Melatonin, Circadian Dysregulation, and Sleep in Mental Disorders

Seithikurippu R. Pandi-Perumal, MSc, Ilya Trakht, PhD, Gregory M. Brown, MD, PhD, FRCPC, FRSC, and Daniel P. Cardinali, MD, PhD

ABSTRACT

Sleep is a behavioral process that is governed by both homeostatic and circadian processes. While the intensity and duration of sleep is governed mainly by the homeostatic process (sleep debt), the timing of sleep is orchestrated by the anterior hypothalamic suprachiasmatic nuclei (SCN). Disturbances in the organization of the sleep/wake cycle as well as circadian (approximately 24-hour periodicity) dysregulation are often noted in mental illness. The circadian rhythm of pineal melatonin secretion, which is controlled by the SCN, is reflective of mechanisms that are involved in the control of the sleep/wake cycle. Melatonin influences sleep-promoting and sleep/wake rhythm-regulating actions through the specific activation of melatonin (MT₁) and MT₂ receptors, highly concentrated in the SCN. In healthy humans, melatonin induces sleep by a process influenced by the circadian phase. The hypnotic and rhythm-regulating properties of melatonin and its agonists (ramelteon, agomelatine) make them an important addition to the armamentarium of drugs for treating sleep disturbances and circadian rhythm sleep disorders associated with mental illness.

INTRODUCTION

Most physiologic processes in a wide range of organisms show daily cyclical changes. In mammals, including humans, a central circadian pacemaker, or biological clock, is the site of generation and entrainment of circadian rhythms. It is
The central circadian oscillator adjusts its functioning via the integration of various parameters of the light signal (e.g., time of presentation, duration, intensity, wavelength). Light presented in the evening and early night (before the core body temperature [cBT] minimum) affects the human circadian pacemaker to phase-delay its rhythms, while a light stimulus given in late night and early morning (after cBT minimum) produces a phase advance (phase response curve).

During the past decade, enormous progress has been made in determining the molecular components of the biological clock. The molecular mechanisms that underlie the function of the clock are universally present in all cells and consist of gene-protein-gene feedback loops in which proteins can down-regulate their own transcription and stimulate the transcription of other clock proteins. At the start of circadian day, core clock genes "period" (PER) and "cryptochrome" (CRY) are activated by protein "circadian locomotor output cycles kaput\brain and muscle aryl hydrocarbon receptor nuclear translocator-like" (CLOCK/BNP1) heterodimers via E-box sequences. Following a delay, protein PER/CRY complexes accumulate in the nucleus late in the day and turn off their own expression, establishing the primary feedback loop of the oscillation. Clearance of PER/CRY complexes during the circadian night allows for reactivation of the loop on the following day. In addition, over the course of the day, REV-ERBα accumulation, which is also driven by CLOCK/BNP1, suppresses Bmal expression. The clearance during early circadian night of REV-ERBα derepresses Bmal, thereby cueing the next circadian cycle of gene expression. Clock-controlled gene products transduce the core oscillation to downstream output systems. Via neural pathways (the autonomic nervous system) and humoral pathways (melatonin, cortisol) the SCN impose their rhythmicity on the peripheral oscillators.

Disruption in circadian organization occurs in numerous affective disorders, such as major depressive disorder (MDD), bipolar depressive disorder, seasonal affective disorder (SAD), and premenstrual dysphoric disorder (PMDD). Whether altered rhythmicity is a cause or effect of altered affective states remains a matter of debate. However, it is agreed that the large prevalence of circadian dysfunction in affective states certainly supports a major role of the circadian system in the etiology and the treatment of affective disorders.

As a major circadian rhythm, the abnormality of the sleep/wake rhythm constitutes one of the most prevalent symptoms of mental illness and forms part of the diagnostic criteria for most mood disorders as well as for several anxiety disorders. CLOCK gene polymorphisms have been associated with an increased rate of recurrence in patients with bipolar disorder and relapse in recurrent MDD.
polymorphisms could affect the occurrence of insomnia in depressed patients and its response during antidepressant treatment. Other polymorphisms were found to be significantly associated with susceptibility to SAD.7,8

TWO PROCESSES OF SLEEP REGULATION

Two different processes participate in sleep regulation, namely, a homeostatic mechanism depending on sleep debt (referred to as process “S,” for sleep) and the circadian system that regulates sleep induction and wakefulness (process “C,” for circadian).9 Non-rapid eye movement (NREM) sleep and, in particular, slow wave sleep (SWS), are controlled by the homeostatic process. Periods of NREM sleep constitute nearly 80% of the total sleep time while REM sleep accounts for 20% of the sleep time. During each night, individuals experience approximately five ultradian cycles of NREM sleep and REM sleep that last 70–90 minutes each. REM sleep grows longer with each successive ultradian cycle.10 The S component controls NREM sleep and the C component controls both REM sleep and the ratio of NREM/REM sleep. The SCN interacts with both sleep regulatory mechanisms, S and C, and it has been proposed that functional disruption of the master clock plays a major role in disorders of sleep and wakefulness.11

The function of the SCN in the control of sleep has been studied in various species including non-human primates. Squirrel monkeys with SCN lesions suffer from the absence of a consolidated sleep/wake cycle.12 The circadian signal produced by the SCN promotes wakefulness during the subjective day and consolidation of sleep at night.12 Neurons present in the hypothalamic ventral subparaventricular zone (SPZ) are needed for the circadian sleep/wake rhythm and project to the dorsomedial hypothalamus (DMH). Hence, the sleep/wake rhythms are controlled by two relays, one from the SCN to the ventral SPZ and a second one from the ventral SPZ to the DMH.10 Although rhythmic SCN neurons express Per-1 and Per-2 during photophase, independently of diurnal or nocturnal activity nature of the individual,13 their output neurons in the ventrolateral preoptic area are active during night; orexin-containing neurons of DMH, however, are predominantly active during daytime.10

MELATONIN’S ROLE IN THE REGULATION OF SLEEP

That the nocturnal increase of melatonin secretion starts approximately 2 hours prior to the individual’s habitual bedtime and that this correlates well with the onset of evening sleepiness have prompted many investigators to sug-
Phase resetting effects of endogenous as opposed to administered melatonin are evidenced by studies of polymorphisms of the gene for the enzyme arylalkylamine N-acetyltransferase (AA-NAT), which is a key factor in triggering synthesis of melatonin in the pineal gland. Polymorphisms of this gene are reported to be associated with advanced sleep phase syndrome (ASPS) and delayed sleep phase syndrome (DSPS), conditions in which individuals have extreme difficulty in falling asleep and in arising at desired times. In DSPS, there is a delay in sleep onset and wakening together with a delay in onset of the nocturnal melatonin rise.\textsuperscript{36,37} A single nucleotide polymorphism (SNP) of the AA-NAT gene has been associated with the DSPS.\textsuperscript{38} In familial ASPS,\textsuperscript{39,40} affected family members on average have sleep onset and wakening 3–3.5 hours earlier than unaffected members, and the nocturnal melatonin onset is also 3.5 hours earlier. SNP of the promoter region of AA-NAT was found to be associated with ASPS.\textsuperscript{41}

Exogenous melatonin administration can induce sleepiness at night even at very low doses.\textsuperscript{29} Unlike some other hypnotic drugs, melatonin does not cause hangover effects the next morning.\textsuperscript{29} A meta-analysis of 17 studies involving 284 subjects\textsuperscript{42} concluded that melatonin is effective in reducing sleep onset latency and in increasing sleep efficiency. However, another survey,\textsuperscript{43} which included all age groups, failed to confirm whether exogenously administered melatonin had any clinically meaningful effects on sleep. It is important to stress that in this report an increase in sleep efficiency in people with secondary sleep disorders (approximately 2%) was statistically significant with melatonin, but the authors considered this effect to be clinically unimportant due to its small magnitude. Nevertheless, the authors’ conclusions may merit reconsideration inasmuch as the noted reductions in sleep onset latency were of the same magnitude as those observed with some marketed hypnotics. In any event, it seems possible that a prerequisite for exogenous melatonin effects is the existence of low endogenous melatonin secretion.\textsuperscript{44} There is a very large interindividual variation in nocturnal melatonin levels.\textsuperscript{45–47} It is, therefore, possible that those with a higher endogenous output of melatonin could need a larger dose for effective treatment.

In view of this factual evidence, the use of a melatonin analog with a longer half life and increased potency than melatonin, which might have a greater effect on melatonergic receptors in the SCN and other regions of the brain, have been advocated.\textsuperscript{48} Ramelteon is a novel melatonin receptor agonist for MT\textsubscript{1} and MT\textsubscript{2} receptors approved for its clinical use by the United States Food and Drug Administration and it is being tried clinically to treat sleep problems of the elderly. Ramelteon is effective in increasing total sleep time in the elderly.\textsuperscript{49–51}

**THE LINK BETWEEN SLEEP AND MOOD DISORDERS**

Considerable controversy exists concerning the question of whether sleep disturbances in depression are a “trait-like” feature.\textsuperscript{52} Patients with MDD have nightmares at least twice a week and, compared to normal, have significantly higher suicide scale scores.\textsuperscript{53} Some studies\textsuperscript{54} of patients with depression have shown changes in sleep architecture that persist even during the remission phase. Changes in sleep architecture often precede changes in patients’ ongoing clinical state or can signal relapse.

Depressed patients experience difficulty falling asleep, difficulty staying asleep, and early morning awakenings.\textsuperscript{55} Analysis of SWS in NREM sleep has shown that delta wave counts in patients with MDD are decreased when compared to controls. Fast frequency beta and elevated alpha activities have been recorded during sleep in depressed patients, indicating that hyperarousal and increased sleep fragmentation are major characteristics of sleep in depression.\textsuperscript{56} These changes are present in non-medicated patients or in clinical remission, suggesting that they are trait-like features of depressive illness.\textsuperscript{56}

Disturbances in the organization of the sleep/wake cycle in MDD patients are thought to be due to abnormalities in the timing of the REM/NREM sleep cycle.\textsuperscript{57} The temporal distribution of REM sleep is altered during overnight sleep in depressives. Decreased REM latency has been shown to be common in severe or endogenous depression. It has been suggested that reductions in REM latency in depression are due to reduction of NREM sleep, particularly SWS.\textsuperscript{58} Patients with least amounts of SWS also showed the greatest psychomotor retardation.\textsuperscript{59} These findings support the conclusion that disruptions to sleep homeostasis are a major form of sleep disturbance in depression. Additionally, increases in REM sleep density have also been found to be specific to affective disorders\textsuperscript{59} and are now thought to be a reliable sleep marker for depression.\textsuperscript{60} Consistent with this view are findings that suggest that many of the antidepressants produce REM sleep suppression as well as increases in REM latency.

**ANTIDEPRESSANTS AND THE ROLE OF MELATONIN**

Many antidepressants increase melatonin levels,\textsuperscript{61–67} and the central nervous system distribution of melatonin receptor messenger ribonucleic acid (mRNA) is modified by prolonged treatment with antidepressants such as desipramine, clomipramine, or fluoxetine. With the exception of fluoxetine, those...
Melatonin, Circadian Dysregulation, and Sleep in Mental Disorders

Evidence that antidepressant treatment can promote favorable melatonin receptor expression has led to the suggestion that combination therapy using an antidepressant plus a melatonergic agent may be an effective strategy for treating sleep disorders in the context of depression.68,69 One such antidepressant combining both properties in a single molecule is the newly developed agent agomelatine (Valdoxan, Servier). Agomelatine is an MT₁ and MT₂ receptor agonist with serotonin-2C antagonist properties that has been found to be beneficial in treating patients with MDD.77,78 Agomelatine is a naphthalene compound with an overall selectivity (>100 fold) for MT₁ and MT₂ receptors but has no significant affinities to muscarinic, histaminergic, adrenergic, or dopaminergic receptor subtypes.82 The proven chronobiotic action of agomelatine is due to its agonist activity on MT₁ and MT₂ receptors in the suprachiasmatic nucleus.83-86 Inasmuch as disruptions in circadian rhythms are linked to depressive states, agomelatine’s effectiveness in treating these symptoms support the conclusion that it has a broader range of effect than other antidepressants and may add complexity to the depressive illness more effectively. PP

REFERENCES


