Sleep Medicine Reviews (2005) 9, 71–80

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SLEEP MEDICINE reviews

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CLINICAL REVIEW

Melatonin as a hypnotic: Con

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KEYWORDS
Melatonin;
Hypnotic;
Sleep;
Soporific;
Exogenous;
Endogenous;
Circadian rhythms

Summary The physiological roles of melatonin are still unclear despite almost 50 years of research. Elevated melatonin levels from either endogenous nocturnal production or exogenous daytime administration are associated in humans with effects including increased sleepiness, reduced core temperature, increased heat loss and other generally anabolic physiological changes. This supports the idea that endogenous melatonin increases nocturnal sleep propensity, either directly or indirectly via physiological processes associated with sleep. The article "Melatonin as a hypnotic—Pro", also in this issue, presents evidence to support this viewpoint. We do not entirely disagree, but nevertheless feel this is an overly simplistic interpretation of the available data. Our interpretation is that melatonin is primarily a neuroendocrine transducer promoting an increased propensity for 'dark appropriate' behavior. Thus, it is our view that exogenous melatonin is only hypnotic in those species or individuals for which endogenous melatonin increases sleep propensity and is consequently a dark appropriate outcome. Evidence supporting this position is drawn primarily from studies of exogenous administration of melatonin and its varied effects on sleep/wake behavior based on dose, time of administration, age and other factors. From this perspective, it will be shown that melatonin can exert hypnotic-like effects but only under limited circumstances.

Introduction

The initial isolation of the pineal hormone melatonin[1] marked the start of an increasing research effort to identify the endogenous role of melatonin and the mechanisms by which it regulates the physiology of both mammalian and non-mammalian species. While our current understanding of melatonin has therefore increased substantially, especially regarding melatonin's involvement in the circadian timing system, the putative role that

Abbreviations: EEG, electroencephalograph; $(GABA)_A$, γ-aminobutyric acid receptor complex; NREM, non-rapid eye movement (sleep); REM, rapid eye movement (sleep).

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doi:10.1016/j.smrv.2004.07.001

endogenous melatonin may play in regulating sleep and how this role is mediated remains unclear.

In diurnal species, the nocturnal production of melatonin and occurrence of sleep are closely related. In humans, the onset of melatonin production typically coincides with an increase in the propensity to fall asleep (sometimes termed the 'sleep gate') and follows a forbidden zone for sleep in the early evening.[2] This relationship may not be purely coincidental. Under conditions that force the circadian system to free run (i.e. an ultra-short sleep/wake cycle), the onset of melatonin production and the timing of the sleep gate have been observed to remain time-locked to each other.[3] While such data do not confirm a causal role of endogenous melatonin in the regulation of normal sleep/wake behavior, they are generally consistent with studies examining the effect of exogenous melatonin on sleep propensity.

Potential mechanisms by which melatonin may increase sleep propensity

Whether melatonin regulates sleep/wake behavior by increasing sleep propensity or by inhibiting wakefulness,[4] studies with daytime oral administration of either melatonin or hypnotics typically show that increased sleepiness occurs in association with decreasing core temperature.[5–8] In contrast, agents such as caffeine, amphetamines, nicotine and cocaine decrease sleepiness and increase body temperature.[9] This association has been documented in humans for at least half a century, leading to consistent suggestions that circadian changes in body temperature, at least partly mediated by endogenous melatonin secretion, are involved in the regulation of sleep/wake behavior.[9–11] Nevertheless, evidence of a causal link between core hypothermic effects and sleep-induction following ingestion of melatonin is lacking and should be addressed in future research. In addition, it has been suggested that melatonin may exert sleep-promoting effects via indirect chronobiotic effects on the circadian timing system[12] or directly through occupation of the γ-aminobutyric acid $(GABA)_A$ receptor complex, although there is some evidence that central GABA receptors are not involved in mediating melatonin's effects in humans.[13] While it is important here to introduce possible mechanisms, a detailed exploration is, however, beyond the scope of the current paper.

This review instead aims to examine the evidence that is inconsistent with melatonin acting as a hypnotic agent when administered exogenously. While ingested melatonin may sometimes have effects compatible with a hypnotic mode of action, we contend that these are only apparent under a limited set of circumstances. In Section 3, we briefly present some evidence that has historically led to suggestions that melatonin possesses significant hypnotic effects. However, we anticipate that this area will be covered extensively in the article "Melatonin as a Hypnotic—Pro", also in this issue. Thereafter, we present some key exceptions to the rule, or in other words, evidence that supports the suggestion that melatonin may be hypnotic, but only under specific conditions. In particular, we present evidence from various studies suggesting that the effects of exogenous daytime melatonin are attenuated or absent completely in nocturnal species, at physiologically relevant levels, at different times of the day or phases of the menstrual cycle, in conditions not conducive to sleep or where there is motivation not to initiate sleep, and in elderly individuals and insomniacs.

Hypnotic-like effects following melatonin administration

In a letter to the editor of the Journal of Sleep Research, Wirz-Justice and Armstrong[14] referred to a hypnotic as, "A drug which produces drowsiness and facilitates the onset and maintenance of a state of sleep that resembles natural sleep in its electroencephalogram (EEG) characteristics, and from which the recipient can be aroused easily". They point out, however, that the classical hypnotic drugs (e.g. benzodiazepines) do not fully comply with this definition, as the sleep-induced does not typically resemble 'natural' sleep. Specifically, benzodiazepine administration typically decreases the amount of REM sleep, slow wave sleep and EEG power in the delta and theta range when compared with normal (unmedicated) sleep. In addition, with increasing dose hypnotics tend to produce greater sedation and eventually, coma and death. This appears not to be the case with melatonin, as even with large pharmacological doses[15,16] no *involuntary* loss of consciousness has ever been reported. In any case, Wirz-Justice and Armstrong[14] favor the term soporific to hypnotic in description of melatonin's effects on humans, and we use it hereafter to refer specifically to its ability to increase sleep propensity and induce sleep.

Studies with human volunteers to whom melatonin has been administered exogenously, typically report a dose–response effect on sleep propensity across doses that produce physiological and low