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MELATONIN AND HUMAN RHYTHMS

Josephine Arendt

Centre for Chronobiology, School of Biomedical and Molecular Sciences, University of Surrey, Guildford, England

Melatonin signals time of day and time of year in mammals by virtue of its pattern of secretion, which defines 'biological night.' It is supremely important for research on the physiology and pathology of the human biological clock. Light suppresses melatonin secretion at night using pathways involved in circadian photoreception. The melatonin rhythm (as evidenced by its profile in plasma, saliva, or its major metabolite, 6-sulphatoxymelatonin [aMT6s] in urine) is the best peripheral index of the timing of the human circadian pacemaker. Light suppression and phase-shifting of the melatonin 24 h profile enables the characterization of human circadian photoreception, and circulating concentrations of the hormone are used to investigate the general properties of the human circadian system in health and disease. Suppression of melatonin by light at night has been invoked as a possible influence on major disease risk as there is increasing evidence for its oncostatic effects. Exogenous melatonin acts as a 'chronobiotic.' Acutely, it increases sleep propensity during 'biological day.' These properties have led to successful treatments for serveal circadian rhythm disorders. Endogenous melatonin acts to reinforce the functioning of the human circadian system, probably in many ways. The future holds much promise for melatonin as a research tool and as a therapy for various conditions.

Keywords Melatonin, Light, Circadian and Circaanual Rhythms, Chronobiotic, Sleep, Sleep Disorders, Photoperiodism

INTRODUCTION

It has been nearly 50 yrs since Aaron Lerner identified melatonin and, after self-administration, reported that it made him feel sleepy (Lerner et al., 1958). It has been 30 yrs since the first practical radioimmunosorbant assay) (RIA) was developed to measure melatonin in peripheral body fluids (Arendt et al., 1975; Kennaway et al., 1977; Rollag and Niswender, 1976), 25 yrs since bright white light was shown to suppress melatonin completely (Lewy et al., 1980), and around 20 yrs

Address correspondence to Josephine Arendt, Centre for Chronobiology, School of Biomedical and Molecular Sciences, University of Surrey, Guildford GU2 7XH, England. E-mail: arendtjo@surrey.ac.uk

since the chronobiotic properties of melatonin in humans were uncovered (Arendt et al., 1984, 1985) and melatonin binding sites in the suprachiasmatic nuclei (SCN) and pars tuberalis were discovered (Vanecek et al., 1987; Williams and Morgan, 1988). These stages in the study of the pineal hormone have enhanced our current understanding of the role and effects of melatonin in humans. The eventual demonstration of entrainment of human free-running rhythms by melatonin (Lockley et al., 2000; Middleton et al., 1997; Sack et al., 2000) after the first demonstration of the synchronization of activity in rats (Redman et al., 1983) finally convinced even the most skeptical of melatonin's therapeutic merit as a chronobiotic, and at present the first agonists are coming of age (Millan et al., 2005; Anon, 2005).

During the intervening years, the elucidation of the control mechanisms of melatonin secretion provided the rationale for an enormous number of investigations into the function of the central circadian clock: melatonin is the most direct peripheral link to clock timing and its profile in plasma, saliva, and/or its metabolite 6-sulphatoxymelatonin (aMT6s) in urine remains the most precise and reliable measure of human circadian timing (Arendt, 2005).

PHYSIOLOGICAL ROLE OF MELATONIN

Seasonal Rhythms/Photoperiodism

Animal studies identified the fundamental role of melatonin as a photoneuroendocrine transducer of information on day length. Melatonin, by its changing duration of secretion at different day lengths (the longer the night the greater the duration of hormone secretion), is probably a universal biological signal indicating darkness (Arendt, 1995; Goldman, 2001; Malpaux et al., 2001). It is the only solidly established humoral method of signalling time of day and time of year to physiological systems, and it is essential for the timing of seasonal responses in photoperiodic seasonal species. Research conducted on photoperiodic seasonal species has informed human studies. Imposition of different day lengths in humans reveals a conserved photoperiodic response, and the evidence to date indicates that melatonin acts as a biological signal for dawn and dusk in humans, as in other species (Arendt, 1999; Vondrasova-Jelinkova et al., 1999; Wehr, 1991, 2001). The effects of melatonin on sleep, within an extended 'sleep opportunity,' seem to be exclusive of gross alterations of sleep structure or total sleep time. Rather, melatonin redistributes the timing of sleep in a manner comparable to that of sleep in long and short nights in animals (Rajaratnam et al., 2004).

Human seasonality is a much understudied subject. It is impossible to keep normal healthy humans in constant conditions for long periods of

time to investigate endogenous circannual rhythms and their possible timing by melatonin secretion. Such experiments were conducted on sheep for 5 yrs (Woodfill et al., 1994). We are left only with correlative observations and experiments on short-term possible seasonal effects of melatonin in humans. Some of the most important observational studies were conducted at high latitudes. Here, increased duration of melatonin secretion (Beck-Friis et al., 1984; Makkison and Arendt, 1991) was reported, and higher daytime levels in winter (Ronnberg et al., 1990) were associated with diminished reproductive function (Kauppila et al., 1987). Studies in both Polar (Broadway et al., 1987; Yoneyama et al., 1999) and temperate regions (Bojkowski and Arendt, 1988) revealed a phase advance from winter to summer. Also of interest is preliminary evidence that human pinealectomy is associated with a decrease in seasonality (Macchi et al., 2002).

Analysis of human conception rates for very large numbers of births at different latitudes (Smolensky et al., 1972; Roenneberg and Aschoff, 1990) suggests a photoperiodic influence on fertility (greater in lengthening days). Morning bright-light exposure is reported to stimulate production of both human luteinizing hormone (LH) and cortisol (Leproult et al., 2001; Yoon et al., 2003). There is evidence that timed light treatment can regulate and restore disturbed menstrual cycle function (Lin et al., 1990). Light-dark conditions influence the immune system (Nelson and Drazen, 2000; Prendergast et al., 2002). The incidence of detected breast cancer is reported to vary by season (Mason and Holdaway, 1991), and the success of *in vitro* fertilization is also reported to depend on season (Rojansky et al., 2000).

If melatonin is transducing information on light-dark conditions in humans, there is considerable scope for its role, both endogenous and therapeutic, in human fertility and other seasonal phenomena.

CIRCADIAN RHYTHMS

The importance of melatonin on the human circadian system remains a matter for debate. Preliminary work shows that human pinealectomy is associated with decrements in sleep (Macchi et al., 2002), although there is little evidence to suggest that melatonin is essential to normal function. Perhaps, however, it is essential to optimal function. There is no doubt that the timing of melatonin secretion is closely associated with the timing of sleep propensity and certain aspects of the electro encephalogram (EEG) (Dijk and Cajochen, 1997; Wehr et al., 2001). The timing of peak melatonin concentration coincides closely to the nadirs of core body temperature, alertness and performance, clearence of plasma triglycerides, and other night-time phenomena (Rajaratnam and Arendt, 2001). However, this finding does not prove that melatonin is causal. There is also

evidence for melatonin's influence on glucose homeostasis (la Fleur et al., 2001), the immune system (Maestroni, 1998), and cardiovascular function (Scheer et al., 2004). To the author's knowledge, no animal knockout of the hydroxyindole-O-methyl transferase (HIOMT) gene (the final step in melatonin synthesis) exists; such a construct would be of great interest for investigating the physiological role of melatonin.

The use of melatonin antagonists in humans has yet to be reported, but it will no doubt cast much light on this subject. The adrenergic β_1-receptor antagonist atenolol suppresses melatonin and is sometimes associated with disturbed sleep. In one experiment, acute restoration of melatonin reversed the short-term deleterious effects on sleep (Van Den Heuvel et al., 1997). Long-term treatment with atenolol resulted in a 50% reduction in melatonin production, but showed no relationship to effects on sleep in the report by Rommel and Demisch (1994).

There is no doubt that humans sleep better if sleep is taken during the appropriate period of melatonin secretion; however, is this due to melatonin itself, or to other factors, or to the whole circadian system being at odds with behavior? If melatonin is present at an abnormal phase during the day, it is strongly associated with daytime naps (Lockley et al., 1997b). Some of the evidence for an important role of melatonin in sleep is that pharmacological suppression of daytime melatonin production diminishes daytime sleepiness, and treatment with exogenous melatonin at night restores night-time sleep (De Leersnyder et al., 2001a, b). Pharmacological suppression of endogenous melatonin by atenolol enhances the human phase-shifting response to light (Deacon et al., 1998). Exogenous melatonin can act in concert with light and also act to partially counter light for phase-shifting, if given at an appropriate circadian phase (Deacon and Arendt, 1996b; Wirz-Justice et al., 2004). Thus, its presence modifies circadian responses. As a result of these few observations, it is possible to predict that the presence of melatonin hinders rapid adaptation to phase-shift as originally observed in rats (see Arendt, 1995 for references) and that persons treated with β_1 antagonists are likely to suffer less jet lag and to adapt more readily to night work than untreated individuals. We can also predict (as has been noted on numerous occasions) that appropriate combinations of light and melatonin treatment should be more efficient in changing phase than either treatment alone, although there is little information on this subject.

Suppression of melatonin by light does not seem to be an essential part of the phase-shifting effects of light (Krauchi et al., 1997). The acute elevation of core body temperature by light at night, however, does seem to depend in part on melatonin suppression (Cagnacci et al., 1992; Strassman et al., 1991), but does not correlate with increased alertness induced by light during the day (Ruger et al., 2005); albeit, there is a

strong correlation between increased alertness and melatonin suppression at night (Cajochen et al., 2000).

IMPORTANCE TO HUMAN HEALTH

Characteristics of the Human Circadian System

Importantly, one of the first (and some subsequent) demonstrations that light pulses could shift the human circadian clock used melatonin as the marker rhythm (Broadway et al., 1987; Shanahan and Czeisler, 1991). The phase-response curve (PRC) to light in humans in highly controlled conditions is now well defined and serves as a template to calculate appropriate light exposure times to shift circadian phase (Khalsa et al., 2003). The assessment of the free-running human circadian period has relied extensively on melatonin and/or aMT6s as a marker rhythm, both in sighted and blind subjects (Czeisler et al., 1999; Lewy and Newsome, 1983; Lockley et al., 1997a; Middleton et al., 1996; Lewy et al., 2005). However, much remains to be done in this area. Although melatonin is the best index of clock function to date, there are situations in which it may not reflect clock function adequately (Gordijn et al., 1999). Moreover, ambient photoperiod influences the phase-shifting response to light, and seasonal variations in adaptation to shiftwork (and possibly jetlag) may be related to this phenomenon (Barnes et al., 1998; Burgess and Eastman, 2005). Whether or not the human free-running circadian period is related to previous ambient photoperiod is a question of some interest. Related evidence suggests that sensitivity of melatonin suppression may be a function of short- and long-term photoperiodic history (Hebert et al., 2002; Owen and Arendt, 1992); controlled investigations into photoperiod-dependent phase shifting in humans have only just begun.

Evaluating Adaptation to Phase-Shift in Real Life

As a marker of clock timing, melatonin (and its metabolite aMT6s in urine) has enabled robust definitions of the state of adaptation to shift work and jet lag in field situations (Arendt, 2005; Rajaratnam and Arendt, 2001). A combination of light and activity monitoring by wrist actigraphy and measurement of urinary aMT6s provides a wealth of information on circadian phase, sleep, and light exposure in field situations. Such data are essential prior to invoking strategies—such as advice, light treatment/light avoidance, and/or melatonin treatment (see below)—to counter the problems of circadian desynchrony. For the majority of night workers and time-zone travellers, the response to an abrupt shift of time cues varies on an individual basis (Deacon and Arendt, 1996a; Gibbs et al., 2002; Sack and Lewy, 1997; Waterhouse et al., 2005; Griefahn, 2006).

Circadian Photoreception: Therapeutic Consequences

Most recently, the suppression and phase-shifting of melatonin by light has provided endpoints for the identification of a novel circadian photoreceptor system, maximally responsive to short-wavelength light (Brainard et al., 2001; Foster, 2004; Freedman et al., 1999; Lucas et al., 1999; Thapan et al., 2001). These latter observations are of very great importance to human health. In urban environments, many people are rarely exposed to bright natural light (Okudaira et al., 1983). In an environment with impoverished time cues, there is drift of circadian phase, and the net result is that the timing of sleep and activity, imposed for social and economic reasons, is not optimal to the state of the internal clock. Moreover, with extended sleep opportunities, subjects will initially sleep for many hours more than usual (Rajaratnam et al., 2004; Wehr, 1991). Thus, many people are presumed to live in an extended state of sleep deprivation. The problem is even worse for night-shift workers and time-zone travellers, who are obliged to live in desynchrony with their internal clock, usually in the short-term after time-zone flight, but repeatedly if not continuously in night and rotating shiftwork (Akerstedt, 2005). At worst, living counter to the internal clock may lead to increased risk of major disease, including heart disease (Knutsson, 2003, 2004) and cancer (Schernhammer et al., 2001); even the current obesity epidemic may be related in part to insufficient quality sleep (Morgan et al., 2003, 2004; Spiegel et al., 1999). These phase abnormalities can now be treated by appropriate light exposure (intensity, timing, and spectral composition) or avoidance of light exposure (particularly short-wavelength light), owing to the use of melatonin as a marker rhythm and index of circadian photoreception.

Sleep and Psychiatric Disorders

The diagnosis of rhythm disorders underlying delayed-sleep-phase insomnia and the non-24 h sleep-wake disorder of many blind and a few sighted people relies on measurement of melatonin and aMT6s rhythms. Other conditions for which a robust rhythm marker will be valuable as a diagnostic aid will no doubt emerge.

Melatonin transduction of photoperiodic information in animals and its suppression by bright light at night initiated the first light treatments of seasonal affective disorder (SAD) (Rosenthal et al., 1984) as well as delayed melatonin phase in winter, which is present in healthy subjects but exaggerated in SAD (Lewy et al., 1987), and have suggested possible mechanisms for SAD. However, the precise relationship between melatonin production and SAD is not clear. Most recently, light treatment has been used with some success to manage major depression, and it has

been particularly efficacious in combination with appropriate medication (Kripke, 1985, 2005; Murray et al., 2005).

Is Endogenous Melatonin Suppression Deleterious to Health?

There is nevertheless a possible disadvantage to the use of light treatment during biological darkness in humans. It is hypothesized that the increased risk of cancer, particularly breast cancer in nurse shiftworkers, is due to light experienced at night and to the presumed suppression of melatonin (Stevens and Davis, 1996). This hypothesis is based on accumulating evidence for the anti-cancer effects of melatonin in animals (Blask et al., 1999, 2002) and on some preliminary evidence for its anti-cancer effects in humans when used as part of combination chemotherapy (Lissoni et al., 2003). The hypothesis as stated is generating a considerable amount of research. A study by Feychting and colleagues (1998) found that blind subjects who lack light perception may have a decreased incidence of cancer attributable to lack of melatonin suppression; however, some confounding factors could not be eliminated. Morning void urine aMT6s levels appear to be lower in those who develop breast cancer than in healthy subjects; however, this finding may represent a change in phase rather than suppression of the melatonin rhythm (Schernhammer and Hankinson, 2005).

Little evidence exists for a decline in melatonin production during night shiftwork, but it is likely that this can occur. In a light-induced, forced 9 h phase-shift, a clear decline in aMT6s production was noted (Deacon and Arendt, 1996a). Unpublished reports (Hall, English, and Arendt) suggest that, during a 3-day fast rotation shift schedule (3 early shifts, 3 late shifts, 3 night shifts, rest days), the amplitude of the aMT6s circadian rhythm is significantly reduced by approximately 30% during the 3 night shifts. In an even faster (2-day) rotation, however, significant changes were not observed (Costa et al., 1994).

Actual light exposure at night needs to be evaluated carefully in field studies. Light at night exerts numerous other effects. The frequent disruption of all circadian rhythms, not just melatonin secretion, is effectively a major physiological insult. Most importantly, perhaps, light directly influences the expression of the clock-gene feedback loops that drive circadian rhythms (Reppert, 2000). A series of recent animal studies (Filipski et al., 2004; Fu and Lee, 2003; Fu et al., 2002) indicate that disruption of clock-gene function is associated with increased cancer risk.

Melatonin as a Chronobiotic

Photoperiodic effects on the circadian waveform of factors like the 24 h rhythm of prolactin secretion and core body temperature, plus sleep distribution as transduced by melatonin, initiated the first attempts to modify

human circadian rhythms by exogenous melatonin administration (Arendt et al., 1984, 1985). In the dose range of 0.5 to 10 mg, melatonin can both advance or delay circadian timing, when administration is appropriately timed (Lewy et al., 1992). There is, however, some controversy regarding the ability of melatonin to phase delay the circadian system using a single morning dose (Wirz-Justice et al., 2002; Smith et al., 2005). Phase advances, and possibly phase delays, are dose-dependent using a single dose in the range of 0.05 to 5 mg (Deacon and Arendt, 1995; Lewy et al., 2005). As for light, the appropriate timing of treatment to delay or advance can in principle be predicted from the melatonin PRC in subjects whose body clock phase is known (Lewy et al., 1998), although there is considerable scatter in the data. The reported PRC to melatonin is essentially the reverse of that to light.

In a recent experiment, subjects were given a 1.5 mg surge-sustained melatonin preparation at 16:00 h daily for 8 days and then placed recumbent in very dim light for the next 16 h. Large phase advances were observed in all the measured variables (Rajaratnam et al., 2003) evaluated under constant-routine conditions before and after the treatment, and within 3 days in core body temperature, which was monitored continuously (Middleton et al., 2005).

Free-running sighted and blind subjects have been investigated for the entraining properties of melatonin. Melatonin (5 mg of a rapid-release formulation daily at 20:00 h) was able to maintain entrainment in sighted subjects placed in a very dim-light, free-running environment, and to re-entrain some, but not all, subjects after a period of free-run (Middleton et al., 1997). Initial field studies on the blind with free-running rhythms indicated that melatonin could stabilize sleep to a 24 h period and improve subjective sleep, without entrainment of the cortisol, endogenous melatonin, and core temperature rhythms (Aldhous and Arendt, 1991; Arendt et al., 1988; Folkard et al., 1990). Now we know that most, but not all, blind subjects can be entrained to a 24 h day by 0.5 to 5 mg daily dosing with a rapid-release melatonin formulation, as would be expected from the phase-shifts obtained in experimental PRCs (Lockley et al., 2000; Sack et al., 2000). Once subjects are entrained, it may well be possible to maintain entrainment with even lower doses. As yet, the reasons why some subjects do not entrain are unknown (see Arendt and Skene, 2004 for discussion). Significant improvements in sleep and alertness are reported, whether or not subjects are entrained; however, in the absence of entrainment, some residual relative coordination is observed (Arendt et al., 1988; Folkard et al., 1990; Hack et al., 2003).

Sleep Inducing Properties of Melatonin

During the 'biological day,' *i.e.*, when endogenous secretion is low, melatonin induces sleepiness or sleep and lowers core body temperature

if subjects are recumbent or semi-recumbent in dim light (Cagnacci et al., 1992; Cajochen et al., 1997; Dollins et al., 1994). Rapid-release single melatonin doses of 0.3 to 10 mg have similar effectiveness, and are as effective as temazepam in one report (Stone et al., 2000). Despite extensive recent reviews of this subject, it is difficult to envision exogenous melatonin as a hypnotic medication. Melatonin exerts little effect on sleep when taken during the time of its endogenous secretion. The term 'chronohypnotic' has been coined. The author prefers, however, to consider these acute sleep-inducing and temperature-lowering effects as 'masking' and as constituent attributes of its actions as a zeitgeber. Certainly to maximize both the acute and phase-shifting effects on sleep, melatonin is best taken at a phase-advance point on the PRC by subjects with circadian $\tau > 24$ h when it occurs within 1 h or so of the desired sleep time. In the previously described experiment, when subjects were given a 1.5 mg surge-sustained melatonin preparation at 16:00 h daily and then placed in recumbency under very dim light for the next 16 h, large phase-shifts with redistribution of sleep were observed. These findings are in contrast to the few effects on sleep found using a similar protocol applied as a field experiment involving an evening and morning dose of 0.5 mg melatonin to extend the endogenous melatonin profile (Haimov et al., 1999). The data clearly show that the net effect of melatonin is a combination of acute and phase-shifting effects.

Clinical Results in the Treatment of Rhythm Disorders

The classical circadian rhythm disorders of sleep/alertness problems related to jet lag and night-time-shiftwork, delayed sleep-phase syndrome (DSPS), advanced sleep-phase syndrome (ASPS), and non-24 h sleep-wake disorder of free-running blind subjects are all, in theory, responsive to treatment by melatonin or its agonists. Sleep disorders among the elderly, possibly related to a rhythm disorder, are an important treatment target given their prevalence. The subject has been reviewed recently (Arendt and Skene, 2004).

Numerous publications have addressed the treatment of jet lag and shiftwork (Arendt et al., 2004). Two recent meta-analyses on treatments of jet lag came to different conclusions. One considers that the existing evidence shows a robust positive effect of melatonin (Herxheimer and Petrie, 2002), while the other (reporting on the use of nutritional supplements) posits little evidence for a consistent effect on sleep after time-zone change (Agency for Healthcare Research and Quality, http://www.ahrq.gov/news/press/pr2004/melatnpr.htm). Likewise, the data are inconsistent for shiftwork. Exceptions to these inconsistencies are studies in which careful treatment timing was used in field or simulation laboratory studies (Burgess et al., 2002; Folkard et al., 1993). Timing is critical to

avoid precipitating phase shifts in the 'wrong' direction. Preflight treatment with melatonin can be timed to initiate a shift in the 'right' direction, but this has rarely been done. (Arendt, 1997; Arendt et al., 1986; Samel et al., 1991). In field studies, individual variability is large and exposure to conflicting natural bright light is always a problem, although one simulation study infers that melatonin can partially counter conflicting light (Deacon and Arendt, 1996b).

The treatment of free-running blind subjects with melatonin is of particular interest. Refinements of dose, preparation, and timing of treatment continue to be assessed. However, anecdotal reports suggest that many blind subjects are now prescribed melatonin (at least in the United Kingdom), with the prescribing clinicians recognizing its benefits. Only a small number of subjects have been described in the literature to date, and thus large clinical trials are of great interest. Our group has studied a free-running blind man for nearly 20 yrs, after he initially contacted the author for help. His sleep is stabilized to a reasonable 24 h cycle; however, he never achieved full entrainment (Arendt, 1997; Arendt et al., 1988). He is, nevertheless, healthy and satisfied with his treatment.

Results of melatonin studies on DSPS have also been consistently good, and here the timing of treatment is relatively easy to predict. Patients are entrained, albeit with a delay, and it is evident that early evening melatonin treatment will induce shifts in the right direction (reviewed in Arendt and Skene, 2004).

To the author's knowledge, there is little information about the treatment of ASPS by melatonin. Hack (Thesis, University of Surrey, UK, 2004) successfully delayed a blind subject with ASPS by the stepwise shifting of melatonin treatment to later times.

The findings of studies on the utility of melatonin for the treatment of sleep disorders in the elderly have been somewhat inconsistent. It is possible that melatonin is most effective if the sleep problem is a rhythm disorder. A 'melatonin deficiency' syndrome has been invoked, whereby melatonin treatment of the elderly replaces a deficiency in endogenous melatonin. However, while a decline of melatonin in the elderly has frequently been reported, this does not necessarily relate to sleep problems or disorders (Arendt and Skene, 2004).

There has been considerable success in treating sleep and behavioral problems in multiply disabled children, usually those with neurological disorders (Jan and Freeman, 2004). However, to what extent this involves changes in circadian rhythms remains unclear.

Melatonin Used as a 'Sleep Aid'

Even if people are day-active, the circadian clock can drift away from its normal phase (usually by delay) with insufficient time cues

(Middleton et al., 2002). The most important of these cues is sufficiently bright light of suitable spectral composition, with short wavelengths being most effective (Lockley et al., 2003; Warman et al., 2003). This drift is particularly evident in the Polar winter in which there is no sunlight at all (Broadway et al., 1987; Francis et al., 2005), but it may be prevalent in urban indoor workers, especially those with a strong evening ('owls') chronotype preference. DSPS is a manifestation of extreme delay, and insufficient and poor quality sleep can be a result of suboptimal timing of the internal clock. Phase advance by melatonin may optimize the timing of the clock relative to the desired sleep time when taken in the biological evening by a person whose clock has drifted into a phase that is too late for optimal sleep at a conventional time. The extensive use of melatonin as a sleep aid *e.g.*, in the USA, probably results from the correction of delayed phase by evening melatonin.

CONCLUSIONS

The acute and phase-shifting effects of melatonin can be maximized by suitable dose and timing. These properties have inspired new pharmacological approaches to the treatment of health problems, and it is possible that the optimization of circadian timing will have many yet to be determined health benefits. There is very little evidence in the short-term to suggest toxicity or undesirable effects of melatonin in humans. Indeed, accumulating evidence supports the anti-cancer properties and other potential benefits of melatonin. The existence of properly evaluated and registered preparations of melatonin and/or its agonists, together with light of suitable spectral composition, constitute effective tools to counter the ill effects of the 24 h society. Future research holds the exciting prospect of dissecting out the mechanisms of action of the universal message of melatonin, from genetics to behavior.

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