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Review

Melatonin, sleep, and circadian rhythms: rationale for development of specific melatonin agonists

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Abstract

Circadian rhythm sleep disorders (CRSDs), whether chronic or transient, affect a broad range of individuals, including many elderly, those with severe visual impairments, shift workers, and jet travelers moving rapidly across many time zones. In addition, various forms of insomnia affect another large sector of the population. A feature common among CRSDs and some forms of insomnia is sensitivity to the hormone melatonin, which is secreted by the pineal gland. Accumulating evidence suggests that melatonin may regulate the circadian clock located in the suprachiasmatic nucleus (SCN) of the hypothalamus. Although the light–dark cycle is the primary signal that entrains the circadian clock to environmental cycles, exogenous melatonin has been shown to entrain the clock in individuals with no light perception and free-running circadian rhythms. Furthermore, studies have reported beneficial effects of melatonin for treatment of certain insomnias. Together, these studies suggest that melatonin may be useful for treating some insomnias and CRSDs. In these contexts, use of melatonin as a supplement has been popular in the United States. Unfortunately, the therapeutic potential of melatonin has been difficult to realize in clinical trials, possibly owing to non-specific actions of the agent and its unfavorable pharmacokinetic properties when administered orally. In an attempt to take advantage of the therapeutic opportunities available through the brain's melatonin system, researchers have developed several melatonin agonists with improved properties in comparison to melatonin. Some of these agents are now in clinical trials for treatment of insomnia or CRSDs.

Keywords: Melatonin; Circadian rhythm; Sleep; Suprachiasmatic nucleus; Pineal gland; Insomnia

1. Introduction

Melatonin, first identified in 1958 [1], is secreted by the pineal gland during the night in a wide range of species. This cycle of melatonin secretion is a robust hormonal signal that can act as a 'time-giver' (zeitgeber) to indicate time of environmental darkness [2]. In photoperiodic species such as hamsters and sheep, in which reproductive cycles are dependent on the seasons, seasonal changes in night length are encoded as changes in melatonin secretion. This hormonal signal synchronizes the onset of the reproductive cycle during the appropriate season [3,4]. In non-photoperiodic species such as humans, the circadian rhythm of melatonin secretion is thought to contribute to other functions of the circadian clock, such as consolidation of sleep [5] and regulation of the circadian rhythm of core body temperature [6].

The master clock controlling circadian rhythms is located in the suprachiasmatic nucleus of the hypothalamus [7]. Lesions of the SCN appear to abolish all circadian rhythms in rodents [8,9]. In primates, SCN lesions disrupt many circadian rhythms, but leave some intact, suggesting that other neuronal centers contribute to circadian rhythmicity in primates [10–13]. However, the rhythms that persist after SCN ablation are often less stable or robust, suggesting that the SCN is important for maintaining these rhythms as well. The SCN clock is also regulated by factors outside the SCN, including signals from the retina encoding

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environmental light levels [14] and melatonin secreted from the pineal gland [2,15–21]. Early studies in birds implicated melatonin in the control of circadian rhythms, since removal of endogenous melatonin by pinealectomy could abolish free-running circadian rhythms of sparrows housed in constant darkness [15]. Furthermore, continuous treatment with exogenous melatonin could alter free-running circadian rhythms [16] and pineal transplants could restore rhythmicity in pinealectomized birds [17]. The pineal gland does not play such a central role in the regulation of circadian rhythm in mammals, since pinealectomy does not disrupt mammalian rhythms to any large extent. However, studies in rats demonstrate that exogenous melatonin can also entrain free-running rhythms of mammals [17]. Further support for melatonin as an important regulator of the circadian clock comes from findings that neurons of the SCN express high levels of melatonin receptors, and from observations that treatment of SCN neurons with melatonin can acutely alter neuronal activity [20] and phase-shift the neuronal firing rate in vitro [18,21].

In addition to its effects on the circadian clock, melatonin may have sleep-promoting properties. In some studies of human subjects, melatonin has been found to induce sedation, lower core body temperature, and induce other changes associated with sleep [5,6,22–24]. However, in nocturnal animals, melatonin is also secreted during the dark phase of the circadian cycle—the time when these animals are increasing their activity [25]. Thus, melatonin is not a universal sleep-inducing hormone but, rather, acts as a hormonal signal indicating time of darkness [26–28].

In humans, administration of exogenous melatonin in the early evening advances the phase of circadian rhythms; administration in the early morning delays the phase [27]. However, the phase-delaying effects of melatonin are less robust and are not consistently observed [29]. Because of its phase-shifting properties, melatonin has been studied as a potential treatment for circadian rhythm sleep disorders (CRSDs) (e.g. delayed-phase sleep syndrome, advanced-phase sleep syndrome, and free-running rhythms in blind people) [28,30]. In addition, the sedative and mild hypnotic properties of melatonin, and its availability as a 'natural supplement', have led to widespread use of the agent for insomnia, especially in the United States. However, both uses are supported by only limited clinical trial data. Furthermore, melatonin has some properties that would be expected to limit its usefulness as an oral agent-properties such as a short half-life, high first-pass metabolism, and binding to multiple melatonin receptors [31–36].

Several analogs of melatonin have been developed in an effort to find better treatments for CRSDs or insomnia. Some of these agents are selective for specific melatonin receptors and have other advantageous properties. Clinical trials of specific agents are underway, although limited data are available to date. After reviewing the neurobiology of the melatonin system and the possible use of melatonin for treating sleep and circadian disorders, we will discuss some of the results with the most promising melatonin agonists in clinical trials.

2. Neurobiology of the melatonin system

2.1. Melatonin receptors

The older literature on melatonin describes two major classes of receptors: ML_1 (high affinity) and ML_2 (low affinity) receptors. The ML_1 receptor is a member of the large family of receptors with 7 membrane-spanning domains—a family that includes the serotonin and β-adrenergic receptors. In contrast, the ML_2 receptor is a distinct molecular species.

ML_1 receptors are of clear importance to the nervous system. Molecular cloning revealed that there are at least 3 subtypes of ML_1 receptors: Mel_{1a}, Mel_{1b}, and Mel_{1c} [32]. To date, Mel_{1c} receptors have not been found in mammals. Of particular interest to our discussion are the Mel_{1a} and Mel_{1b} receptors, which are now referred to as the MT_1 and MT_2 receptors, respectively. These receptors are classic G-protein-linked receptors that inhibit adenylate cyclase. Additionally, MT_1 receptors activate protein kinase C-β, whereas MT_2 receptors inhibit the soluble guanylate cyclase pathway [37] while stimulating protein kinase C [21,38]. MT_1 receptors have the most widespread distribution in the rodent brain, account for the majority of melatonin-binding sites in most target tissues, and are widely believed to account for many melatonin actions in the brain [20]. Both MT_1 and MT_2 subtypes of the ML_1 receptor appear to have roles in regulating the SCN circadian clock (see later) [38].

The ML_2 (also named MT_3) receptor was poorly characterized and enigmatic until a recent study identified it as a form of quinone reductase [39]. This enzyme is widely distributed in different tissues and across different species [40]. The importance of melatonin-binding to this enzyme is unclear. Specific melatonin agonists are becoming available, which lack binding to the MT_3/quinone reductase receptor [36,41,42]; these agents will help to isolate the specific effects mediated by the high-affinity melatonin receptors, and may become important options for pharmacologic treatment of insomnia or CRSDs without the potential for side effects from interactions with the MT_3/quinone reductase binding site (see Section 4).

2.2. Control of melatonin release

As with most other circadian rhythms, the circadian pattern of melatonin release is controlled by the SCN. The primary source of melatonin is the pineal gland, which secretes the hormone into the cerebrospinal fluid and circulation. Some melatonin is also generated in the retina, but this source is thought not to contribute to circulating levels [43]. The SCN controls pineal melatonin release through a multi-synaptic pathway, the final link of which is

a noradrenergic synapse from the superior cervical ganglion to the pineal gland [44]. The projections from the superior cervical ganglion release norepinephrine onto pinealocytes during the night. Norepinephrine, acting mostly through β_1 adrenergic receptors, increases intracellular cAMP levels in the pinealocytes leading to an increase in synthesis of melatonin [45,46]. Indeed, it has been shown that the final enzyme in the synthetic pathway for melatonin (*N*-acetyltransferase) is expressed in pinealocytes in a circadian fashion; that rhythm is abolished by lesions of the SCN [47].

Several neurotransmitters—and drugs that interact with neurotransmitter systems—modify melatonin synthesis in the pineal gland; such agents include α_2-adrenoceptor agonists [48], β-adrenoceptor antagonists [49], and benzodiazepines acting through GABA receptors [50]. Nocturnal exposure to bright light immediately and acutely suppresses melatonin secretion via degradation of pineal *N*-acetyltransferase [52,53]. The signal by which light mediates this regulation is transmitted from the retina through the SCN to the pineal.

In the absence of environmental signals such as light input from the retina, the SCN maintains a circadian rhythm with a period either slightly shorter or longer than 24 h (i.e. about a day or 'circa diem'). Under such conditions, the organism is said to be free-running, and the rest-activity/sleep–wake cycles will gradually become out of phase with the 24-h day/night cycle. When the organism is exposed to normal daylight cycles, the circadian rhythm is entrained to the 24-h cycle of the sun. Such entrainment is mediated, in large part, by light signals received by the retina and relayed to the SCN through the retino-hypothalamic tract [7]. This pathway is activated by melanopsin-containing photoreceptors in the ganglion cell layer of the retina [53,54]. Unlike the visual pathways of the eye and brain, which are concerned with image formation and processing, the retinohypothalmic pathway is dedicated to transmitting information about the presence and intensity of light.

Nocturnal exposure to light has been shown to affect the expression of specific genes in the SCN known as clock genes, such as period (*per*) [55,56]. The level of per expression within cells of the SCN determines the phase of the circadian clock. Thus, exposure to bright light in the evening causes a phase delay in the circadian clock, whereas similar exposure in the late night causes a phase advance [56]. Because the SCN clock controls pineal melatonin release, such phase shifts will be manifest as changes in the timing of melatonin secretion. Indeed, the level of circulating melatonin is one of the most reliable measures of the phase of the circadian clock in humans [2,30].

2.3. Effects of melatonin on the circadian clock

As mentioned earlier, melatonin receptors are expressed in specific nuclei in the brain, including the SCN. Interestingly, while the SCN clearly controls the timing of the melatonin rhythm, melatonin exerts reciprocal effects on the SCN. For example, in rats maintained in constant darkness, exogenous melatonin entrained the activity cycle [17]. The direct effects of melatonin on the SCN have been examined using an isolated brain slice preparation, in which the circadian clock continues to cycle for several days [18]. In this preparation, application of melatonin at times corresponding to dusk or dawn caused phase shifts in the circadian rhythm of electrical activity recorded from SCN neurons. Melatonin applied at other times had little or no effect on the SCN clock [21].

Later studies extended this work and described two distinct effects of melatonin on SCN neurons: acute inhibition of electrical activity and phase-shifting of the clock [20]. Transgenic mice with disrupted MT_1 receptors were used to study the role of MT_1 versus MT_2 receptors in these effects. In SCN neurons from mice lacking MT_1 receptors, melatonin failed to acutely inhibit electrical activity as it does in normal mice, but the phase-shifting effects of melatonin were largely intact. Other experiments, using pharmacological or transgenic approaches, further support the importance of MT_2 receptors in the phase-shifting effects of melatonin on the SCN clock [37,38,57,58]. For example, transgenic mice with a disruption in the MT_2 gene exhibited no evidence that the circadian clock was sensitive to melatonin, although melatonin still elicited acute inhibition of SCN neurons [57].

The receptor specificity for phase-shifting and acute inhibitory effects of melatonin may vary across species. For example, a species of hamster that naturally lacks MT_2 receptors still exhibits circadian rhythms, and the rhythm phase-advances in response to exogenous melatonin [59]. In general, however, the results from various animal studies suggest that the MT_1 and MT_2 receptors have distinct functional roles in the SCN, albeit with some overlapping function. These distinct roles provide great potential for receptor-specific pharmacological agents to affect specific aspects of the sleep–wake cycle and/or circadian rhythmicity.

The distinct functional roles of MT_1 and MT_2 receptors may provide the opportunity to develop specific agents that promote sleep without phase-shifting the circadian clock, or the converse. Ligands that are highly selective for one subtype (MT_1 or MT_2) of receptor have become available in recent years, but are still the subject of structure–activity studies [41,58,60–63]. Progress in the development of such compounds will lead to a much greater understanding of the distinctive roles of the melatonin receptor subtypes. Furthermore, such compounds hold promise as potentially useful for treating sleep disorders or CRSDs. At this time, these agents require further study in experimental systems before their efficacy in humans can be assessed.

2.4. Circadian cycle of melatonin sensitivity

Melatonin receptors in the SCN are not expressed at constant levels. Several studies in different mammalian

species have reported that receptor protein and mRNA levels in the SCN vary on a circadian basis, and that expression levels are influenced by light and melatonin [64–68]. In general, levels of MT_1 receptors are low during the subjective day and highest during the subjective night, when melatonin secretion is also peaking. The implications of these findings for pharmacological use of melatonin are not clear. For example, exogenous melatonin is known to promote sedation in humans when administered during the day [69,70], at a time when SCN melatonin receptor levels are expected to be low. If the sedative properties of exogenous melatonin are mediated by the SCN, these findings suggest that exogenous melatonin is able to activate the small number of receptors present in the SCN during the day. Alternatively, the sedative effects of melatonin may be mediated by other brain centers regulating sleep, or perhaps even sites in the peripheral circulation involved in regulation of core body temperature [5,24,71,72].

3. Melatonin for insomnia and circadian rhythm sleep disorders

3.1. Sleep in healthy subjects

In humans, as in other animals, circulating levels of melatonin are highest during the night [73]. Furthermore, electrophysiological studies have found that the timing of highest urinary excretion of 6-sulfatoxymelatonin (a reliable indicator of melatonin levels in the general circulation) is correlated with the greatest increase in nocturnal sleepiness [72]. Such studies have engendered great interest in the potential for use of exogenous melatonin as a sleep-promoting agent.

Melatonin is not required for sleep in humans. For example, patients who have had their pineal gland removed for medical reasons often experience little disturbance in their sleep–wake cycle [2]. Nevertheless, several studies have examined the ability of exogenous melatonin to promote sleep in humans, often with conflicting results [28,74–80]. Here we focus on the mechanisms that may underlie the differential effects of melatonin on the sleep–wake cycle.

In healthy human subjects, administration of 0.3 or 1 mg of melatonin in the early evening was associated with reduced sleep latency and improved sleep efficiency [23,81]. Another study, which used EEG to monitor sleep parameters, found no effect of 5 mg melatonin on normal sleep [82]. Overall, melatonin has had variable efficacy when studied as a hypnotic agent [75]. There are several possible explanations for this variability.

One possible explanation is that the sedative or hypnotic effects of melatonin are dependent on the time of day, or the phase of the circadian rhythm. For example, the hypnotic effects of melatonin in humans vary depending on the time of administration [70], consistent with the circadian phase-resetting properties of melatonin, which also depend on time of administration [17,18,21,27]. A recent, well-controlled study in healthy human volunteers compared the effects of melatonin on nocturnal sleep (melatonin administered at 23:30 h) with its effects on evening sleep (melatonin administered at 18:00 h) [22]. The two times of administration were examined in separate, double-blind, placebo-controlled studies that also involved administration of temazepam as a positive control using a crossover design. Patients were monitored by EEG, measurement of core body temperature, and testing of cognitive performance after awakening. Melatonin administered at night (23:30) had no significant effect on nighttime sleep in healthy individuals. In contrast, melatonin administered in the early evening (18:00) had hypnotic activity similar to temazepam.

Other studies have concluded that 'physiologic' doses of melatonin have little or no effect on nighttime sleep in healthy individuals, but that high 'pharmacologic' doses can have hypnotic activity [24]. It is widely believed that the lack of effect of exogenous melatonin on nighttime sleep is a result of high levels of endogenous melatonin–melatonin receptors in the SCN may already be exposed to saturating concentrations of the endogenous hormone. This hypothesis has not been thoroughly tested. Furthermore, so-called 'physiologic' concentrations are often based on levels found in the general circulation. However, studies in sheep have suggested that melatonin levels in the cerebrospinal fluid (CSF) from the third ventricle may be as much as 20-fold higher than levels in the general circulation [83]. Thus, when administering melatonin by the oral route, high doses may be needed to influence the levels of melatonin perfusing the relevant brain structures, such as the SCN. Alternatively, a lower dose of a melatonin receptor agonist with improved solubility, bioavailability, or transport properties may be able to act on brain melatonin receptors to influence sleep propensity at nighttime, even in healthy individuals with normal levels of endogenous melatonin.

Another difficulty associated with pharmacologic use of exogenous melatonin is that serum levels vary widely among individuals [31]. Such variability can have a detrimental effect on clinical trials, introducing variability that obscures potential efficacy. Improved agents with better absorption and lower first-pass metabolism are likely to improve the consistency of clinical trials and may prove more efficacious than melatonin itself.

An ideal hypnotic agent will increase total sleep time and sleep efficiency, in addition to reducing sleep latency. While some studies have reported that exogenous melatonin improves sleep efficiency, this effect is not consistently observed [75]. The lack of effect on sleep efficiency or total sleep time may not be surprising given the short half-life of melatonin in the circulation (less than 1 h) [31]. An agent with a longer half-life may have a better opportunity to activate brain melatonin receptors and influence sleep properties long enough to improve sleep efficiency and total sleep time. Indeed, accumulating evidence supports

the concept that melatonin participates in the consolidation of sleep into prolonged nighttime episodes [5]. And, it has been suggested that a continuous delivery system for melatonin may be beneficial for some patients with impaired sleep efficiency or sleep consolidation [5]. A longer-acting melatonin receptor agonist may be a viable alternative.

It has also been suggested that methodological differences in monitoring the sleep–wake cycle may underlie some of the conflicting data regarding the effects of melatonin on sleep. While the gold standard for monitoring sleep is the use of EEG/EMG recordings to monitor brain state and sleep stages, the use of actigraphy for monitoring movement to define sleep–wake activity is often used as an easy and reliable substitute. It has been hypothesized that melatonin may act as a muscle relaxant, reducing body movements, thereby leading to more sleep as defined by actigraphy measurements [84]. Indeed, this proposed effect of melatonin may underlie its soporific effects.

3.2. Sleep in subjects with insomnia

Several studies have examined the use of melatonin for elderly or medically ill patients with insomnia [85–89]. Melatonin levels decline as an individual ages [90–93], and it has been suggested that sleep disruption in the elderly is related to declining melatonin levels. Others have argued, however, that much of the decline in melatonin secretion occurs during adolescence [94] and that there is little additional decline during adulthood in healthy individuals [95]. However, some brain degenerative diseases, particularly Alzheimer's disease, are associated with markedly low levels of melatonin [96–98]. Many of these patients experience insomnia or other disturbances associated with the sleep–wake cycle, such as 'sundowning' syndrome [74,99,100]. Several small studies have shown beneficial effects associated with use of melatonin in such patients [101–104].

Insomnia is a common complaint in elderly populations; the most common therapies prescribed for these patients are benzodiazepines or benzodiazepine agonists. Long-term use of benzodiazepines is not recommended because of concerns about the potential for dependence or abuse. Unfortunately, many elderly patients experience difficulty discontinuing benzodiazepine hypnotics. Melatonin has been studied as an agent to help reduce or eliminate the use of benzodiazepines among these patients [105]. This study found that elderly patients with insomnia who received controlled-release melatonin were significantly more likely to successfully discontinue benzodiazepines in comparison to those receiving placebo.

3.3. Circadian rhythm sleep disorders

Melatonin has also been proposed and studied as a treatment for CRSDs, or for treatment of conditions associated with misalignment of activity rhythms with the light–dark cycle, such as shift work and jet lag. The rationale for these studies comes from observations that exogenous melatonin can entrain or phase-shift circadian rhythms under appropriate circumstances [29,30,106–110]. However, because circadian rhythms can also be entrained by light and other environmental signals, the effects of melatonin can be obscured. The phase-shifting effects of melatonin can be observed only at certain phases of the circadian cycle, nearly 12 h out of phase from the phase-shifting effects of light [111]. Light also affects endogenous melatonin secretion [51], as does posture [106]. All these influences on the circadian cycle, and on melatonin secretion, have made it difficult to fully understand melatonin's ability to phase-shift human circadian rhythms.

Perhaps the clearest examples of the effects of melatonin on circadian rhythmicity have come from studies of exogenous melatonin administered to blind individuals, especially those with no perception of light. Such individuals often experience free-running rhythms of endogenous melatonin secretion, and concomitant sleep disturbances because their activity rhythms are at times out of phase with social cues for sleeping and wakefulness [112–115]. In many instances, exogenous melatonin is able to stably entrain the sleep–wake cycle of these individuals to a 24-h cycle [113,116–118].

Several studies have also examined the use of melatonin for shift workers or for jet lag [119–121]. In two placebo-controlled studies simulating shift work, subjects receiving melatonin exhibited significantly better adaptation to a phase shift in the light–dark cycle as compared to those receiving placebo [122,123]. Such adaptation included modest improvements in ability to sleep during the day [123] and shifts in circadian rhythms of endogenous melatonin and core body temperature [122]. A systematic review of melatonin for jet lag has concluded that melatonin may be useful for minimizing effects of the phase shift imposed by flights across many time zones [124].

As with treatment of insomnia, a melatonin receptor agonist with enhanced pharmacological properties may be more effective than exogenous melatonin for phase-shifting human circadian rhythms, and may lead to more reliable results from clinical trials. As discussed earlier, a melatonin receptor agonist with a longer half-life may be more suitable for promoting sleep. However, for inducing phase shifts or for maintaining circadian phase, the situation is more complex. Indeed, there is evidence that a short-acting agonist may be more effective for inducing phase shifts. For example, multiple doses of melatonin are often less effective for inducing phase shifts in comparison to a single dose administered early in the subjective night [29,125,126]. These results are likely a consequence of the phase-response curve for the phase-shifting effects of melatonin. Long-acting melatonin, or a long-acting agonist, may be active during both phase-advance and phase-delay portions of the phase-response curve, thereby canceling or weakening any

phase-shifting effects. These issues will need to be resolved before melatonin agonists become useful and reliable for inducing circadian phase shifts.

4. Melatonin receptor agonists

In mechanistic and preclinical studies, melatonin has shown much potential for treatment of sleep disturbances and CRSDs. Unfortunately, that potential has been difficult to realize in clinical studies, owing to some of the physical, biological, and pharmacokinetic properties of melatonin we have discussed, as well as the relative lack of large-scale clinical trials partially owing to the fact that melatonin cannot be patented. In an effort to take advantage of the biological actions of melatonin for treatment of sleep disturbances in humans, several groups have developed melatonin analogs that act as agonists or antagonists at melatonin receptors. In general, the melatonin receptor agonists have so far shown the greatest potential for clinical usefulness. Here we discuss three of the more prominent examples of melatonin receptor agonists that are furthest along in clinical development.

4.1. Agomelatine (S20098); developed by Servier

Agomelatine is a napthalenic analog of melatonin that is a high-affinity agonist at MT_1 and MT_2 receptors [42]. In terms of published studies in animal models, it is the most thoroughly characterized melatonin receptor agonist to date. However, agomelatine is an antagonist at 5-HT_{2C} and 5-HT_{2B} receptors [127]. This action has been shown to be associated with changes in dopaminergic and adrenergic pathways in the frontal cortex of rats [127]. Owing to its unique pharmacologic profile, agomelatine is being developed for treatment of anxiety disorders and depression [128,129]. In addition, experiments performed with this agent have provided valuable information about the actions of melatonin receptor agonists.

Agomelatine has effects on electrical activity of SCN neurons that are similar to those of melatonin [130]. In addition, in a manner that mimics the effects of melatonin, agomelatine is able to facilitate re-entrainment of circadian rhythms in response to a phase shift in the light–dark cycle [131–133]. Importantly for its implications to human studies, this effect of agomelatine has been observed in diurnal species [132]. In addition, like melatonin, agomelatine is able to entrain the free-running circadian rhythms of rats maintained in constant darkness; this effect is abolished by lesions of the SCN but not by pinealectomy [134]. Overall, experiments with agomelatine establish that a selective melatonin receptor agonist can mimic the regulatory effects of melatonin on circadian rhythms.

In most cases, the effects of agomelatine on sleep and circadian rhythms have been attributed to its agonist activity at melatonin receptors. Nevertheless, agomelatine has other effects in the CNS attributable to antagonism at 5-HT receptors. The agent is currently in phase I clinical trials for treatment of anxiety disorders and depression.

4.2. Ramelteon (TAK-375); developed by Takeda

Ramelteon is an indenofuran derivative that has high selectivity and high affinity for MT_1 and MT_2 receptors [135,136]. It has a longer half-life than melatonin in humans [137], and thus may have superior properties as a sleep-promoting agent. Unlike agomelatine, ramelteon exhibited no binding to any of a large number of receptors or potential binding sites in receptor-binding studies [138]. Although a metabolite of ramelteon did exhibit some binding to 5-HT_{2B} receptors, this interaction occurred with such low affinity that it is unlikely to influence pharmacologic use of this agent.

Ramelteon has been studied in animal models of insomnia as well as CRSDs. The agent promotes sleep in freely moving monkeys [135] and cats [36]. In addition, like agomelatine and melatonin, it is able to enhance the rate of re-entrainment in response to a shift in the light/dark cycle in rats [139]. The effects of ramelteon are associated with very little impairment of cognitive or motor performance, and there is no evidence that the drug has rewarding properties that could lead to dependence [139].

In early-stage clinical studies, ramelteon has shown promise in patients exposed to the first-night effect model of transient insomnia and in patients with chronic insomnia [140,141]. It is currently in phase III studies for insomnia and circadian rhythm sleep disorders.

4.3. LY 156735; developed by Eli Lilly

LY 156735 is a β-substituted analog of melatonin that was developed to have a higher potency than the parent compound [142]. In addition, LY 156735 is reported to have a better pharmacokinetic profile in comparison to melatonin. For example, when administered orally LY 156735 is reported to have a bioavailability that is nearly an order of magnitude higher than melatonin, and an area under the curve that was about 6-fold higher than melatonin [143].

In early-stage clinical studies, LY 156735 reduced sleep onset time in patients with moderate sleep-onset insomnia [144]. Interestingly, the agent had little effect on sleep latency in healthy volunteers when administered at bedtime [145]. In contrast to melatonin, it did not lower core body temperature when administered during daytime [145]. LY 156735 was administered to healthy volunteers in a study of its ability to improve adaptation to a phase-advance in the light–dark cycle [143]. Subjects were housed in a temporal isolation unit and exposed to a phase-advance of 9 h. One of two doses of LY 156735 (5 or 0.5 mg) or placebo was administered at times just preceding lights-out of the post-phase-advance schedule. Subjects adapted to the phase shift significantly faster when receiving the high dose of

the study drug as compared to the low dose or placebo [143]. LY 156735 is still in early stages of clinical development.

5. Conclusion

The melatonin system has a well-established role in regulating the circadian clock and the rhythms the clock controls. In pre-clinical studies, melatonin has shown great promise for treatment of insomnia or CRSDs. However, the physicochemical and pharmacokinetic properties of melatonin have slowed realization of that potential. The development of selective melatonin agonists with improved properties has enhanced the prospects of manipulating the melatonin system to treat patients with a range of sleep disorders.

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