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Melatonin, Circadian Dysregulation, and Sleep in Mental Disorders

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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 $(MT)_1$ and MT_2 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

Needs Assessment: A new class of melatonergic drugs that are prescribed for mood or sleep disorders have a radically different type of action than earlier drugs used for these treatments. Doctors who prescribe these drugs should have an understanding of the organization of the circadian system and the way that these drugs act on it.

Learning Objectives:

- Display familiarity with the way in which the circadian timing system is organized.
- Explain the role of melatonin in sleep regulation.
- Understand the linkage of sleep with mood disorders.
- Understand how the melatonergic antidepressant, agomelatine, differs from earlier drugs used for treating depression.

Target Audience: Primary care physicians and psychiatrists.

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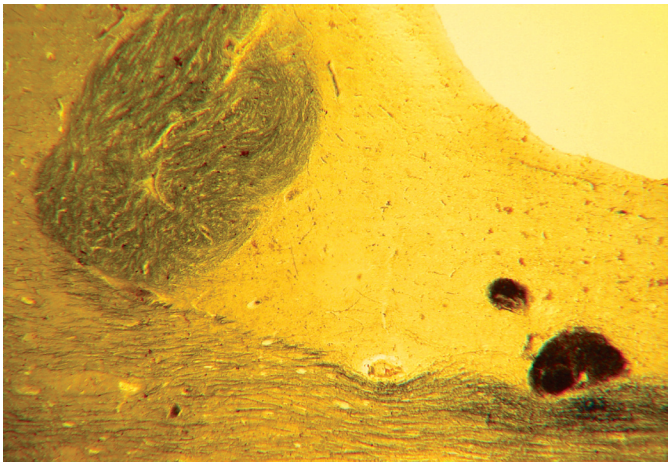
located in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus (Image). This clock generates a genetically programmed endogenous rhythmicity, which is slightly different from 24 hours and needs to be synchronized (entrained) to the 24-hour day cycle by external timekeeping cues (mainly the light/dark cycle, and secondarily the timing of meals or social contacts). In the absence of these "Zeitgebers," circadian rhythms persist and express their own period that is "circa" but not exactly 24 hours. In humans, the endogenous period of the circadian clock has a mean value of 24.2 hours; that is, every day our biological clock is delayed by approximately 12 minutes as compared with the environmental light/dark cycle.

The SCN receive direct light information through the retino-hypothalamic tract, which is a visual tract not linked to behavioral visual processes, and indirect light information through the thalamus, using the retino-geniculo-hypothalamic tract. The photic entrainment of the pacemaker is achieved by a specialized subset of intrinsically photosensitive ganglion cells that are spread throughout the retina rather than concentrated in the fovea. These specialized, melanopsin-containing ganglion cells also receive input from rods and cones, acting as a redundant input pathway for synchronizing the circadian system, but can still function even if the rods and cones are so severely damaged that the individual is behaviorally blind.[1]

IMAGE

PHOTOMICROGRAPH OF THE SUPRACHIASMATIC NUCLEUS*



*The SCN is located in the lateral region of the hypothalamus and functions as the brain's "master clock," regulating circadian rhythms. The SCN has the highest density of melatonin $(MT)_1$ and MT_2 receptors and controls the periodicity of sleep and wakeful states.

SCN=suprachiasmatic nucleus.

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The central circadian oscillator adjusts its functioning via the integration of various parameters of the light signal (eg, 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.[2] 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/BMAL) 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/BMAL, 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.[2] 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.[3] CLOCK gene polymorphisms have been associated with an increased rate of recurrence in patients with bipolar disorder and relapse in recurrent MDD.[4-6] Similar

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 suggest that melatonin is involved in the physiologic regulation of sleep.[14] The period of wakefulness immediately prior to the increase of sleep propensity ("opening of sleep gate") is known as the "forbidden zone" for sleep.[15] During this time, the sleep propensity is lowest and SCN neuronal activity is high.[16,17] The transition from wakefulness/arousal to high sleep propensity coincides with the nocturnal rise of endogenous melatonin secretion.[18]

Melatonin exerts its physiologic actions on sleep by acting through Gi protein linked to specific melatonin $(MT)_1$ and MT_2 receptors which are present on cell membranes in the SCN and elsewhere.[19] While the MT_1 receptor decreases neuronal firing rate, the MT_2 receptor regulates phase shifts. The G protein-coupled receptor 50 (GPR50), although lacking the ability to bind melatonin itself, can dimerize with the MT_1 receptor and inhibit it.[21,22] A study by Thomson and colleagues[23] reported a sex-specific association between bipolar affective disorder in women in Southeastern Scotland and a polymorphism in the gene for GPR50. Nuclear receptors for melatonin have also been described.[24] In addition, melatonin exerts direct effects on intracellular proteins such as calmodulin[25] and has strong free radical scavenger properties[26] which are non-receptor mediated. The possibility that melatonin, a major hormone involved in the regulation of sleep, could be one of the triggering factors underlying the pathogenesis of MDD, bipolar depressive disorder, SAD or PMDD has been considered.[27]

The first evidence that melatonin affects sleep came from Lerner and colleagues,[28] who discovered melatonin in 1958. When they started to treat patients suffering from vitiligo, a human pigmentation disease, the patients fell asleep. After this initial observation, several clinical trials have examined the role of melatonin in sleep and have pointed out the value of melatonin as a hypnotic agent.[29] In human studies, administration of either physiologic or pharmacologic doses of melatonin promotes both sleep onset and sleep maintenance.[30-32]

Brain imaging studies have revealed that melatonin modulates brain activity pattern in wake subjects in a manner resembling actual sleep.[33] Melatonin administration attenuated activation in the rostromedial aspect of the occipital cortex during a visual-search task and in the auditory cortex during a music task.[33] However, phase-resetting actions of melatonin have also been advocated as the major mechanism by which exogenous melatonin affects sleep regulation.[34] Melatonin administration is useful to effectively synchronize sleep/wake cycles in blind individuals as well as in people suffering from jet lag, delayed sleep phase syndrome, or advanced sleep phase syndrome.[35]

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.[36,37] A single nucleotide polymorphism (SNP) of the AA-NAT gene has been associated with the DSPS.[38] In familial ASPS,[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.[41]

Exogenous melatonin administration can induce sleepiness at night even at very low doses.[29] Unlike some other hypnotic drugs, melatonin does not cause hangover effects the next morning.[29] A meta-analysis of 17 studies involving 284 subjects[42] concluded that melatonin is effective in reducing sleep onset latency and in increasing sleep efficiency. However, another survey,[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.[44] There is a very large interindividual variation in nocturnal melatonin levels.[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.[48] Ramelteon is a novel melatonin receptor agonist for MT_1 and MT_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.[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.[52] Patients with MDD have nightmares at least twice a week and, compared to normal, have significantly higher suicide scale scores.[53] Some studies[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.[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.[56] These changes are present in non-medicated patients or in clinical remission, suggesting that they are trait-like features of depressive illness.[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.[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.[58] Patients with least amounts of SWS also showed the greatest psychomotor retardation.[56] 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[59] and are now thought to be a reliable sleep marker for depression.[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,[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

drugs were found to increase the amount of mRNA for MT_1 receptors and to decrease that for MT_2 receptors in the hippocampus.[68,69] Based on these findings, it was hypothesized that endogenous levels of melatonin could contribute to antidepressant effects depending upon the expression pattern of melatonin receptors in the brain.

It has been suggested that diminished melatonin secretion is at least partially responsible for the deterioration of sleep maintenance that is seen in insomniacs. In a study[70] undertaken in 382 postmenopausal women with a family history of depression, a delay in urinary 6-sufatoxymelatonin excretion was found. Other studies in aging women have documented that reductions in circulating melatonin levels accompany menopause, and programs of melatonin-replacement therapy have been proposed.[71,72] In a study conducted on 10 patients with MDD, slow release melatonin tablets in the doses of 5 mg/day (which was raised to 10 mg/day at the end of 2 weeks) were administered for 4 weeks along with fluoxetine 20 mg/day.[73] Melatonin treatment promoted a significant improvement in sleep quality, as evidenced from scores on the Pittsburgh Sleep Quality Index. As reported earlier,[74] despite the melatonin-induced enhancements of sleep quality, no improvements were found in the clinical status of the depressed patients.[73] In another study[75] of patients suffering from both delayed sleep phase syndrome and depression, melatonin treatment not only significantly improved the total sleep time but also significantly reduced psychometric scores for depression. In two studies[73,76] of combination therapy in patients with MDD or treatment-resistant depression, the combination of melatonin (slow-release formulation) plus fluoxetine or other antidepressants was found to improve the sleep quality of the patients, but there was no additive effect of melatonin on the depressive symptoms.

CONCLUSION

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 MT_1 and MT_2 receptor agonist with serotonin-2C antagonist properties that has been found to be beneficial in treating patients with MDD.[77-84] Agomelatine is a naphthalenic compound with an overall selectivity (>100 fold) for MT_1 and MT_2 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 MT_1 and MT_2 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 address the complexities of depressive illness more effectively. ***PP***

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