

## Melatonin and Its Receptors: A New Class of Sleep-Promoting Agents

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Melatonin plays a crucial role in the synchronization of internal biological events to external environmental cues. Its rhythmic secretion by the pineal gland is regulated by the suprachiasmatic nucleus (SCN) of the anterior hypothalamus, with the light-dark cycle being the main synchronizer. Melatonin secretion is stimulated by darkness and inhibited by light, and in coordination with the SCN, it is centrally involved in maintaining circadian rhythmicity and regulating sleep. The SCN regulates the timing of melatonin release, while melatonin feeds back to the SCN to decrease SCN neuronal firing. This process is controlled by two high-affinity melatonin (MT) receptors located in the SCN: MT<sub>1</sub> and MT<sub>2</sub>.

The ability of melatonin to entrain, or synchronize, the circadian clock by its direct action on the SCN has led to the investigation of melatonin as a remedy for treating disordered circadian rhythms that occur in jet lag, shift work, and certain types of insomnia. However, results on its effectiveness have not been conclusive. Ramelteon is a selective agonist at the MT<sub>1</sub> and MT<sub>2</sub> receptors and is approved by the US Food and Drug Administration (FDA) for the treatment of insomnia. Other melatonin receptor agonists that are currently being investigated for the treatment of sleep disorders include agomelatine: a high-affinity MT<sub>1</sub> and MT<sub>2</sub> receptor agonist; VEC-162; and LY 156735, a melatonin analog.

### CIRCADIAN AND HOMEOSTATIC REGULATION OF SLEEP

#### The Circadian Clock – The Suprachiasmatic Nucleus (SCN)

In many living organisms, the main physiological functions such as core body temperature, hormone production, heart rate, and blood pressure fluctuate in cycles lasting approximately 24 hours, also referred to as circadian rhythms. The sleep-wake cycle is the most widely recognized circadian rhythm in humans. These

cycles range from minutes (eg, stages of sleep) to days (eg, the menstrual cycle) and are governed by a biological “clock,” an internal timekeeping system, located in the SCN of the hypothalamus that ensures that specific internal temporal changes take place in coordination with one another. The internal circadian clock is in turn synchronized with, or entrained to, the environmental light-dark cycle by external time cues, such as variations in intensity of light.<sup>1</sup> Circadian rhythms ensure that certain functions are held in conformity with environmental needs so that maximal adaptation occurs to the environment; these functions include reproduction, hibernation, and migration. Disturbances in circadian rhythms in humans, such as jet lag or shift work sleep disorder, can have a negative impact on safety, performance, and productivity.<sup>2</sup>

For most mammals, the light-dark cycle is the major synchronizing stimulus for regulating the expression of 24-hour rhythms at the behavioral, physiological, and biochemical levels.<sup>3</sup> In humans, the free-running (“endogenous”) daily circadian cycle is greater than 24 hours. The environmental light-dark cycle provides an accurate measurement of environmental time for the SCN “master” clock which, in turn, resets the human daily cycle each day so that it is in conformity with the 24-hour rhythm.<sup>4</sup> The circadian rhythm of sleep and wakefulness is dependent on both positive and negative feedback mechanisms regulating the genetic transcription of a number of core circadian clock genes located within the SCN neurons. Polymorphisms in three of these genes, *Clock*, *Per2*, and *Per3*, have been shown to cause variations in the circadian clock gene mechanism and have been implicated in certain human sleep disorders.<sup>5,6</sup> These genes and their encoded proteins are responsible for setting the length of periods of activity and inactivity within cells that regulate various physiological processes throughout the body.

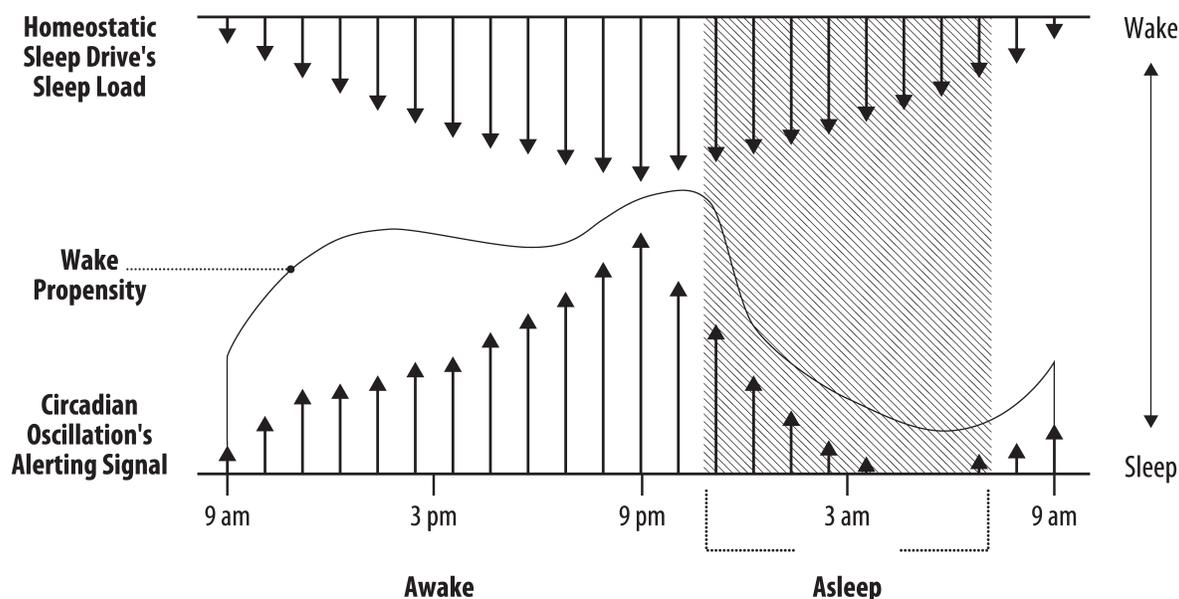
#### Homeostatic and Circadian Regulation of Sleep

The physiologic drive to obtain the required amount of sleep is homeostatically regulated.<sup>7</sup> Therefore, as the day progresses, the need, or “pressure,” for sleep accumulates during wakefulness and dissipates during sleep (Figure 1). The pressure for sleep is opposed, however, by the circadian process, which is regulated by the SCN. The latter process promotes wakefulness by transmitting stimulatory signals throughout the central nervous system from the SCN. During the wake period, these alerting signals are dominant, reaching a peak about 2-3 hours before one’s habitual bedtime and serving to offset the homeostatic drive for sleep that accumulates during waking hours. During the evening, this alert-

#### Disclosure Statement

Dr. Doghramji has served on the advisory board of Ortho McNeil; has participated in speaking engagements for Boehringer Ingelheim, King, Sanofi-Aventis, Sepracor, and Takeda Pharmaceuticals; and has consulted for BMS, Neurocrine Biosciences, Ortho McNeil, Sanofi-Aventis, Takeda Pharmaceuticals and Pifzer.

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**Figure 1**—Circadian and Homeostatic Regulation of Sleep. Adapted with permission from Kiduff and Kushida<sup>75</sup> and Edgar et al.<sup>8</sup> The circadian cycle and the homeostatic drive interact to produce sleep and wakefulness at the appropriate times. The need for sleep (ie, sleep load) accumulates during wakefulness and dissipates during sleep.

ing signal is diminished, in part, via increased melatonin levels, eventually allowing sleep to occur.<sup>8</sup> Sleep deprivation prolongs the hours spent awake, during which the homeostatic sleep drive continues to intensify as sleep debt builds which, in turn, results in prolonged sleep on the subsequent night's sleep opportunity.<sup>4</sup> There are a number of other factors that affect sleep homeostatic drive, including neuromodulators such as adenosine. Adenosine levels accumulate in the brain during wakefulness periods, eventually activating sleep-promoting neurons and inhibiting neurons promoting wakefulness.<sup>9</sup>

## MELATONIN AND ITS RECEPTORS

### Melatonin and the Sleep-Wake Cycle

Melatonin (N-acetyl-5-methoxytryptamine), the primary neurohormone of the pineal gland, plays a fundamental role in circadian rhythmicity.<sup>10</sup> The master clock is reset by the transmission of photic information from the retina to the pineal gland through the SCN (Figure 2). Photoreceptors in the eye are connected through a retinohypothalamic tract (RHT) to the SCN.<sup>3,9</sup> Ambient light stimulates ganglion cells in the retina, resulting in the transfer of neural signals into the anterior hypothalamus and SCN. The SCN relays retinal information to the pineal gland via a multisynaptic pathway with connections being made sequentially to the paraventricular nuclei of the hypothalamus, the preganglionic sympathetic neurons in the upper thoracic cord, the superior cervical ganglia, and finally to the pineal gland<sup>1</sup> where norepinephrine release stimulates the rate-limiting steps in melatonin synthesis.<sup>11</sup> In vertebrates, melatonin synthesis and release are stimulated by darkness and inhibited by light. In humans, the nocturnal rise of melatonin begins after the onset of darkness, peaks in the middle of the sleep period (between 2 and 4 a.m.), and gradually falls during the second half of the night.<sup>12</sup>

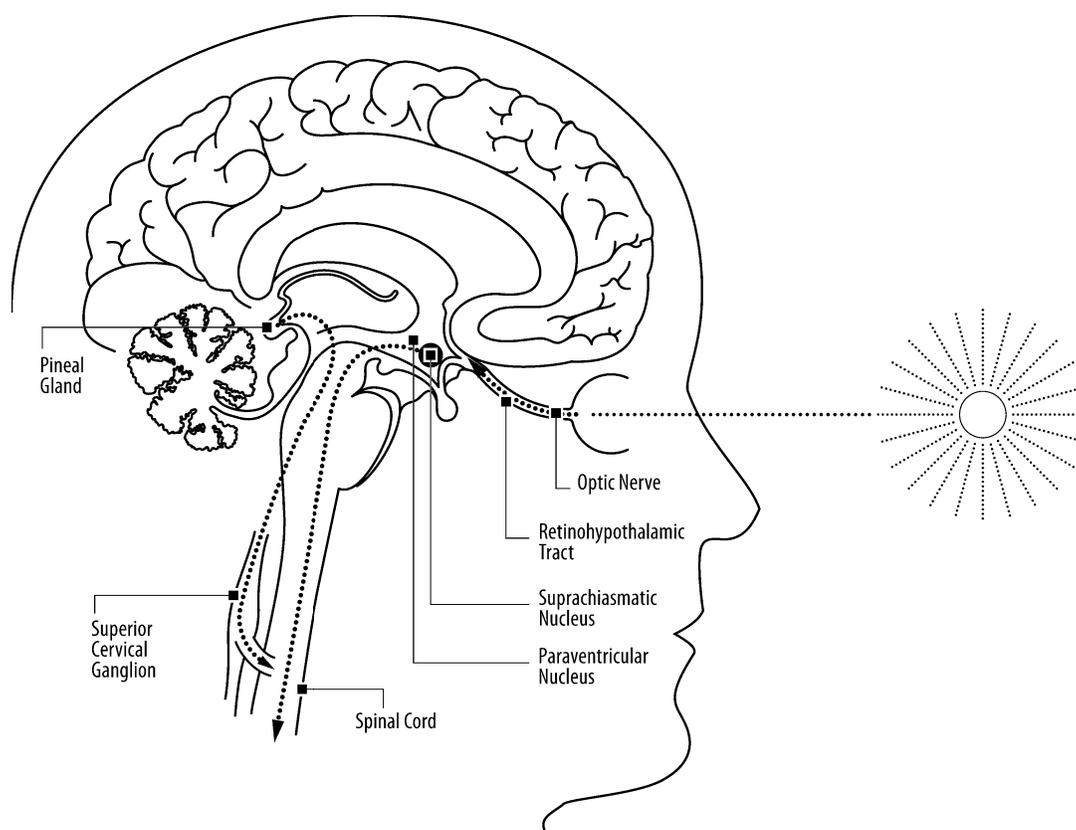
The daily rhythm of melatonin secretion is dictated by signals originating in the SCN and parallels the daily cycle of light and darkness.<sup>13,14</sup> In humans, melatonin shifts endogenous circadian

rhythms according to a phase-response curve that is nearly opposite in phase to that of light exposure.<sup>15</sup> Endogenous circadian rhythms can be delayed with melatonin treatment in the morning and advanced with treatment in the evening.<sup>16</sup> Therefore, melatonin reinforces the entraining effects of the photoperiod and acts as a darkness signal, providing feedback to the SCN circadian pacemaker, thereby facilitating the synchronization of circadian rhythms.

In addition to its rhythm-synchronizing actions, melatonin may have sleep-promoting or soporific properties, for which it has been extensively studied.<sup>17</sup> Melatonin has been found to induce sedation and lower core body temperature.<sup>18-22</sup> It is thought that the endogenous cycle of melatonin is involved in the regulation of the sleep-wake cycle by muting the SCN-alerting signals, or wakefulness-producing mechanisms.<sup>23</sup> In this capacity, increased night-time melatonin levels allow the homeostatic drive to remain unopposed, resulting in sleep onset. Therefore, melatonin not only plays a role in communication between the environmental light-dark cycle and the circadian-generating mechanisms, but may also play a role in the mediation between the circadian pacemaker and sleep-wake behavior.<sup>23</sup>

### SCN Melatonin Receptors and Sleep-Wake Regulation

The physiological actions of melatonin are mediated by two G-protein coupled membrane receptors,  $MT_1$ <sup>24</sup> and  $MT_2$ ,<sup>25</sup> and the  $MT_3$  binding site,<sup>26</sup> which belongs to the family of the quinone reductases. The majority of the high-affinity  $MT_1$  and  $MT_2$  receptors are expressed in the SCN and have distinct functional roles in sleep regulation. Activation of the  $MT_1$  receptor suppresses neuronal firing rate in the SCN, while  $MT_2$  acts mainly by inducing circadian rhythm phase shifts.<sup>27</sup> Both  $MT_1$  and  $MT_2$  receptors are also expressed in peripheral organs and cells and contribute to other physiological functions. In animals, activation of  $MT_1$  receptors inhibits prolactin secretion from the pars tuberalis,<sup>28</sup> regulates *Per1* gene expression<sup>27</sup> in the anterior pituitary, and mediates vasoconstriction in cerebral and peripheral arteries.<sup>27</sup>



**Figure 2**—Melatonin Physiology. Melatonin synthesis and release by the pineal gland are inhibited by light and stimulated by darkness. Neural signals from stimulated ganglion cells are transferred to the anterior hypothalamus and SCN via the retinohypothalamic tract (RHT), then to the superior cervical ganglion, and finally to the pineal gland.

MT<sub>2</sub> receptors are involved in retinal physiology, vasodilation, inhibition of dopamine release in the retina, as well as enhancement of splenocyte proliferation.<sup>27</sup> MT<sub>3</sub> binding sites are widely distributed in the brain, liver, heart, kidneys, and lungs.<sup>26,27</sup> Recent findings from animal studies suggest possible roles in the regulation of intraocular pressure<sup>29</sup> and in inflammatory responses in the microvasculature.<sup>30</sup>

Evidence for the distinct roles of MT<sub>1</sub> and MT<sub>2</sub> receptors in sleep-wake regulation comes from studies in MT<sub>1</sub>- and MT<sub>2</sub>-receptor-deficient transgenic mice. In SCN slices from mice lacking MT<sub>1</sub> receptors, melatonin failed to acutely inhibit neuronal firing, but its phase-shifting effects remained intact.<sup>31</sup> In contrast, mice with targeted disruption of the MT<sub>2</sub> receptor had no obvious circadian phenotype; however, melatonin suppressed neuronal firing in the SCN as effectively as in wild-type controls.<sup>32</sup> Additionally, pharmacological studies support the phase-shifting effect of melatonin on circadian rhythms. Using *in situ* hybridization, selective MT<sub>2</sub> receptor antagonists blocked melatonin-mediated phase advances of circadian rhythms.<sup>33</sup> These distinct roles of the MT<sub>1</sub> and MT<sub>2</sub> receptor subtypes provide great prospects for subtype-selective pharmacological agents affecting distinct aspects of the sleep-wake cycle and other endogenous circadian rhythms.

### Melatonin – Clinical Efficacy and Safety

Because of its circadian phase-modulating and hypnotic/soporific effects, exogenously administered melatonin has been studied as a potential treatment for: (1) circadian rhythm sleep disorders, conditions associated with misalignment of sleep-wakefulness rhythms from the light-dark cycle (eg, shift work, jet lag); and

(2) insomnia. According to the FDA, melatonin, a neurohormone, is classified as a dietary supplement. Following administration, melatonin has a short half-life (0.5 to 5.6 minutes)<sup>34</sup> and its effects are short lived.<sup>35</sup> Melatonin products vary from fast-release to sustained-release formulations. Dosages used in clinical trials have ranged widely, with typical dosages in the 0.1 to 10 mg range, administered 30 minutes to 2 hours before bedtime.

Despite extensive research, results from clinical studies have been conflicting, and the usefulness of melatonin for the treatment of sleep disorders remains controversial. Discrepancies in sleep outcomes between trials may be due to differences in physical, biological, and pharmacokinetic properties of exogenous melatonin utilized in these trials. Variations have been described in the purity of commercially available melatonin formulations.<sup>36</sup> Studies have also utilized variable methodologies regarding timing, frequency, and duration of melatonin administration.<sup>17, 37</sup> Adding to this complexity, clinical studies evaluating the efficacy of melatonin have not used consistent inclusion and exclusion criteria and outcome measures to evaluate insomnia.

Several meta-analyses and systematic reviews have evaluated the efficacy and safety of melatonin in the management of primary sleep disorders. In these studies, clinical efficacy was measured on such outcomes as sleep onset latency (time period measured from “lights out,” or bedtime, to the onset of sleep), sleep efficiency (ratio of total sleep time to time in bed), as well as alertness, mood, and performance.<sup>37</sup> A meta-analysis of 139 published studies conducted by the Agency of Healthcare Research and Quality (AHRQ) concluded that melatonin is not effective in treating most primary sleep disorders with short-term use, although there is some evidence to suggest that melatonin is ef-

fective in treating delayed sleep phase syndrome with short-term use. It also indicated that melatonin is not effective in treating most secondary sleep disorders with short-term use, and that data were lacking to support its efficacy in alleviating the sleep disturbance aspect of jet lag and shift-work disorder. Nevertheless, it also indicated that melatonin is safe with short-term use.<sup>37</sup> A more recent meta-analysis of 14 randomized controlled trials (N=279) concluded that melatonin reduced sleep onset latency to a greater extent in delayed sleep phase syndrome than in other forms of insomnia.<sup>38</sup> In contrast, another meta-analysis using 17 published studies (N=284), which comprised heterogeneous populations of normal healthy volunteers, insomniacs, and individuals with various psychiatric conditions, concluded that melatonin is effective in increasing sleep efficiency and decreasing sleep onset latency.<sup>39</sup>

No serious side effects have been associated with melatonin administration; however, adverse effects have not been well investigated in long-term use. The most common adverse events accompanying short-term (3 months or less) melatonin administration in clinical trials were headaches, dizziness, nausea, and drowsiness; however, no significant differences were observed between placebo and melatonin.<sup>38</sup> High doses of melatonin may lead to a daytime “hangover” or headache and prolonged use at high doses can lead to suppression of ovulation by decreasing the mid-cycle surge of luteinizing hormone.<sup>40</sup>

## MELATONIN RECEPTOR AGONISTS

It has been suggested that the lack of consistency in efficacy of melatonin in treating insomnia and circadian rhythm sleep disorders may be due to its pharmacological properties, including short half-life, high first-pass metabolism, and binding to multiple melatonin receptors. Therefore, melatonin analogs that act as agonists or antagonists with increased selectivity for MT<sub>1</sub> and MT<sub>2</sub> receptors have been examined as pharmacological agents for the treatment of insomnia and CRSDs.

### Ramelteon

Ramelteon, approved in 2005 by the FDA for the treatment of insomnia characterized by difficulty with sleep onset, is a selective MT<sub>1</sub>/MT<sub>2</sub> receptor agonist and is the first in this class of insomnia therapies to be introduced. Results from *in vitro* studies showed that the selectivity of ramelteon for MT<sub>1</sub>/MT<sub>2</sub> receptors over MT<sub>3</sub> binding sites is 1000-fold greater than that of melatonin.<sup>41</sup> Ramelteon exhibits linear pharmacokinetics and is rapidly absorbed, reaching mean peak plasma concentrations less than 1 hour after oral administration.<sup>42-44</sup> Due to extensive first-pass metabolism, its bioavailability is less than 2% following a single oral dose (16 mg).<sup>45,46</sup> The major metabolite, M-II, shows weak MT<sub>1</sub>/MT<sub>2</sub> agonist activity compared with ramelteon *in vitro* and has a half-life of 2 to 5 hours.<sup>43</sup> The mean elimination half-life of ramelteon ranges from 0.8 to 2.6 hours.<sup>42-44,47</sup> Ramelteon is indicated for the treatment of insomnia characterized by difficulty with sleep onset. Its recommended dose is 8 mg.<sup>47</sup>

The efficacy of ramelteon in reducing time to sleep onset has been examined in several placebo-controlled studies of patients with chronic primary insomnia. In a randomized, placebo-controlled, five-period crossover study of 107 patients (18-64 years) with DSM-IV<sup>48</sup> primary chronic insomnia,<sup>49</sup> patients were ran-

domized into a dosing sequence of 4, 8, 16 and 32 mg of ramelteon and placebo with a 5- or 12-day washout between each treatment. Each patient underwent five 2-day treatment periods. Each treatment was administered 30 minutes prior to habitual bedtime and sleep variables were assessed via polysomnography (PSG). For every ramelteon dose, the latency to persistent sleep (LPS) was reduced ( $P<0.001$ ) compared to placebo.

A 5-week randomized study of 405 adults with chronic insomnia compared the efficacy of two doses of ramelteon, 8 mg and 16 mg, with placebo.<sup>50</sup> Using PSG, sleep parameters were assessed at weeks 1, 3, and 5. Both ramelteon doses were associated with a reduction in mean LPS at each time point ( $P\leq 0.01$ ). A post-hoc analysis further revealed that a greater percentage of patients treated with ramelteon 8 mg demonstrated at least 50% or greater LPS reduction compared to those treated with placebo (63% vs. 40%,  $P<0.001$ ) at week 1.<sup>51</sup> These results were sustained throughout the study at week 5 (66% vs 48%,  $P<0.005$ ).<sup>51</sup> Ramelteon was also evaluated in older patients (64-93 years) with chronic insomnia in a 5-week randomized, double-blind study.<sup>52</sup> Patients received bedtime medication of ramelteon 4 or 8 mg or placebo nightly for 5 weeks, followed by a 7-day placebo period. Patient-reported sleep data were collected using sleep diaries. Compared to placebo, both doses of ramelteon produced reductions in sleep latency at week 1 ( $P=0.008$ ) and at week 5 (4 mg,  $P=0.028$ ; 8 mg,  $P<0.001$ ).

Clinical trial data show no evidence of next-day residual effects with ramelteon<sup>49</sup> (determined using standard measures and exclusively collected “next morning”) or any rebound insomnia or withdrawal effects following treatment discontinuation.<sup>50,53</sup> The most commonly reported adverse events that differ >2% compared to placebo are somnolence (5% vs 3% for placebo), dizziness (5% vs 3% for placebo), and fatigue (4% vs 2% for placebo).<sup>47</sup> Recently, the FDA has requested that all sedative-hypnotic drug products include product labeling concerning potential risks such as severe allergic reactions and complex sleep-related behaviors, which may include sleep-driving.<sup>54</sup>

Since ramelteon is primarily metabolized via CYP1A2, it should not be used in combination with fluvoxamine.<sup>47</sup> It should also be administered with caution in less strong CYP1A2 inhibitors. Long-term nightly administration of ramelteon has been associated with increases in serum prolactin<sup>55</sup> and reductions in testosterone.<sup>53</sup> Ramelteon treatment was not associated with respiratory depressant effects in 26 patients with mild-to-moderate chronic obstructive pulmonary disease<sup>56</sup> and in 26 patients with mild to moderate obstructive sleep apnea syndrome.<sup>57</sup> However, it has not been studied in severe forms of these disorders. Ramelteon has demonstrated no abuse potential or behavioral impairment at up to 20 times the proposed therapeutic dose.<sup>58</sup>

### Agomelatine

Another selective melatonin agonist that is currently being investigated for the treatment of sleep disorders is agomelatine, which shows a high affinity for MT<sub>1</sub> and MT<sub>2</sub> receptors in the range of melatonin.<sup>59</sup> Additionally, it has affinity for 5-HT<sub>2c</sub> receptors.<sup>59, 60</sup> Antagonism of 5-HT<sub>2c</sub> receptors is reported to be an effective antidepressant in humans.<sup>61</sup> Therefore, agomelatine is currently being developed for treatment of anxiety disorders and depression.

Several preclinical studies have demonstrated that agomelatine has chronobiotic properties similar to those of melatonin in rodent models of sleep-wake phase disorders,<sup>62-65</sup> and therefore,

may have potential use in the treatment of conditions involving disruption of circadian rhythms. Agomelatine resynchronizes experimentally disrupted circadian rhythms in an animal model of delayed-sleep phase syndrome,<sup>65</sup> presumably by its effects on electrical activity of SCN neurons.<sup>66</sup>

In clinical studies, agomelatine resynchronized human circadian rhythms in healthy volunteers<sup>67,68</sup> and improved sleep efficiency in depressed patients.<sup>69,70</sup> A double-blind, placebo crossover study evaluated the phase-shifting capacity and thermoregulatory effects of a single oral administration of melatonin (5 mg) or agomelatine (5 or 100 mg) at 18 hours in 8 healthy young men.<sup>67</sup> Both melatonin and agomelatine induced an earlier onset of the endogenous circadian nocturnal decline in core body temperature. A double-blind, two-period, crossover study of 15 days of daily agomelatine 50 mg or placebo evaluated the phase-shifting of circadian rhythms in 8 healthy elderly men.<sup>68</sup> Following agomelatine administration, phase advances were observed in the 24-hour profiles of body temperature and in cortisol secretion.

Agomelatine was able to relieve sleep complaints of depressed patients in several clinical studies. A double-blind, randomized multicenter trial of 332 patients with major depressive disorder compared the effects of agomelatine 25-50 mg/day and venlafaxine 75-150 mg/day on improving subjective sleep (onset and quality).<sup>69</sup> The subjective sleep onset and sleep quality were evaluated based on the "ease of getting to sleep (GTS)" and "Quality of Sleep (QOS)" items of the Leeds Sleep Evaluation Questionnaire (LSEQ). As early as the end of the first week of treatment, significantly better improvements were observed with agomelatine compared to venlafaxine on LSEQ-GTS items ( $P=0.007$ ) and also on QOS items ( $P=0.015$ ).

In a 42-day pilot study of patients with major depressive disorder ( $N=15$ ), agomelatine 25 mg/day improved sleep continuity and quality.<sup>70</sup> Sleep efficiency increased by 4% (95% CI, 0.03 – 8.69), and the wake after sleep onset decreased from 42 to 19 minutes. Patients reported improvements in sleep quality and ease of falling asleep as soon as 7 days after agomelatine initiation.

### LY 156735

LY 156735 is a new investigational melatonin agonist under development to treat circadian rhythm disorders. A double-blind, three-period crossover pilot study of 8 healthy males (25-33 years) assessed the efficacy of LY 156735 0.5 mg and 5 mg compared to placebo in improving adaptation to a phase advance in the light-dark cycle.<sup>71</sup> Subjects were exposed to a phase advance of 9 hours while being housed in a temporal isolation unit, and medications were administered just preceding lights-out of the post-phase-advance schedule. The 5.0 mg dose enhanced the readaptation speed of all physiological rhythms that were assessed.

In a double-blind, placebo-controlled, crossover trial, LY 156735 produced improvements in sleep latency in patients with primary insomnia.<sup>72</sup> A total of 40 patients received 3 doses of LY 156735 (20, 50, and 100 mg) or placebo on each of 2 consecutive nights with 5-day washout periods between treatments. An improvement in PSG sleep latency of 31%, 32%, and 41% was observed for the 20, 50, and 100 mg doses of LY 156735, respectively (20 mg,  $P=0.0082$ ; 50 mg,  $P=0.0062$ ; and 100 mg,  $P<0.0001$ ). Improvements in subjective measures of sleep latency and lack of next-day psychomotor impairment were also observed. Adverse events

were mild to moderate in severity and did not differ in frequency between placebo and all doses of LY 156735.

Another randomized, placebo-controlled, double-blind, crossover study evaluated the efficacy of LY 156735 (20-100 mg) in 18 patients with moderate-to-severe primary insomnia.<sup>73</sup> Compared to placebo, LY 156735 reduced PSG latency to persistent sleep by 57%, 54%, and 62%, respectively, for the 20, 50, and 100 mg doses ( $P=0.0001$ ). Additionally, LY 156735 produced reductions in subjective sleep latency at all doses compared to placebo ( $P=0.0035$ ).

### VEC-162

VEC-162 is a selective agonist at  $MT_1$  and  $MT_2$  receptors currently being studied in the US for its efficacy in sleep disorders and depression. A randomized, double-blind, placebo-controlled study of 39 healthy subjects (18-50 years) evaluated the efficacy of VEC-162 (10, 20, 50 and 100 mg) in shifting circadian rhythms in a model of transient insomnia.<sup>74</sup> Primary outcome measures were plasma melatonin concentrations and improvements in PSG time to persistent sleep. Compared to placebo, VEC-162 phase-advanced melatonin onset on first administration, improved sleep efficiency, reduced sleep latency, and attenuated REM reduction due to a phase advance. VEC-162 is still in early states of clinical development.

### CONCLUSION

Melatonin is centrally involved in the regulation of sleep and the timing of various biological rhythms. Numerous studies have explored the effects of melatonin administration on sleep and circadian rhythms. However, due to methodological issues and conflicting results regarding the efficacy of melatonin in the treatment of sleep disorders, the focus has been to develop agonists of the melatonin receptors with predictable and well-defined clinical properties. This new class of hypnotics has high-binding affinity at the  $MT_1$  and  $MT_2$  receptors. The first FDA-approved drug in this class is ramelteon. The efficacy of ramelteon in reducing time to sleep onset has been demonstrated in several clinical trials. Other agents under development include agomelatine, LY 156735 and VEC-162.

### REFERENCES

1. Pace-Schott EF, Hobson JA. The neurobiology of sleep: genetics, cellular physiology and subcortical networks. *Nat Rev Neurosci* 2002;3:591-605.
2. Vitaterna MH, Takahashi JS, Turek FW. Overview of circadian rhythms. *Alcohol Res Health* 2001;25:85-93.
3. Turek FW, Dugovic C, Zee PC. Current understanding of the circadian clock and the clinical implications for neurological disorders. *Arch Neurol* 2001;58:1781-7.
4. Richardson GS. The human circadian system in normal and disordered sleep. *J Clin Psychiatry* 2005;66 Suppl 9:3-9.
5. Piggins HD. Human clock genes. *Ann Med* 2002;34:394-400.
6. Hamet P, Tremblay J. Genetics of the sleep-wake cycle and its disorders. *Metabolism* 2006;55 Suppl 2:S7-S12.
7. Saper CB, Chou TC, Scammell TE. The sleep switch: hypothalamic control of sleep and wakefulness. *Trends Neurosci* 2001;24:726-31.
8. Edgar DM, Dement WC, Fuller CA. Effect of SCN lesions on sleep in squirrel monkeys: evidence for opponent processes in sleep-wake regulation. *J Neurosci* 1993;13:1065-79.

9. Mignot E, Taheri S, Nishino S. Sleeping with the hypothalamus: emerging therapeutic targets for sleep disorders. *Nat Neurosci* 2002;5 Suppl:1071-5.
10. Cassone VM. Effects of melatonin on vertebrate circadian systems. *Trends Neurosci* 1990;13:457-64.
11. Reiter RJ. Melatonin: clinical relevance. *Best Pract Res Clin Endocrinol Metab* 2003;17:273-85.
12. Brzezinski A. Melatonin in humans. *N Engl J Med* 1997;336:186-95.
13. Lynch HJ, Wurtman RJ, Moskowitz MA, Archer MC, Ho MH. Daily rhythm in human urinary melatonin. *Science* 1975;187:169-71.
14. Waldhauser F, Dietzel M. Daily and annual rhythms in human melatonin secretion: role in puberty control. *Ann N Y Acad Sci* 1985;453:205-14.
15. Lewy AJ, Ahmed S, Jackson JM, Sack RL. Melatonin shifts human circadian rhythms according to a phase-response curve. *Chronobiol Int* 1992;9:380-92.
16. Brown GM. Light, melatonin and the sleep-wake cycle. *J Psychiatry Neurosci* 1994;19:345-53.
17. Turek FW, Gillette MU. Melatonin, sleep, and circadian rhythms: rationale for development of specific melatonin agonists. *Sleep Med* 2004;5:523-32.
18. Dijk DJ, Cajochen C. Melatonin and the circadian regulation of sleep initiation, consolidation, structure, and the sleep EEG. *J Biol Rhythms* 1997;12:627-35.
19. Krauchi K, Wirz-Justice A. Circadian clues to sleep onset mechanisms. *Neuropsychopharmacology* 2001;25:S92-6.
20. Stone BM, Turner C, Mills SL, Nicholson AN. Hypnotic activity of melatonin. *Sleep* 2000;23:663-9.
21. Zhdanova IV, Wurtman RJ, Lynch HJ, et al. Sleep-inducing effects of low doses of melatonin ingested in the evening. *Clin Pharmacol Ther* 1995;57:552-8.
22. Lavie P. Melatonin: role in gating nocturnal rise in sleep propensity. *J Biol Rhythms* 1997;12:657-65.
23. Lavie P. Sleep-wake as a biological rhythm. *Annu Rev Psychol* 2001;52:277-303.
24. Reppert SM, Weaver DR, Ebisawa T. Cloning and characterization of a mammalian melatonin receptor that mediates reproductive and circadian responses. *Neuron* 1994;13:1177-85.
25. Reppert SM, Godson C, Mahle CD, Weaver DR, Slaugenhaupt SA, Gusella JF. Molecular characterization of a second melatonin receptor expressed in human retina and brain: the Mel1b melatonin receptor. *Proc Natl Acad Sci USA* 1995;92:8734-8.
26. Nosjean O, Ferro M, Coge F, et al. Identification of the melatonin-binding site MT3 as the quinone reductase 2. *J Biol Chem* 2000;275:31311-7.
27. Dubocovich ML, Rivera-Bermudez MA, Gerdin MJ, Masana MI. Molecular pharmacology, regulation and function of mammalian melatonin receptors. *Front Biosci* 2003;8:d1093-108.
28. Morgan PJ. The pars tuberalis: the missing link in the photoperiodic regulation of prolactin secretion? *J Neuroendocrinol* 2000;12:287-95.
29. Pintor J, Martin L, Pelaez T, Hoyle CH, Peral A. Involvement of melatonin MT(3) receptors in the regulation of intraocular pressure in rabbits. *Eur J Pharmacol* 2001;416:251-4.
30. Lotufo CM, Lopes C, Dubocovich ML, Farsky SH, Markus RP. Melatonin and N-acetylserotonin inhibit leukocyte rolling and adhesion to rat microcirculation. *Eur J Pharmacol* 2001;430:351-7.
31. Liu C, Weaver DR, Jin X, Shearman LP, Pieschl RL, Gribkoff VK, Reppert SM. Molecular dissection of two distinct actions of melatonin on the suprachiasmatic circadian clock. *Neuron* 1997;19:91-102.
32. Jin X, von Gall C, Pieschl RL, et al. Targeted disruption of the mouse Mel(1b) melatonin receptor. *Mol Cell Biol* 2003;23:1054-60.
33. Dubocovich ML, Yun K, Al-Ghoul WM, Benloucif S, Masana MI. Selective MT2 melatonin receptor antagonists block melatonin-mediated phase advances of circadian rhythms. *Faseb J* 1998;12:1211-20.
34. Iguchi H, Kato KI, Ibayashi H. Melatonin serum levels and metabolic clearance rate in patients with liver cirrhosis. *J Clin Endocrinol Metab* 1982;54:1025-7.
35. Waldhauser F, Waldhauser M, Lieberman HR, Deng MH, Lynch HJ, Wurtman RJ. Bioavailability of oral melatonin in humans. *Neuroendocrinology* 1984;39:307-13.
36. Melatonin. *Med Lett Drugs Ther* 1995;37:111-2.
37. Buscemi N, Vandermeer B, Pandya R, et al. Melatonin for Treatment of Sleep Disorders. Evidence Report/Technology Assessment No. 108. (Prepared by the University of Alberta Evidence-based Practice Center, under Contract No. 290-02-0023). AHRQ Publication No. 05-E002-2. Rockville, MD: Agency for Healthcare Research and Quality; 2004.
38. Buscemi N, Vandermeer B, Hooton N, et al. The efficacy and safety of exogenous melatonin for primary sleep disorders. A meta-analysis. *J Gen Intern Med* 2005;20:1151-8.
39. Brzezinski A, Vangel MG, Wurtman RJ, et al. Effects of exogenous melatonin on sleep: a meta-analysis. *Sleep Med Rev* 2005;9:41-50.
40. Karasek M, Reiter RJ, Cardinali DP, Pawlikowski M. Future of melatonin as a therapeutic agent. *Neuro Endocrinol Lett* 2002;23 Suppl 1:118-21.
41. Kato K, Hirai K, Nishiyama K, et al. Neurochemical properties of ramelteon (TAK-375), a selective MT1/MT2 receptor agonist. *Neuropharmacology* 2005;48:301-10.
42. Hibberd M, Stevenson SJ. A phase-I open-label study of the absorption, metabolism, and excretion of (14C)-ramelteon (TAK-375) following a single oral dose in healthy male subjects (abstract). *Sleep* 2004;27(suppl):A54.
43. Karim A, Tolbert D, Cao C. Disposition kinetics and tolerance of escalating single doses of ramelteon, a high-affinity MT1 and MT2 melatonin receptor agonist indicated for treatment of insomnia. *J Clin Pharmacol* 2006;46:140-8.
44. Stevenson S, Cornelissen K, Clarke E, Hibberd M. Study of the absorption, metabolism, and excretion of (14C)-ramelteon (TAK-375) (abstract). *Clin Pharmacol Ther* 2004;75:22.
45. Amakye DD, Hibberd M, Stevenson SJ. A phase I study to investigate the absolute bioavailability of a single oral dose of ramelteon (TAK-375) in healthy male subjects (abstract). *Sleep* 2004;27(suppl):A54.
46. Stevenson S, Bryson S, Amakye D, Hibberd M. Study to investigate the absolute bioavailability of a single oral dose of ramelteon (TAK-375) in healthy male subjects (abstract). *Clin Pharmacol Ther* 2004;75:22.
47. Rozerem™ [package insert], Takeda Pharmaceuticals America, Inc., Lincolnshire, Illinois (August 2005).
48. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders D-IV-TR. Washington, DC: American Psychiatric Association; 2004.
49. Erman M, Seiden D, Zammit G, Sainati S, Zhang J. An efficacy, safety, and dose-response study of Ramelteon in patients with chronic primary insomnia. *Sleep Med* 2006;7:17-24.
50. Zammit G, Erman M, Wang-Weigand S, Sainati S, Zhang J, Roth T. Evaluation of the efficacy and safety of ramelteon in subjects with chronic insomnia. *J Clin Sleep Med* 2007;In press.
51. Mini L, Wang-Weigand S, Zhang J, Kasten K. Reduction in sleep latency during 5 weeks of treatment with ramelteon 8 mg versus placebo in patients with chronic insomnia. *Neurology* 2006;66(suppl 2):A9.
52. Roth T, Seiden D, Sainati S, Wang-Weigand S, Zhang J, Zee P. Effects of ramelteon on patient-reported sleep latency in older adults with chronic insomnia. *Sleep Med* 2006;7:312-8.
53. Richardson G, Wang-Weigand S, Zhang J, DeMicco M. Long-term safety of ramelteon treatment in adults with chronic insomnia. *Sleep* 2006;29(suppl):A233.
54. Sleep Disorder (Sedative-Hypnotic) Drug Information. FDA Press Release P07-45, March 14, 2007. Accessed at <http://www.fda.gov/>

- bbs/topics/NEWS/2007/NEW01587.html on April 30, 2007.
55. Richardson GS, Wang-Weigand S, Sainati S, Demissie S. Long-term effects of ramelteon on endocrine function in patients with chronic insomnia in a double-blind, placebo-controlled phase III study. *Clin Pharmacol Ther* 2006;79:P68.
  56. Sainati S, Tsymbalov S, Demissie S, Roth T. Double-blind, placebo-controlled, two-way crossover study of ramelteon in subjects with mild to moderate chronic obstructive pulmonary disease (COPD). *Sleep* 2005;28(suppl):A162.
  57. Sainati S, Tsymbalov S, Demissie S, Roth T. Double-blind, single-dose, two-way crossover of ramelteon in subjects with mild to moderate obstructive sleep apnea. *Sleep* 2005;28(suppl):A163.
  58. Johnson MW, Suess PE, Griffiths RR. Ramelteon: a novel hypnotic lacking abuse liability and sedative adverse effects. *Arch Gen Psychiatry* 2006;63:1149-57.
  59. Yous S, Andrieux J, Howell HE, et al. Novel naphthalenic ligands with high affinity for the melatonin receptor. *J Med Chem* 1992;35:1484-6.
  60. Millan MJ, Gobert A, Lejeune F, et al. The novel melatonin agonist agomelatine (S20098) is an antagonist at 5-hydroxytryptamine<sub>2C</sub> receptors, blockade of which enhances the activity of frontocortical dopaminergic and adrenergic pathways. *J Pharmacol Exp Ther* 2003;306:954-64.
  61. Loo H, Hale A, D'Haenen H. Determination of the dose of agomelatine, a melatonergic agonist and selective 5-HT<sub>2C</sub> antagonist, in the treatment of major depressive disorder: a placebo-controlled dose range study. *Int Clin Psychopharmacol* 2002;17:239-47.
  62. Van Reeth O, Olivares E, Turek FW, Granjon L, Mocaer E. Resynchronization of a diurnal rodent circadian clock accelerated by a melatonin agonist. *Neuroreport* 1998;9:1901-5.
  63. Redman JR, Guardiola-Lemaitre B, Brown M, Delagrangé P, Armstrong SM. Dose dependent effects of S-20098, a melatonin agonist, on direction of re-entrainment of rat circadian activity rhythms. *Psychopharmacology (Berl)* 1995;118:385-90.
  64. Weibel L, Turek FW, Mocaer E, Van Reeth O. A melatonin agonist facilitates circadian resynchronization in old hamsters after abrupt shifts in the light-dark cycle. *Brain Res* 2000;880:207-11.
  65. Armstrong SM, McNulty OM, Guardiola-Lemaitre B, Redman JR. Successful use of S20098 and melatonin in an animal model of delayed sleep-phase syndrome (DSPS). *Pharmacol Biochem Behav* 1993;46:45-9.
  66. Ying SW, Rusak B, Delagrangé P, Mocaer E, Renard P, Guardiola-Lemaitre B. Melatonin analogues as agonists and antagonists in the circadian system and other brain areas. *Eur J Pharmacol* 1996;296:33-42.
  67. Krauchi K, Cajochen C, Mori D, Graw P, Wirz-Justice A. Early evening melatonin and S-20098 advance circadian phase and nocturnal regulation of core body temperature. *Am J Physiol* 1997;272:R1178-88.
  68. Leproult R, Van Onderbergen A, L'Hermite-Baleriaux M, Van Cauter E, Copinschi G. Phase-shifts of 24-h rhythms of hormonal release and body temperature following early evening administration of the melatonin agonist agomelatine in healthy older men. *Clin Endocrinol (Oxf)* 2005;63:298-304.
  69. Guilleminault C. Efficacy of agomelatine versus venlafaxine on subjective sleep of patients with major depressive disorder (abstract). *Eur Neuropsychopharmacol* 2005;15 (Suppl 3):S419.
  70. Quera-Salva MA, Vanier B, Chapotot F, Bohic M, Andre S, Moulin C. Effects of agomelatine on the sleep EEG in patients with major depressive disorder (abstract). *Eur Neuropsychopharmacol* 2005;15 (Suppl. 3):435-6.
  71. Nickelsen T, Samel A, Vejvoda M, Wenzel J, Smith B, Gerzer R. Chronobiotic effects of the melatonin agonist LY 156735 following a simulated 9h time shift: results of a placebo-controlled trial. *Chronobiol Int* 2002;19:915-36.
  72. Zemlan FP, Mulchahey JJ, Scharf MB, Mayleben DW, Rosenberg R, Lankford A. The efficacy and safety of the melatonin agonist beta-methyl-6-chloromelatonin in primary insomnia: a randomized, placebo-controlled, crossover clinical trial. *J Clin Psychiatry* 2005;66:384-90.
  73. Zemlan F, Mulchahey J, Mayleben D, Scharf M, Rosenberg R, Lankford A. Multicenter study of the melatonin agonist LY 156735 in moderate-to-severe primary insomnia. In: Program No 3106 2005 Abstract Viewer/Itinerary Planner. Washington, DC: Society for Neuroscience, 2005. Online, 2005.
  74. Rajaratnam SM, Polymeropoulos MH, Fischer DM, Scott CH, Birznies G, Klerman EB. The melatonin agonist VEC-162 immediately phase-advances the human circadian system (abstract). In: 20th Anniversary Meeting of the Associated Professional Sleep Societies; 2005; Salt Lake City, UT; 2005.
  75. Kilduff TS, Kushida CA. Circadian regulation of sleep. In: Chokroverty S, ed. *Sleep Disorders Medicine: Basic Science, Technical Considerations, and Clinical Aspects* 2nd ed. Boston, MA: Butterworth-Heinemann, 1999:135-45.