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GUEST EDITORIAL

Melatonin, sleep, and circadian rhythms

Melatonin regulation

In mammals, melatonin plasma levels are high during darkness at night and low during the day. Even in an environment free of time cues and in constant dim light, melatonin continues to express its circadian (or 'approximately 24-h') rhythm. This endogenous circadian rhythm is driven by the circadian pacemaker located in the hypothalamic suprachiasmatic nucleus (SCN), via a multi-synaptic pathway involving the spinal cord and the sympathetic nervous system.[1,2] Light exposure during the night can acutely suppress melatonin levels. However, darkness does not stimulate melatonin, it is merely permissive for the production of melatonin. In humans, even moderate light intensities, similar to indoor intensities, are able to cause substantial suppression of melatonin production.[3] While light is the most important environmental factor influencing melatonin levels, various drugs, such as beta-blockers, can also profoundly affect melatonin levels.[4] The notion that melatonin decreases with age, as reported by Arendt and Skene[5] and Zhdanova[6], has more recently been challenged. In a comparison between healthy and drug-free older subjects (65–81 years) and younger subjects (18–30 years), no significant difference was found in the duration, mean, or area under the curve of the plasma melatonin profile as assessed during highly controlled laboratory conditions (constant routine protocol).[7] This finding, which has been confirmed by a number of other independent investigators,[8–10] should have been considered when evaluating the impact of age on melatonin secretion. Further investigation is necessary to determine whether insomnia and other health issues, medication use and/or experimental light conditions, and not age per se, might account for some of these discrepancies between these studies of healthy older subjects without sleep complaints[8–10] and those cited in the reviews in this issue.

Melatonin as a chronobiotic

Melatonin has been shown to phase-shift and entrain the circadian timing system in a variety of species. This has been shown in an in vitro slice preparation of the rodent SCN,[11] in vivo in rodents under constant conditions,[12] and in humans under more and less stringent conditions.[13] The influence of melatonin as a chronobiotic in humans is discussed in detail by Arendt and Skene[5]. In designing future studies to investigate the phase-shifting and entraining potential of melatonin in humans, several methodological considerations should be kept in mind: (1) Melatonin may promote sleep[6,14,15], which would then affect light exposure (since eyes are closed during sleep). Observed phase shifts after melatonin administration may thus in part be due to changes in the timing of light exposure, given the powerful phase-shifting effects of light. Moreover, this sleep-inducing effect of melatonin may induce phase shifts due to direct non-photic resetting effects of sleep itself; (2) A high melatonin dosage could lead to spill-over of high melatonin plasma levels from the phase-advance to the phase-delay portion of the melatonin phase-response curve, or vice versa, resulting in the underestimation of the phase-shifting capacity of melatonin. Desensitization or down regulation of melatonin receptors could be an alternative explanation why higher dosages may be less effective (see also Zhdanova[6]); (3) Melatonin may result in transient phase shifts or changes in circadian period. Longer studies under forced desynchrony conditions would be required to distinguish these effects from phase shifting; (4) Since melatonin can have acute sleep-promoting influences,

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the sleep–wake cycle cannot be used as a reliable circadian phase marker in such studies. Dim light melatonin onset, cortisol acrophase, or the core body temperature minimum, as collected under well-controlled laboratory conditions, are examples of circadian phase markers that could be used to evaluate phase shifts in such studies.[16] Recent studies in non-entrained completely blind subjects demonstrate that daily melatonin administration is able to entrain at least some of these individuals.[17,18] These studies further demonstrate that melatonin is able to cause daily phase advances of at least half an hour, although this magnitude may be a reflection of an interaction between melatonin and non-photic environmental and/or behavioral synchronizers.

Interestingly, but not discussed in the review of the chronobiotic effects of melatonin by Skene and Arendt, is the finding by Sack and coworkers thats melatonin as compared to placebo reportedly elicited phase delays of up to ~9 h within 7 days in shift workers.[19] In these individuals the timing of the dim light melatonin onset was assessed in the laboratory before and after 1 week of night work (21:30–07:30 h) during which time they received melatonin (0.5 mg) or placebo daily before their daytime sleep episode (starting between 08:00 and 10:00 h) in a single-blind, placebo controlled, crossover design. Although there was a large interindividual variability, 6 of the 24 subjects when treated with melatonin showed a phase delay of 3 to 9 h, as compared to a minimal shift when on placebo. The mechanism underlying these large phase shifts by melatonin remains unknown, although an interaction between melatonin and light exposure might be involved. However, in simulated shift-work studies by Dawson et al.[20] and by Crowley et al.,[21] no such synergistic effects were observed. The potential of the interaction between melatonin and light warrants further investigation.

The effect of melatonin on sleep

Species-dependent effects of melatonin

The statement that melatonin has a sleep-promoting effect should be placed in the context of the species under investigation. In humans and other day-active mammals, melatonin is high during their resting/sleep phase, whereas in night-active mammals, melatonin is high during their activity/wake phase. Indeed, it has thus been argued that melatonin is 'a hormone of darkness'[5,6,15,22] rather than a 'sleep hormone'. In line with this, melatonin might even be wake-promoting rather than sleep-promoting in some nocturnal mammals.[23] Melatonin may be described as a sleep-promoting hormone in humans, but this cannot be generalized to all mammals.

In the meta-analysis by Brezinski et al.[14] in which 17 studies were included to investigate the sleep-promoting potency of melatonin, the general conclusion was drawn that melatonin has only a modest sleep-promoting effect, with an increase in sleep efficiency of 2–3%. This is consistent with the conclusion of the recently published, rigorous meta-analysis on the effect of melatonin as a sleep-promoting substance conducted by the Agency for Healthcare Research and Quality as part of its Evidence Based Practice program.[24] From the results of that federal review it was concluded that "…the magnitude of the effects of melatonin appears of no clinical significance [in people with sleep disorders], except for people suffering from delayed sleep phase syndrome". However, it was also stated that "the presence of substantial heterogeneity in the conduct of and results across studies… limits one from drawing firm conclusions regarding the effectiveness of melatonin in these populations". Therefore, more rigorously controlled studies under well-defined conditions are required. In the meta-analysis by Brzezinski et al.,[14] data were combined irrespective of: (1) the time-of-day of administration; (2) whether subjects had reduced sleep quality; and (3) whether melatonin was administered a single dose or as a daily repeated dose. In the meta-analysis conducted by the AHRQ, the data were categorized, e.g., by primary versus secondary sleep disorders, by time of day, by duration of administration, and by dose, separately for each category. However, each analysis remained complicated by the heterogeneity in the remaining categories. With the exception of when the preferred sleep episode is advanced into the wake maintenance zone, i.e. earlier than the habitual time, the efficacy of melatonin in the promotion of sleep in patients with sleep disorders is yet to be determined. Differences in study design can result in markedly different efficacy of melatonin in promoting sleep and complicate a general conclusion of the effect of melatonin on sleep. Some of these issues are discussed briefly below.

Daytime versus nighttime administration

There is general consensus that administration of melatonin during the daytime when no endogenous

melatonin is present has a sleep-promoting effect in healthy subjects (see Zhdanova[6], and van den Heuvel et al.[15]). Also administration of melatonin during the 'wake maintenance zone'—the circadian phase of the strongest wake drive, which occurs just before habitual bedtime—results in reliable promotion of sleep.[25,26] The influence of nighttime melatonin administration seems more dependent on subject selection, the duration of administration, and the dosage used.[13] Taking into account the timing of melatonin administration relative to the phase of the circadian timing system is therefore crucial when comparing the sleep-promoting efficacy of melatonin between studies.

Subject selection

Studies of melatonin in healthy sleepers during their habitual sleep episode does not result in improvements in sleep due to an inability to improve sleep efficiency when pretreatment levels are above ~90%.[27] In subjects with sleep disturbances, it has been suggested that those with reduced nighttime melatonin levels may benefit from nighttime melatonin supplementation, although the correlation of the effectiveness of exogenous melatonin administration with endogenous melatonin production requires further investigation.[28,29] The absence of a correlation between variations in endogenous melatonin levels and sleep quality might be due to inter-individual differences in melatonin receptor sensitivity and/or density and due to a threshold phenomenon in that the dose-response relationship of melatonin and sleep may be restricted to a limited range (see Zhdanova[6]).

Single versus repeated administration

For nighttime melatonin administration a daily repeated dose before bedtime over several weeks has been reported to be more effective in improving sleep as compared to a single dose or even nightly doses for one week in melatonin-deficient elderly insomniacs and patients with essential hypertension.[30,31] However, in the recent meta-analysis by the AHRQ in sleep disorders, no overall difference in efficacy of melatonin to promote sleep was found between administration for less than 1 week, 1-2 weeks, and 3-4 weeks.[24] Further studies are required that are specifically designed to investigate the time-course of effect of melatonin on sleep, including the change in efficacy within 1 week. Furthermore, the effect of prolonged nighttime melatonin administration on sleep has been reported to outlive the administration period by several days to weeks.[32] If these findings were confirmed in larger studies, this would suggest that the sleep-promoting mechanism of melatonin is different from that of current hypnotics (e.g. benzodiazepines). Nighttime melatonin might then be especially beneficial in the treatment of those patients with chronic insomnia. Multi-center clinical trials are needed to investigate whether chronic melatonin administration may be beneficial for the treatment of chronic insomnia. In addition to the potential beneficial influences on sleep, chronic melatonin administration may also be of clinical relevance in the treatment of essential hypertension.[31] Prolonged nighttime melatonin administration (and not a single dose) resulted in a blood pressure reduction in patients with essential hypertension (see also Claustrat et al.[22]). This study warrants further research into the clinical potential and fundamental mechanism involved in the blood pressure reduction by repeated nighttime melatonin administration in essential hypertension, a condition that affects approximately one-third of US adults.[33]

Endogenous melatonin and sleep

The quality of sleep scheduled at a phase when no melatonin is present ("biological day") is compromised as compared to that during a phase when melatonin is present ("biological night"). To determine whether this is due to the presence or absence of melatonin or to a difference in circadian phase can be assessed by investigating the effect of exogenous melatonin administration during the daytime and by investigating the effect of suppressing endogenous melatonin levels at night. Exogenous melatonin administration resulting in physiological plasma concentrations are able to improve sleep propensity during the middle of the day and during the 'wake maintenance zone' just prior to habitual bedtime[6,25,43] Suppressing endogenous melatonin levels at night by light or beta-blockers results in compromised sleep.[34,35] A limitation of these studies is that light and beta-blockers also cause physiological changes other than the suppression of melatonin, which may result in changes in sleep quality. Furthermore, none of these studies address the question as to whether a chronic absence or presence of melatonin production would have any noticeable effect on sleep quality. In a recent study, we found that patients with chronic spinal cord injury that interrupted the pathway in the regulation of melatonin, and who thus did not produce melatonin at night, had a significantly decreased sleep quality

as compared to patients with chronic spinal cord injury with intact nighttime melatonin surge.[36] This provides further evidence that also a chronic absence of endogenous melatonin production is associated with decreased sleep quality.

Mechanism

Evidence from studies in both day-active animals[37] and human[38,39] that the circadian pacemaker promotes wakefulness at certain times of day, together with evidence that neuronal firing of the mammalian suprachiasmatic nucleus (SCN) is inhibited by SCN Mel_{1a} receptor-specific melatonin binding,[40] has led to the hypothesis that melatonin may act to facilitate sleep by inhibiting the circadian drive for waking that emanates from the SCN.[26,41,42] If this hypothesis were proven to be correct, we propose that it would be more appropriate to classify the action of melatonin as a chronohypnotic, rather than simply as a hypnotic.

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