

Potential Action of Melatonin in Insomnia

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THE HORMONE MELATONIN, SECRETED BY THE PINEAL GLAND, IS INVOLVED IN THE CONTROL OF THE CIRCADIAN SYSTEM AND HAS BEEN IMPLICATED IN THE CONTROL OF SLEEP (FOR A REVIEW, SEE CAJOCHEN ET AL¹). Melatonin secretion occurs primarily across the night, with onset of secretion temporally related to a decrease in core body temperature and an increase in sleepiness levels.

Melatonin levels are highest during adolescence and begin to gradually decline from the mid-20s.² As a consequence, melatonin levels are decreased in the middle and latter years of life. In addition, the hypothermic response to melatonin may attenuate with increasing age.³ A concurrent increase in the incidence of insomnia also occurs during these latter years.⁴ It has been previously proposed that decreased melatonin levels may underlie the increased incidence of insomnia.⁵ Hence, it has been suggested that administration of melatonin may be a potential treatment for insomnia.

Administration of melatonin to young healthy subjects during the daytime has been widely reported to produce both soporific and hypothermic effects.¹ Few studies, however, have administered melatonin at night prior to the primary sleep period. Despite this apparent shortcoming, several studies have examined the effectiveness of melatonin as a potential treatment for insomnia. These studies have administered melatonin to insomniac subjects at night and have investigated the effects on subsequent sleep, with mixed results.

While some researchers have reported a positive effect of melatonin administration,⁵⁻⁹ others have reported little or no effect.¹⁰⁻¹³ For example, some studies reported decreased sleep latency and increased sleep efficiency, while others reported no change in sleep parameters. Further, negative effects of melatonin administration to insomniacs have also been reported. For example, Dawson et al¹³ reported increased wake after sleep onset during transbuccal melatonin administration to individuals with sleep-maintenance insomnia.

One explanation for the differences between various studies is the dose of melatonin administered. For the studies where no positive effect of melatonin administration was evident, doses ranged between 0.5 mg and 5.0 mg, using both immediate- and sustained-release formulations. In those studies where an improvement in the sleep of insomniacs was reported, the administered doses ranged between 0.3 mg and 75.0 mg, with both immediate- and sustained-release preparations. Therefore,

there does not seem to be a clear dose effect that predicts successful treatment of insomnia. Another explanation may be in the timing of the dose, relative to bedtime. Traditional hypnotics, such as benzodiazepines, are typically ingested 15 to 30 minutes prior to the desired bedtime. If melatonin's soporific effects are mediated via its hypothermic effects, it may be necessary to ingest melatonin at an earlier time, relative to bedtime, to allow sufficient time for the hypothermic-soporific cascade to occur. Similar to the doses of melatonin administered in these studies, the timing of administration has varied between studies but not consistently between those studies that report a positive effect and those that don't, with some overlap between the 2 groups.

Despite the lack of consistency between studies, several researchers have supported the use of melatonin therapy for the treatment of non-circadian-based insomnia. Following nocturnal administration of melatonin to insomniacs, both Wurtman and Zhdanova⁸ and Ellis et al¹¹ reported increased subjective sleepiness, MacFarlane et al⁶ reported increased subjective sleep duration, and James et al¹⁰ reported decreased subjective sleep duration but increased subjective sleep quality. In contrast, Mendelson et al¹⁴ reported a decrease in both subjective sleep duration and sleep quality.

Using polysomnography, Mendelson et al¹⁴ reported no effect of melatonin administration on sleep-onset latency or sleep efficiency. Similarly, James et al¹⁰ reported a decrease in latency to rapid eye movement sleep but no effect on other polysomnographic variables. Hughes et al,¹² using polysomnography, reported decreased sleep latency with 3 different dosages of melatonin but no effect on total sleep time, sleep efficiency, wake after sleep onset, or sleep offset relative to placebo. In a further study, Dawson et al¹³ also reported no effect of melatonin administration on any polysomnographically measured sleep variables, except for increased wake after sleep onset. To date, only 1 study investigating nocturnal melatonin administration in insomniacs using polysomnographic measures has reported a positive effect of this compound. Zhdanova et al⁹ reported an increase in polysomnographically assessed sleep efficiency in a group of elderly (> 50 years of age) insomniac subjects.

In contrast, studies that use actigraphy as a measure of sleep and sleep quality have consistently reported an improvement in these variables following nocturnal administration of melatonin to insomniac subjects. Garfinkel et al,⁵ Haimov et al,⁷ and Wurtman and Zhdanova et al⁸ all reported a decrease in latency to sleep and either an increase in sleep efficiency^{5,7} or a decreased number of awakenings⁸ using actigraphy. These inconsistencies using objective measures (polysomnography vs actigraphy) of sleep and sleep quality following melatonin administration to insomniacs have yet to be adequately addressed. It is unclear why some studies report an improvement in sleep and sleep quality following nocturnal administration of melatonin to insomniacs, while others report a negative or no effect of melatonin administration. One potential reason for the discrepancies is the tool used to assess sleep. While polysomnography provides a detailed analysis of brain state and sleep stages, actigraphy uses movement to define sleep-wake activity. It is possible, how-

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ever, that it is not the tools per se that are producing the difference in results but, rather, the underlying mechanism of action of melatonin.

The exact means by which melatonin induces its soporific effects have not been fully elucidated. It has been suggested that the hypothermic actions of melatonin may underlie its soporific effects,¹ but as yet only a temporal relationship between increased melatonin levels, decreased core temperature, and initiation of sleep has been demonstrated. Since the positive effects of melatonin treatment in insomniacs appear to manifest almost exclusively in studies using actigraphic measures of sleep, it may be hypothesized that melatonin acts as a muscle relaxant, thereby reducing body movements and increasing the appearance of actigraphically defined *sleep*. In fact, if melatonin does act by reducing muscle tone, this may in itself increase the likelihood of sleep and may promote the soporific actions of melatonin. Indeed, Wurtman and Zhdanova,⁸ using subjective reports, describe decreased activity levels by insomniacs who had received melatonin.

Support for the relaxant effect of melatonin in human insomnia subjects may be derived from animal studies of melatonin. In rodent models, an anxiolytic action of melatonin has been reported, with similarities between the actions of melatonin and benzodiazepines described.¹⁵⁻¹⁷ In addition, analgesic,¹⁸ antidepressant,¹⁹ and anticonvulsant¹⁸ properties of melatonin have been described in various rodent models. It has been suggested that many of these effects are mediated via central benzodiazepine receptors, with a diminished or absent response to melatonin administration in the presence of central benzodiazepine antagonists.¹⁶⁻¹⁹ Other studies, however, have reported no effect of central benzodiazepine antagonists on the soporific effects of melatonin administration in either mice²⁰ or humans.²¹ Despite these findings, many of the actions of melatonin on sleep propensity, anxiety, thermoregulation, and convulsions resemble those reported following administration of benzodiazepines.¹⁵⁻¹⁷ It is possible that some of these actions of melatonin may be mediated via peripheral benzodiazepine receptors (as have been identified by Raghavendra et al¹⁹).

A small number of studies have examined the effectiveness of melatonin administration in children experiencing insomnia. For example, Smits and colleagues²² reported an increase in total sleep time with no effect on sleep-onset latency but with significant advances in time of lights off and time of sleep onset, measured by diary and actigraphy, in children (aged 6-12 years). Similarly, Ivanenko et al²³ reported positive effects of melatonin administration in children and adolescents (aged 2-18 years) who were experiencing various types of insomnia, including sleep-onset insomnia, sleep-maintenance insomnia, sleep-wake cycle disruption, and delayed sleep phase syndrome (DSPS). The findings from these 2 studies, however, may reflect a chronobiotic rather than a primarily soporific or hypnotic effect of melatonin administration. The effects of melatonin administration in children and adolescents, particularly on reproductive development, have not been well studied, however. In adults, melatonin therapy has been demonstrated to improve sleep, via a chronobiotic effect, in patients suffering from DSPS (as has been reviewed by Dagan²⁴). The findings from studies in DSPS patients suggest that using exogenous melatonin to treat DSPS patients may be the most promising clinical application of melatonin at present.

At present the magnitude of beneficial effects following melatonin administration to insomniacs is unclear. Further, the mechanism of action of this hormone with relation to sleep initiation remains to be fully described. Hence, if melatonin does, at least in part, produce a decrease in muscle and body activity, a combination of melatonin administration with relaxation techniques may prove to be positive in the treatment of insomnia.

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