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Multifaceted Roles of Melatonin in Sleep Disorders

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ABSTRACT: Hormone protein melatonin helps regulate the sleep–wake cycle or circadian rhythm, making it a critical substance in sleep regulation. Melatonin synthesis mainly occurs in the epiphysis of the pineal gland, although extra-pineal melatonin has been observed in other sites of the body, such as salivary glands, the gastrointestinal tract, the placenta and breast milk. Over the years, research into melatonin has shown that it has multiple roles in sleep disorders, revealing its mechanisms of action, clinical implications and therapeutic performance. In this paper, we review recent findings on the role of melatonin in sleep disorders which include insomnia, delayed sleep phase disorder (DSPD), jet lag, and shift work sleep disorder (SWSD). In addition, we report results where melatonin agonists and novel therapeutic targets have been designed and utilized to manipulate the melatonin receptors. This paper helps delineate melatonin's role in sleep disorders from the literature, and clarify new perspectives for prevention and treatment of human health.

Keywords: Circadian rhythm, insomnia, melatonin

1. INTRODUCTION

Sleep disorders are well-recognized public health problems that arise across the life-span, and are associated with a number of physical and mental health problems (Hirshkowitz et al., 2015). A typical human sleep is about one-third of the day, and the physiological regulation of sleep-wake cycle is mediated by various neurotransmitters, hormones and environmental cues. However, melatonin is arguably the most dominant factor in mediating sleep-wake cycle, and melatonin

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genetically confers susceptibility to sleep-wake cycle disturbances, including variations in sleep onset and duration, phase shifts, and sleep and circadian rhythm disorders (Pandi‐Perumal et al., 2007). In the recent years, the exact roles of melatonin in sleep disorders have garnered considerable attention, as researchers continue to unravel the precise mechanisms involved in these disorders. This review aims to provide a broad outline of melatonin in sleep disorders and its links, starting with a brief overview of the general physiology and mechanics of melatonin, followed by an outline of the clinical indicators for the various Melatonin-sleep disorders, and lastly a brief indication of whether melatonin could be a useful therapeutic option for MDSDs.

Sleep disorders represent major public health problems for people of all ages in all regions of the world because they are disabling, adversely impact on physical and mental health, and are often associated with serious sequelae such as cardiovascular diseases, diabetes and mental disorders. The processes controlling the sleep-wake cycle are the result of an intricate chain of molecular, physiological and behavioral events that relies on neurotransmitter interactions, hormonal secretion and cues from the environment. Although there are many factors that regulate sleep, melatonin appears to be the most important signal that regulates the circadian system and alters sleep quality.

Melatonin, it's also synthesized in the pineal gland, and secretion of melatonin also has a rhythm with peaks at night and increases in response to darkness (Arendt, 1998). This endogenous rhythm synchronizes the body's clock to the external light-dark cycles, and helps with the initiation of sleep and the quality of sleep. Finally, the suprachiasmatic nucleus (SCN), sometimes called the 'master clock', coordinates melatonin secretion in response to environmental light cues from photoreceptors in the retina (Hattar et al., 2002).

Melatonin acts, from a mechanistic perspective, via specific receptors named MT1 and MT2, ubiquitously located throughout the central nervous system (Dubocovich 1983). Moreover, activation of these receptors modulates neuronal activity, neurotransmitter release and gene expression patterns involved in sleep control (Boutin et al. 2005). Melatonin also acts indirectly on the circadian clock via the control of the expression of clock genes and clock-controlled genes (Reppert Weaver 2001).

Raising an eyebrow at 'folklore', it regulates melatonin production and promotes sleep theory on melatonin and its analogues for the treatment of sleep disorders (insomnia but also, for example, circadian rhythm disorders) has drawn on new findings from molecular, clinical and translational studies and, together with advances in chronobiology and pharmacology, has led to new forms of

targeted intervention that are designed to synchronize circadian rhythms, improve sleep and maximize alertness when needed (Zisapel, 2018).

In this context, melatonin plays a more complex pathophysiological role and seems to be a critical part of the optimal regulation of sleep-wake patterns. Deciphering the mechanisms of action of melatonin and its role in the circle of circadian regulation is a key factor in progress in the development of targeted and effective interventions to counter sleep disorders.

Furthermore, and perhaps most importantly, there is an urgent and unmet therapeutic need for drug discovery in light of the increasing incidence of sleep pathologies and increased recognition for their role in health and wellness. Because of melatonin's diverse physiologic properties and relatively good safety profile, it represents an ideal therapeutic to serve the needs of patients with different sleep disorders. Melatonin supplementation or melatonin receptor agonists may be able to reset circadian rhythms, promote sleep onset and duration, and provide benefit in reducing health risks associated with poor sleep.

Moreover, studies are investigating innovative uses of melatonin in the treatment of sleep disorders, including tailoring treatments to individuals' circadian profiles and genotype (Gallelli et al, 2013). The better understanding of pathophysiology obtained through a genetic, neuroscientific and precision medicine lens may provide the rationale for patient-tailored interventions for each sleep disorder.

2. PHYSIOLOGICAL ROLES OF MELATONIN

Chemically known as N-acetyl-5-methoxytryptamine, melatonin is synthesized primarily in a pea-sized organ in the epithalamus of the brain called the pineal gland. Synthesis and release are controlled by the suprachiasmatic nucleus (SCN), often known as the body's 'master clock', which resides in the hypothalamus just above the pineal gland. Serving as the pacemaker, the SCN receives input from retinal photoreceptors that retrieve light information and relay this information to entrain circadian rhythms to the external environment. In follow-up, in response to low levels of light, the SCN causes the pineal gland (third eye) to release melatonin, with levels rising to a peak at night and declining during daylight hours. This endogenous rhythm controls secretion and release of melatonin and plays a pivotal role in entraining the circadian system to the environment to ensure sleepiness at night (Arendt, 1998; Moore & Eichler, 1972; Hattar et al., 2002; Lewy et al., 1980).

Melatonin is a neurohormone produced from the amino acid tryptophan in a complex cascade initiated by the circadian rhythm and environmental light-dark cycles. It is synthesized and

secreted in the highest amounts from the pineal gland, although other tissues also express the enzymes needed in melatonin production. Melatonin synthesis is tightly controlled by the SCN of the hypothalamus, the body's master circadian pacemaker (Fonken and Nelson, 2011), which responds to input from retinal photoreceptors sensitive to blue light to relay the start of darkness, which triggers melatonin production (Hattar et al., 2002).

The synthesis starts with the formation of serotonin from tryptophan, followed by an acetylation and a methylation to yield melatonin in the pinealocytes (a type of cell) of the pineal gland. Arylalkylamine N-acetyltransferase (AANAT) catalyzes the rate-limiting step in the synthesis of melatonin and SCN and sympathetic input from the superior cervical ganglion controls the activity of AANAT (Pandi-Perumal et al., 2021). Melatonin is released into the blood circulation and to the cerebrospinal fluid, where it exerts its regulatory actions such as circadian rhythms of sleep and wake, body temperature, seasonal reproduction and immune function. Melatonin's actions on those processes are mediated by its receptors, subtypes MT1/MT2. These G protein-coupled receptors (GPCRs) are widely distributed not only in brain (central) but also in peripheral tissues (such as liver, pancreas and gut) and in immune cells. Activation of the melatonin receptors modulates the cell activity through modification of intracellular signaling such as cyclic adenosine monophosphate (cAMP) and phosphoinositide pathways, and various cellular actions including neuronal excitability, neurotransmitter release, and gene expression patterns. Melatonin secretion displays a circadian rhythm, soared during night and minimal during day time. Moreover, it oscillates cyclically to adjust the internal clock of the body with external environment cue, help to sleep onset and produce the regenerative sleep (Pandi-Perumal et al., 2021).

On the other side, pharmacological interventions designed to improve circadian clock-sleep functioning are more recently developed, melatonin analogues are now commonly used in sleep medications. More recent work has revealed molecular pathways involved in melatonin synthesis and receptor signaling, with insights about the mechanisms by which melatonin influences subsequent changes in sleep physiology (Hattar et al., 2002). These molecular mechanisms have been developed further due to progress in molecular biology, neuroimaging and genetic studies about melatonin secretion, the mechanisms involved in entraining the circadian clock and its role in sleep induction. Insights into the pharmacokinetics and pharmacodynamics of the endogenous hormone melatonin, as well as its analogues, are now being used to develop novel drugs that can improve clock-sleep function in sleep disorders. We've come a long way from the use of tapping bones and ancient calendars to stay up late on winter nights (Fonken & Nelson, 2011).

3. MECHANISM OF ACTION

Its actions on sleep physiology occur directly through interactions with melatonin receptors present within the CNS, particularly in the hypothalamus and the brainstem (Dubocovich, 1983). Two main subtypes of melatonin receptor, MT1 and MT2, are members of the family of G protein-coupled receptors (GPCRs) (Reppert et al., 1995). Activation of these receptors modulates the activity of neurons and their release of neuropeptidergic and monoaminergic neurotransmitters into the synaptic cleft and thus alters downstream signaling pathways implicated in promoting sleep initiation and consolidation (Boutin et al., 2005). Furthermore, melatonin has been shown to affect the expression of clock genes and clock-controlled genes at the molecular level and so regulates the circadian rhythm (Reppert Weaver, 2001).

Melatonin is a powerful regulator of sleep and wake rhythms, but it acts by interacting with a variety of melatonin receptors – the most important of which are in the hypothalamus and the brainstem (Dubocovich, 2015). The two main subtypes of melatonin receptors (MT1 and MT2) are members of the G protein-coupled receptor (GPCR) family (Tosini & Owino, 2014). Activation of these receptors leads to a change of neuronal activity, neurotransmitter release and triggered changes in other downstream signaling pathways that control sleep initiation and maintenance (Dubocovich, 2015). Also, melatonin controls expression of the clock genes and of the clock-controlled genes, thus having a role in the regulation of circadian rhythms at the level of the molecule.

Besides the demonstration that sleep is actually a physiological necessity and not a recent invention, researchers have taken big steps in understanding the cellular and molecular mechanisms by which melatonin influences sleep physiology. Recent research in knockout animal models and selective receptor agonist/antagonist identification studies detailed the distinct functions of MT1 and MT2 receptors in sleep (Jockers et al, 2016), and neuroimaging revealed the hypothalamus, thalamus and brainstem nuclei as brain regions involved in melatonin-mediated modulation of sleep (Burgess Fogg, 2008).

Besides, there is an increasing amount of evidence to support the idea that melatonin's impact on sleep is not only through direct operative receptor-mediated mechanisms, but also via antioxidant and anti-inflammatory activities (Hardeland et al., 2011) that are most likely contributing to also its neuroprotective activity and the fine modulation of the sleep architecture (Dubocovich, 2015). Melatonin also acts by interacting with the gamma-aminobutyric acid (GABA) and serotonin neurotransmitter systems to accomplish the regulatory transition from wakefulness to sleep and, hence, to consolidate sleep stages.

Recent efforts in pharmacology and molecular biology have made new melatonin receptor agonists and antagonists accessible and promising for the treatment of sleep disorders (Dubocovich 2015). When acting on the brain, they have selective efficiencies on either the MT1 or MT2 receptors. Their development thus allows for better treatment of sleep disturbances that are linked to a certain subtype of the receptor(s), depending on individual patient's characteristics and its symptoms (Dubocovich 2015).

4. ROLES OF MELATONIN IN SLEEP DISORDERS

A. Insomnia

Insomnia, defined as the inability to initiate or maintain sleep, or non-restorative sleep, is among the most prevalent sleep disorders world-wide (American Psychiatric Association, 2013). The dysregulation of the circadian clock and the alteration of melatonin secretion have both been linked to the pathophysiology of insomnia (Bonnet and Arand, 2010). These findings paved the way for a number of studies to test exogenous melatonin supplementation for its ability to improve sleep-onset latency and overall sleep quality in patients with primary and comorbid insomnia (Ferracioli-Oda et al., 2013). More recently, melatonin receptor agonists or so-called melatonergic hypnotics, including ramelteon and tasimelteon, have emerged as a viable pharmacological treatment for insomnia that avoids the use of traditional sedative-hypnotics, thereby reducing the risk of tolerance and dependence (Roth et al., 2005).

Insomnia, also known as the inability to fall and/or stay asleep, sleep that is not restorative and problems functioning during the day, is the most common of all sleep disorders globally (Roth, 2007). The etiology of insomnia has a multifactorial origin involving psychological, physiological and environmental factors (Riemann et al., 2017). Circadian rhythm disruption, changes in neurotransmitter homeostasis, and increased levels of arousal are all contributory to the pathophysiology of insomnia (Riemann et al., 2017).

Melatonin's role as a sleep-onset signal has made it a top choice as a therapeutic target for insomnia. A number of clinical trials have demonstrated reductions in sleep latency and improvement in sleep quality using exogenous melatonin supplementation in patients with insomnia. The sleep-promoting effects of melatonin have been hypothesized to occur through MT1/MT2 receptor-dependent decreases in neuronal excitability and arousal (Roth, 2007; Ferracioli-Oda et al., 2013; Dubocovich, 2015).

Moreover, melatonin's chronobiotic effects (its ability to entrain the circadian rhythm) could make it a good choice for insomnia with circadian rhythm dysregulation (Roth, 2007). Advancing

the sleep phase and bringing the subject's endogenous clock into alignment with the external light-dark cycle can help bring sleep-wake rhythms into better harmony and improve sleep efficiency (Roth, 2007).

Further studies have examined the differential effects of melatonin formulations, doses, and ways of administration for insomnia symptoms: controlled-release formulations of melatonin may extend the timing of the melatonin curve and improve sleep maintenance in insomniacs (Roth et al 2005). Intranasal use of melatonin ameliorates insomnia and represents a novel way to improve bioavailability because this route avoids hepatic first-pass metabolism (Gallelli et al 2013).

On the other hand, there is also a growing body of literature on combination therapies that leverage the potential of melatonin as a sleep aid by pairing it with other interventions or drugs, including for example cognitive-behavioural therapy for insomnia (CBT-I) or sedative-hypnotic medications (Riemann et al, 2017).

B. Delayed Sleep Phase Disorder

DSPD is characterized by a persistent delay in circadian timing of the sleep period with low melatonin, as manifest by chronic inability to fall asleep and to wake up at desired times despite compulsory or voluntary bed times (American Academy of Sleep Medicine, 2014; Sack et al., 2007). Melatonin analogs, such as agomelatine, are effective at advancing the sleep-wake rhythm in individuals with DSPD. Behavioral management or chronotherapy has emerged to provide an alternative to pharmacotherapy for the disorder, and combined approaches involving light and melatonin therapy have been shown to be efficacious. Behavioral treatment strategies such as chronotherapy can retime the circadian phase so as to coincide with the desired sleep-wake schedules (Gallelli et al., 2013; Crowley et al., 2006).

Sick people with DSPD have an 'intrinsic inability to delay sleep in the evening and to advance sleep in the morning that is persistent and has clinically significant amplitudes, leading to an inadequate nocturnal sleep period, resulting in impaired daytime functioning as well as difficulties with social, occupational and other areas of daytime functioning'. DSPD patients are unable to fall asleep at a socially acceptable 'bedtime' and also unable to wake up at a socially acceptable 'morning' time, leading to daytime dysfunction, impairment to daily functioning and requiring daytime naps. In general, DSPD patients either (a) excrete virtually no melatonin after the evening dip and (b) their melatonin onset and peak occur at a later than normal time; (b) releases melatonin but at a later time and (c) does not adequately increase the secretion of morning melatonin as part of their inborn circadian rhythm, causing impairment of phase 'advancement' (Sack et al., 2007).

Melatonin is one of the most important pacemaker hormones for regulating the circadian rhythm and sleep-wake cycle and therefore remains the main target for the management of DSPD (James et al., 2007). It is now well-demonstrated that melatonin supplementation leads to phase advances in sleep onset and re-synchronization of the circadian rhythm in subjects with DSPD (Suhner et al., 1998; Sack et al., 2007).

A growing body of research examines melatonin dosing regimens and modalities of administration that might improve outcomes in DSPD. CR formulations of melatonin, formulated to approximate the circadian profile of endogenous melatonin secretion, and to provide a pharmacologically sustained effect throughout the night, represent a significant improvement in treating DSPD. For instance, the ability to fall asleep earlier and, for people with DSPD, prevent fragmentation of sleep (Roth et al., 2007).

Moreover, the use of personalized schedules of melatonin administration has been advocated to address intraindividual variability based on people's chronotypes and melatonin rhythm dynamics. Chronotype assessment, in conjunction with measures of circadian phase using objective circadian markers, can guide the timing and dosing of melatonin supplementation, based on individual circadian characteristics (i.e., chronotype and circadian phase) (Gallelli et al, 2013). This personalized approach is the best way to minimize both the risks of mistakes and adverse effects with melatonin administration, and optimize the likelihood of efficacy.

Further, melatonin supplementation was supplemented with behavioral interventions to improve sleep hygiene and expose patients to light at the appropriate times of day: 'Timed exposure to bright light in the morning and avoidance of bright light in the evening may add to the efficacy of oral melatonin in shifting the circadian rhythm and accelerating adaptation to a normal sleep-wake schedule (Sack et al., 2007).

C. Jet Lag

Sent by our internal circadian clock, aligned with the sleep-wakefulness rhythms set by the external light-dark cycle, jet lag arises when travelling across multiple time zones confuses these two inopportune clocks. Melatonin is theorized to be effective in prevention and treatment of jet lag and attenuating associated unpleasant symptoms such as fatigue, difficulty sleeping and falling asleep, impairment of executive functions (ability to think and multitask), and sleepiness and poor sleep quality on arrival (Waterhouse et al, 2007; Herxheimer and Petrie, 2002). A number of recent meta-analyses concluded that melatonin supplementation attenuates jet lag severity and decreases the time required to reset circadian rhythms after travelling across multiple time zones, even when administered in suboptimal times relative to destination time cues

(Herxheimer and Petrie, 2002). Melatonin's effects of expediting the circadian reset allow for appropriating as much sleep as possible on the flight and promote sleep on arrival at the destination. Melatonin supplementation is recommended only for those travelling across two or more time zones, in a time of day commensurate with the destination (Suhner et al, 1998).

Jet lag, or desynchronosis, is a transient sleep disorder caused by crossing multiple time zones in a short amount of time, resulting in disorganized sleep and profound circadian misalignment at the destination, or an upset of the body's internal clock. The symptoms of jet lag include disturbed sleep, daytime fatigue, impaired alertness and cognitive function, gastrointestinal disruptions and mood changes. Given melatonin's pivotal role in the circadian rhythm and the sleep-wake cycle, scientists have developed melatonin as an intervention for reducing jet lag.

This is the likely reason why melatonin supplementation has been shown to help alleviate jet-lag symptoms: it helps the body to shift its circadian rhythm to the local time zone more quickly. Several randomized, controlled clinical trials have found that even modest doses of melatonin (5-10 mg) speed the resynchronization of the body's circadian clock, reducing the severity and duration of jet-lag symptoms in many people – especially when it is taken in the evening after travelling to the new time zone. Melatonin's relatively short half-life and its apparent ability to advance or delay (phase-shift) the timing of the circadian clock helps the body resynchronize with local daylight hours more rapidly (Herxheimer and Petrie, 2002).

Recent studies have also focused on optimizing melatonin dosing regimens and administration protocols to maximize its use in the modulation of jetlag. (Roth et al, 2005; Reid et al., 2019; Waterhouse et al., 2019).

D. Shift Work Sleep Disorder

SWSD is a 'mismatch between an external timing arrangement of the sleep schedule (ie, a shift work schedule) and an internal biological clock, which gives rise to sleep disturbance and excessive sleepiness during waking hours' among shift workers. Melatonin supplementation – including 'the administration of chronobiotic drugs such as melatonin…. receptor agonists and melatonin-containing formulations, synchronized with the caller's evening shift, either immediately or in anticipation of a change in work timing,' – should offer a 'targeted intervention to set the internal biological clock and allow the individual to adapt to night-time work timing' (American Academy of Sleep Medicine, 2014; James et al., 2007; Zisapel, 2018).

It is one of two circadian rhythm sleep disorders (the other is advanced sleep-wake phase disorder) due to misalignment of the sleep–wake cycle with the external environment, resulting

in clinically significant insomnia and excessive daytime sleepiness, often accompanied by impaired cognitive function and mood disturbance related to working shifts. Workers on the night shift experience desynchronization of the endogenous circadian rhythm from the environmental 24-hour light–dark cycle that regulates this rhythm and, as a consequence, the pathological symptomatology of SWSD (Zhu et al, 2018).

As a modulator of the circadian rhythm and sleep-wake cycle, melatonin is an important component of the management of SWSD because dietary supplementation of the hormone has been shown to improve subjective sleep quality, shorten sleep latency and increase daytime alertness in individuals with SWSD. It is used to advance one's circadian phase and to synchronize it with their work hours, and it is most frequently taken during the desired rest period to induce sleep (Rajaratnam et al., 2009).

These studies have targeted the optimization of administration of melatonin or the application of pharmacodynamic regimens that are precisely tailored to the individual's needs. Melatonin can be released in a controlled fashion over several hours, which can either be timed to extend the sleep period or be administered around the middle of the sleep period to provide focused enhancement of sleep. Controlled-release formulations of melatonin are now used quite commonly by shift workers to provide even coverage of the sleep period and help reduce sleep maintenance and circadian difficulties. Other formulations are being designed to provide a release profile with which the circadian timing system can be entrained for greater number of circadian cycles or by locking the sleep period to the circadian rhythm (Rajaratnam et al., 2009).

Moreover, chronotype assessment and subjective or objective measures of circadian phase can be employed to tailor melatonin supplementation to shift workers' individual circadian time profiles, which determines the ideal timing and dosing of the melatonin administration (Barger et al, 2019). This latter tactic would minimize the risk for adverse effects, maximize melatonin efficacy, and consequently improve health outcomes.

Alongside treatments such as melatonin supplementation, behavioral interventions targeting sleep hygiene and light exposure can assist in circadian adaptation and limit the effects of SWSD. Strategic exposure to bright light during night shifts and adhering to a regular sleep-wake cycle during non-working hours is recommended as treatments to promote circadian adoption to the work schedule and optimize sleep quality in night workers (Zhu et al., 2018).

4. CONCLUSION

Melatonin is essential for maintaining normal circadian rhythms and regulation of key processes related to sleep physiology. These observations explain melatonin's role in abnormal sleep states as well as its therapeutic use as melatonin-based treatments show promise in treating the sleep disorders. Future research can expand the understanding of mechanisms of action of melatonin and improve the clinical use of melatonin in the treatment of sleep disorders.

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