein Dc. Melatonin Production: Proteasomal Proteolysis In Serotonin Nacetyltransferase Regulation. Science 1998; 279 (5355): 1358-60

[28] Cassone Wm. Effects Of Melatonin On Vertebrate Circadian Systems. Trends Neurosci. 1990; 13: 457-63.

[29] Levi F, Schibler U. Circadian Rhythms: Mechanisms And Therapeutic Implications. Annu Rev Pharmacoltoxicol 2007; 47: 593-628

[30] Tabandeh H, Lockley Sw, Buttery R, Et Al. Disturbance Of Sleep In Blindness. Am J Ophthalmol 1998; 126 (5): 707-12.

[31] Poza Jj, Pujol M, Ortega-Albás Jj, Romero O, Melatonina En Los Trastornos De Sue˜no. Neurología. 2022;37:575—585

[32] Witt-Enderby Pa, Bennett J, Jarzynka Mj, Firestine S, Melan Ma. Melatonin Receptors And Their Regulation: Biochemical And Structural Mechanisms. Life Sci 2003; 72 (20): 2183-98.

[33] Liu J, Clough Sj, Hutchinson Aj, Adamah-Biassi Eb, Popovska- Gorevski M, Dubocovich Ml. Mt1 And Mt2 Melatonin Receptors: A Therapeutic Perspective. Annu Rev Pharmacoltoxicol. 2016;56:361—83

[34] Touitou Y, Bogdan A. Promoting Adjustment Of The Sleep-Wake Cycle By Chronobiotics. Physiolbehav. 2007;90:294–300
[35] Wan Q, Man Hy, Liu F, Et Al. Differential Modulation Of Gabaa Receptor Function By Mel1a And Mel1b Receptors. Nat Neurosci 1999; 2 (5): 401-3.
[36] Reiter Rj. At The Cutting Edge Melatonin: The Chemical Expression Of Darkness. Mol Cell Endocrinol 1991; 79: C153-C8
[37] Kra¨Uchi K, Cajochenc,Werthe,Wirz-Justice A.Warm Feet Promote The Rapid Onset Of Sleep. Nature 1999; 401: 36–37
[38] Kra¨Uchi K, Cajochen C, Werth E, Wirz-Justice A. Functional Link Between Distal Vasodilation And Sleep-Onset Latency? Am J Physiol 2000; 278: R741–R748.
[39] Cajochen C, Kra¨Uchi K, Wirz-Justice A. The Acute Soporific Action Of Daytime Melatonin Administration: Effects On The Eeg During Wakefulness And Subjective Alertness. J Biol Rhythms 1997; 12: 636–643
[40] Ioannidis Jpa, Evans Sjw, Gotzsche Pc, Et Al. Better Reporting Of Harms In Randomized Trials An Extension Of The Consort Statement. Ann Intern Med. 2004;141:781–8
[41] Dawson D, Armstrong Sm. Chronobiotics— Drugs That Shift Rhythms. Pharmacolther 1996; 69:15–36
[42] Moreno Cr, Vasconcelos S, Marqueze Ec, Et Al. Sleep Patterns In Amazon Rubber Tappers With And Without Electric Light At Home. Sci Rep. 2015;5:14074–14084
[43] Melatonin And Sleep Nava Zisapel* The Open Neuroendocrinology Journal, 2010, 3, 85-95
[44] Shibui K, Uchiyama M, Okawa M. Melatonin Rhythms In Delayed Sleep Phase Syndrome. J Biol Rhythms 1999; 14 (1): 72-6
[45] Dahlitz M, Alvarez B, Vignau J, English J, Arendt J, Parkes Jd. Delayed Sleep Phase Syndrome Response To Melatonin. Lancet 1991; 337 (8750): 1121-4
[46] Yamanaka Y, Hashimoto S, Takasu Nn, Et Al. Morning And Evening Physical Exercise Differentially Regulate The Autonomic Nervous System During Nocturnal Sleep In Humans. Am J Physiolregulintegr Comp Physiol. 2015;309:R1112–R1121
[47] American Academy Of Sleep Medicine. International Classification Of Sleep Disorders. 3rd Ed. Darien (Il): American Academy Of Sleep Medicine; 2014
[48] Costello, R.B.; Lentino, C.V.; Boyd, C.C.; O'connell, M.L.; Crawford, C.C.; Sprengel, M.L.; Deuster, P.A. The Effectiveness Of Melatonin For Promoting Healthy Sleep: A Rapid Evidence Assessment Of The Literature. Nutr. J. 2014, 13, 106
[49] Low, T.L.; Choo, F.N.; Tan, S.M. The Efficacy Of Melatonin And Melatonin Agonists In Insomnia—An Umbrella Review. J. Psychiatr. Res. 2020, 121, 10–23
[50] Takaesu Y, Futenma K, Kobayashi M, Et Al. A Preliminary Study On The Relationships Between Diurnal Melatonin Secretion Profile And Sleep Variables In Patients Emergently Admitted To The Coronary Care Unit. Chronobiol Int. 2015;32:875–879
[51] Lemoine P, Zisapel N (2012). Prolonged-Release Formulation Of Melatonin (Circadian) For The Treatment Of Insomnia. Expert Opinpharmacother 13: 895–905
[52] Comai S, Ochoa-Sanchez R, Gobbi G. Sleep-Wake Characterization Of Double Mt(1)/Mt(2) Receptor Knockout Mice And Comparison With Mt(1) And Mt(2) Receptor Knockout Mice. Behav Brain Res. 2013;243:231–238
[53] Scheer Fa, Morris Cj, Garcia Ji, Et Al. Repeated Melatonin Supplementation Improves Sleep In Hypertensive Patients Treated With Beta-Blockers: A Randomized Controlled Trial. Sleep. 2012;35:1395–1402
[54] Wade, A. G., Ford, I., Crawford, G., Mcmahon, A. D., Nir, T., Laudon, M., &Zisapel, N. (2007). Efficacy Of Prolonged Release Melatonin In Insomnia Patients Aged 55-80 Years: Quality Of Sleep And Next-Day Alertness Outcomes. Current Medical Research And Opinion, 23(10), 2597–2605
[55] Kaminski Rs, Martinez D, Fagundes M, Et Al. Melatonin Prevents Hyperglycemia In A Model Of Sleep Apnea. Arch Endocrinolmetab. 2015;59:66–70
[56] Xie S, Deng Y, Pan Yy, Et Al. Melatonin Protects Against Chronic Intermittent Hypoxia-Induced Cardiac Hypertrophy By Modulating Autophagy Through The 5' Adenosine Monophosphate-Activated Protein Kinase Pathway. Biochembiophys Res Commun. 2015;464:975–981
[57] Boeve Bf. Rem Sleep Behavior Disorder: Updated Review Of The Core Features, The Rem Sleep Behavior disorder neuro degenerative Disease Association, Evolving Concepts, Controversies, And Future Directions. Ann N Y Acad Sci. 2010;1184:15–54
[58] Kunz D, Mahlberg R. A Two-Part, Double-Blind, Placebo Controlled Trial Of Exogenous Melatonin In Rem Sleep Behaviour Disorder. J Sleep Res. 2010;19:591–596.
[59] Campbell Ss, Dawson D. Aging Young Sleep: A Test Of The Phase Advance Hypothesis Of Sleep Disturbance In The Elderly. J Sleep Res 1992;1:205-10
[60] Lewy Aj, Ahmed S, Jackson Jm, Sack Rl. Melatonin Shifts Human Circadian Rhythms According To A Phase-Response Curve. Chronobiolint 1992;9:380-92
[61] Revell Vl, Burgess Hj, Gazda Cj, Smith Mr, Fogg Lf, Eastman Ci. Advancing Human Circadian Rhythms With Afternoon Melatonin And Morning Intermittent Bright Light. J Clinendocrinolmetab 2006;91:54-9