Light, Melatonin and the Sleep-Wake Cycle

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Submitted: August 13, 1993
Accepted: August 20, 1994

Blood levels of the pineal hormone melatonin are high at night and low during the day. Its secretion is regulated by a rhythm-generating system located in the suprachiasmatic nucleus of the hypothalamus, which is in turn regulated by light. Melatonin is regulated not only by that circadian oscillator but acts as a darkness signal, providing feedback to the oscillator. Melatonin has both a soporific effect and an ability to entrain the sleep-wake rhythm. It also has a major role in regulating the body temperature rhythm. Melatonin rhythms are altered in a variety of circadian rhythm disorders. Melatonin treatment has been reported to be effective in treatment of disorders such as jet lag and delayed sleep phase syndrome.

Key Words: insomnia, melatonin, circadian rhythms

INTRODUCTION

Today it is well established that the pineal gland is a major transducer of photoperiodic information which is converted in the light-dark cycle to a hormonal signal. The pineal hormone melatonin is secreted during the hours of darkness and is low during daylight hours. The pineal is regulated by an endogenous rhythm-generating system located in the suprachiasmatic nuclei (SCN) of the hypothalamus. Superimposed on this rhythmic regulation is an overriding, suppressing control by light. The pineal, in turn, regulates other rhythms in the organism *via* its release of melatonin into the general circulation. In man, melatonin has both a sleep-promoting effect and a role in synchronizing the sleep-wake cycle. There are a variety of conditions in which melatonin regulation is altered and melatonin is a promising agent for use in treatment of circadian rhythm disorders.

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Relationship of pineal to the light-dark cycle

In all species studied to date melatonin levels are elevated in darkness and decrease promptly in light (Illnerova 1991). This increase during darkness is due to an increase in the activity of the pineal synthesizing enzyme N-acetyltransferase which results in a rise in the pineal content of melatonin and in release of melatonin into the circulation and is reflected in an increased urinary output of the melatonin metabolite, 6-sulphatoxymelatonin. The duration of secretion of melatonin tracks the duration of darkness in both seasonal and nonseasonal animals and in man so that melatonin has been called the hormone of darkness (Utiger 1992).

In man, the duration of both melatonin and sleep responds to changes in the photoperiod in the laboratory (Wehr 1991). The extent to which such changes occur in a naturalistic seasonal setting is unresolved (Bojkowski and Arendt 1988). The first documented physiological role of melatonin was the timing of the seasonal rhythms in animal physiology and behavior. In these, as the photoperiod changes with season,

a corresponding alteration in the pattern of secretion of melatonin occurs which triggers behavioral and physiologic changes (Karsch et al 1991). The actual timing of these bodily changes depends on the species. In seasonal breeding animals, breeding occurs at the time of year that will result in birth of offspring under optimal environmental conditions. Depending on the length of gestation, some animals are short day breeders and others long day breeders; in both cases the mechanisms producing the required physiologic and behavioral changes are coordinated by the change in pattern of melatonin secretion.

Neural regulation of the pineal

The predominant neural pathway to the pineal is *via* the sympathetic nervous input to the gland from the superior cervical ganglion (Moore and Card 1985; Cassone et al 1988; Illnerova 1991). The dominant transmitter regulation is by noradrenaline acting *via* pineal beta adrenergic receptors with some participation of alpha adrenergic receptors. Other transmitters such as VIP have a modulatory role on the pinealoctye response (Chik et al 1988). Beta adrenergic receptors regulate the synthesis of N-acetyltransferase, the rate-limiting enzyme in melatonin synthesis, by a cyclic AMP dependent mechanism. The sympathetic pathway to the gland is regulated by the SCN *via* innervation of cells of the paraventricular nuclei (Klein et al 1983; Yanovski et al 1987) which in turn project *via* the median forebrain bundle and reticular formation to the intermediolateral cell column of the thoracic cord which innervates the superior cervical ganglia. The transmitters employed in this pathway are not established but both vasopressin and oxytocin immunoreactive nerve fibres are found in the intermediolateral cell column in the rat. The SCN, which form a major rhythm generating system in the brain, receive visual information *via* the retinal-hypothalamic tract, which keeps SCN activity entrained to the photoperiod (Moore and Card 1985; Cassone et al 1988). Glutamate appears to be the primary active transmitter in the retinal projection to the SCN in the rat (Gillette et al 1993; van den Pol 1993). Serotonin inputs from the raphe nuclei together with neuropeptide Y and y-aminobutyrate inputs from the intergeniculate nucleus modulate SCN activity in the rat (Gillette et al 1993; van den Pol 1993). The human SCN contain four different populations of neurons containing vasoactive intestinal peptide, vasopressin, neurotensin and neuropeptide Y (Moore 1993). The efferent projections are widespread and include dense projections to the paraventricular nuclei (Moore 1993).

Actions of light

In man bright light treatment has acute phase-shifting effects resetting the human circadian pacemaker (Czeisler et al 1989). The action of bright light follows a phase response curve; bright light in the evening hours will produce a phase delay in the melatonin rhythm while bright light in the morning will cause a phase advance (Sack et al 1990). In addition to its role in regulating the daily rhythm, light has a unique suppressant effect on pineal activity. In man bright lights turned on during darkness will cause an acute drop in serum melatonin (Lewy et al 1980) while in the rat N-acetyltransferase activity drops within minutes of light exposure (Illnerova 1991). It is thought that the suppressant action of light is important in tailoring the daily rhythm of melatonin so that the nocturnal pattern mirrors the hours of darkness.

Bright light therapy has been used successfully in treating a variety of rhythm disorders including delayed sleep phase syndrome (Rosenthal et al 1990), seasonal affective disorder (Rosenthal et al 1985; 1987; Sonis et al 1987; Winton et al 1989; Thompson et al 1990; Joffe et al 1993) and bulimia nervosa with a seasonal component (Lam et al 1994). It has also been reported to be a useful augmentation therapy in treatment-resistant depression (Levitt et al 1991).

Other regulatory factors

In addition to the controlling effect of light, pineal activity shows changes with age, stress and under the influence of hormones. Nocturnal melatonin levels are highest in early childhood, drop through adolescence, remain fairly constant until late adult life and then show a decline (Touitou et al 1981; Waldhauser et al 1988; Bojkowski and Arendt 1990). Melatonin is relatively unresponsive to stress (Vaughan et al 1978; 1985; Monteleone et al 1992), although intense exercise has been shown to produce elevation of daytime melatonin levels (Ronkainen et al 1986; David et al 1987; Strassman et al 1989; Monteleone et al 1990). Alterations in melatonin have been reported throughout the oestrous cycle in the rat but there are inconsistent reports with a relationship with the menstrual cycle in the human (Brzezinski et al 1988; Berga and Yen 1990; McIntyre and Morse 1990). In humans, binding sites are present in the SCN which may mediate phase-shifting effects (Weaver et al 1993) and in the paraventricular nuclei of the thalamus whose function is currently unknown (Weaver et al 1991). Binding sites in the pars tuberalis, which are common in seasonal breeders including the rhesus monkey, have been found in only one of eight humans studied (Weaver et al 1993).

Actions of melatonin

In mammals the prime brain targets for melatonin are the SCN of the hypothalamus and the pars tuberalis of the pituitary. Early studies established that the SCN contained melatonin as defined by immunohistochemistry, and that local injections of melatonin had major effects on reproduction in the deer mouse. The use of [^{125}I] iodomelatonin as a radioligand has permitted the identification of melatonin receptors in SCN and pars tuberalis in mammals by radiore-

ceptor binding assay (Dubocovich 1988; Duncan et al 1988; Weaver et al 1991) and by autoradiography (Cassone 1990).

Several studies have shown that melatonin administration has entraining effects on circadian rhythms. In species which are nocturnally active, the administration of melatonin around the time of activity onset can entrain the activity-rest cycle. In constant light or dark in which locomotor activity free runs, it will cue to a daily timed injection of melatonin. Under conditions in which the timing of the light-dark cycle is shifted earlier requiring reentrainment of the activity-rest cycle, melatonin injections can facilitate reentrainment (Redman et al 1983; Armstrong 1989; Cassone 1992). There is also evidence that melatonin injections can entrain circadian rhythms in both temperature and melatonin.

In man, melatonin shifts circadian rhythms according to a phase-response curve (Lewy et al 1992) that is nearly opposite in phase to that of light exposure. Circadian rhythms are delayed with treatment in the morning and advanced when treatment is given in the evening.

These findings have led to the concept that melatonin provides a signal that supplements and reinforces the entraining effects of the photoperiod. Although the SCN receive direct information from the retinal-hypothalamic pathway by which light can influence its rhythmic activity and the SCN in turn regulate the pineal, melatonin, acting via receptors in and around the SCN, acts as a dark signal to the SCN (see Figure 1).

Effects of melatonin in man

In man there are both sleep-promoting and rhythm-synchronizing actions of melatonin. Sleep-promoting or soporific effects have been well documented in studies using doses which produce blood levels which exceed the physiological range (Anton-Tay 1974; Cramer et al 1974; Lieberman et al 1984; Waldhauser et al 1990). In a recent double-blind study in volunteers whose sleep was disrupted by noise it was found that a single dose of 80 mg accelerated sleep initiation and increased sleep efficiency without hangover problems (Waldhauser et al 1990). In addition, treatment decreased stage 1 sleep and increased stage 2 sleep. It has recently been shown that very low doses of melatonin,

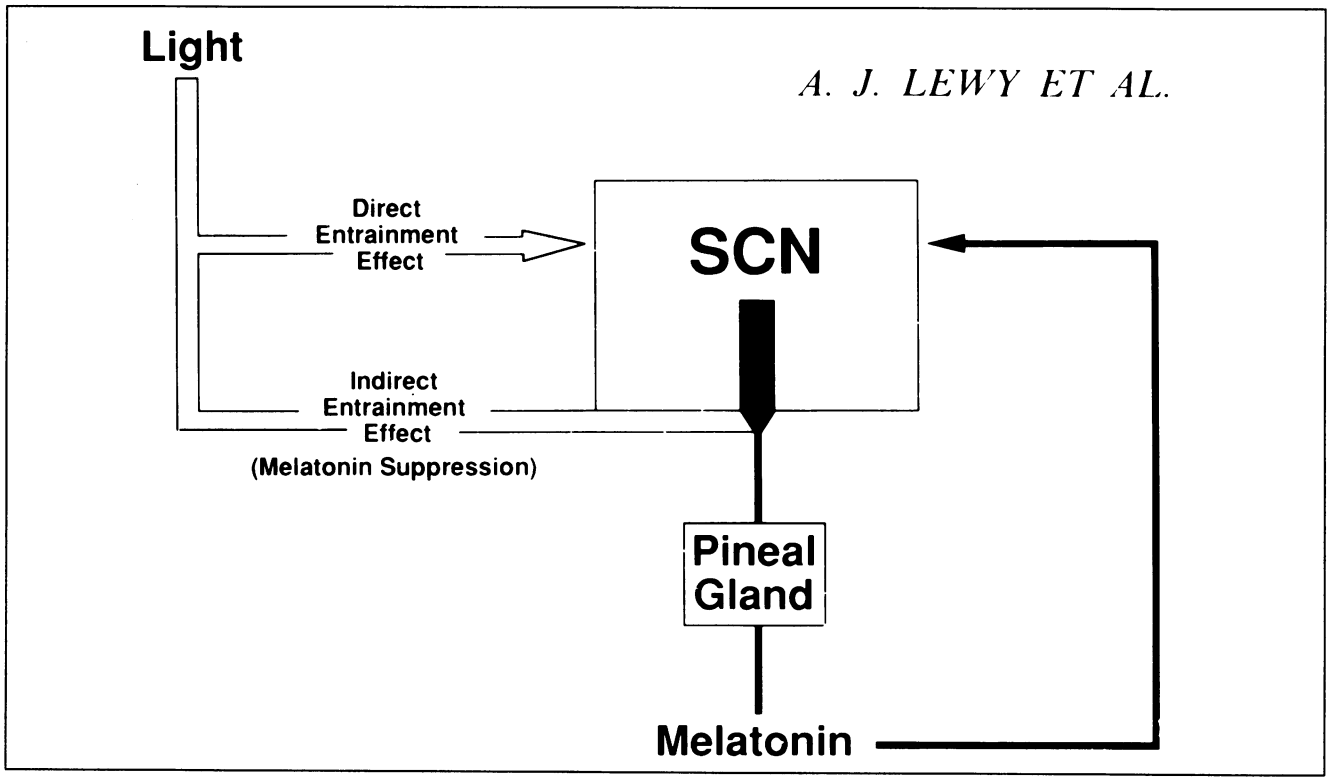

Fig. 1 **Relationships between the light-dark cycle, the endogenous circadian pacemaker, thought to be located in the suprachiasmatic nuclei, and nighttime melatonin production by the pineal gland. Light produces phase shifts following a phase response curve which is determined by the time of night or day while melatonin acts in the opposite direction, thus acting as a darkness signal (indicated by opposing arrows). The suppressant effect of light on melatonin trims the edges of the nighttime melatonin profile, thus reducing melatonin's actions. This suppressant effect is particularly important for phase shifts of the light-dark cycle. Reprinted from Lewy et al (1992) with permission.**

which produce levels in the physiologic range, decrease sleep onset latency and oral temperature when given in the daytime in a darkened room and increase self-reported sleepiness, fatigue and sleep duration (Dollins et al 1994). A study of a single dose of melatonin does not permit an assessment of its hypnotic qualities and withdrawal effects after long-term use. Seven days of melatonin treatment has been used in a double-blind single crossover study in chronic insomnia (MacFarlane et al 1991). A relatively large dose of melatonin (75 mg) caused a significant increase in total sleep as well as a decrease in daytime sleepiness. Sleep time and daytime alertness showed a trend to increase over the seven days of treatment. The delayed sleep phase syndrome (Weitzman et al 1981a), in which patients have a chronic inability to fall asleep at a desired clock time, has also been the object of treatment studies. When not on a strict schedule, patients have a normal sleep pattern and awaken spontaneously feeling refreshed after a sleep of normal length. Following four weeks or more of daily evening treatment with 5 mg of melatonin patients showed a normalization of their sleep pattern with a phase advance in sleep onset and wake time (Dahlitz et al 1991; Tzischinsky et al 1993). It appears that this disorder may be caused by ineffective entrainment of the sleep-wake oscillator by the light-dark cycle and that melatonin acts as a phase-setter which assists in the entrainment process. Neurologically multiply handicapped children can experience chronic sleep-wake rhythm disorders which are reported to respond to 2 mg to 10 mg of oral melatonin given at bedtime (Jan et al 1994a; b). Elderly insomniacs with lower 6-sulphatoxymelatonin output which is phase-delayed (Haimov et al 1993a) are also reported to respond to daily evening treatment with melatonin (Haimov et al 1993b).

One of the first reported uses of melatonin in man was for treating the symptoms of jet lag. Jet lag, which is produced by travelling across several time zones, is characterized by a desynchronization of body rhythms with the external photoperiod. Those experiencing jet lag have disrupted sleep, poor energy and difficulty in concentration (Gunby 1981; Wright et al 1983; Gundel and Wegmann 1989). Several days are required for the body rhythms to adapt to the new photoperiod (Desir et al 1981; 1982; Fevre-Montange et al 1981; Arendt and Marks 1982; Golstein et al 1983; Nickelsen et al 1991). Melatonin treatment in a dose of 5 mg or 8 mg assists with reentrainment (Arendt and Marks 1983; Arendt et al 1985; 1987; Claustrat et al 1992).

Individuals living in a constant environment free of environmental time cues (Kennaway and Van Dorp 1991) have circadian rhythms which free run with a period close, but not equal, to 24 hours (usually it is longer). Many totally blind people also have free-running rhythms of temperature, cortisol and electrolytes (Miles et al 1977), melatonin (Smith et al 1981; Lewy and Newsome 1983; Sack et al 1992b) and 6-sulphatoxymelatonin (Tzischinsky et al 1991).

Disturbed nocturnal sleep, daytime sleepiness and sleep propensity occur as the free-running rhythms move out of phase with the 24-hour sleep schedules and remit as the rhythms move back into phase (Miles et al 1977; Nakagawa et al 1992a; b; Sack et al 1992b). The sleep disruption occurs on a periodic basis as the blind individuals' free-running rhythms, which are longer than 24 hours, repeatedly go in and out of phase with their 24-hour sleep schedules. It has been reported that daily administration of 5 mg or 10 mg of melatonin at a fixed time of day will help synchronize the sleep rhythm in those blind subjects whose sleep patterns are desynchronized from the environment (Arendt et al 1988; Folkard et al 1990; Sack et al 1991; 1992b; Tzischinsky et al 1992). In a single case treated with oral melatonin, synchronization of sleep onset and relief of daytime sleepiness occurred without cuing of the temperature or cortisol rhythm (Folkard et al 1990). In a study of blind subjects whose sleep cycle was free running with a period longer than 24 hours so that the rhythm showed a progressive phase delay, melatonin caused a phase advance in the rhythm which was sufficient to cause entrainment in many of the subjects (Sack et al 1991). In another single case study, response occurred with treatment at 2000 hours but not at 2200 to 2300 hours, indicating that timing of treatment is important (Tzischinsky et al 1992).

In these studies pharmacologic doses of melatonin have been used which clearly have soporific effects. It is not clear whether the soporific or the phase-setting characteristics of melatonin are the key elements in treatment response. Recently, it has been shown that administration of melatonin orally or intravenously to achieve physiologic blood levels can produce phase resetting (Lewy et al 1992; Zaidan et al 1993). During sleep deprivation, suppression of endogenous melatonin by green light is associated with a decrease in sleepiness (Horne et al 1991). It may be that phase-resetting and soporific effects are inseparable.

Melatonin rhythms are also altered in shift workers (Waldhauser et al 1986). In four subjects on fast rotating shifts, marked changes were seen in melatonin with peak levels four times higher in amplitude than in controls (Touitou et al 1990). No apparent phase shift was seen. The authors suggest that the large amplitude of the melatonin and other rhythms (Reinberg et al 1978a; b; Andlauer et al 1979) might be markers for tolerance to shift work which could help the subjects maintain their internal synchronization. In a study of permanent shift workers (Sack et al 1992a), the melatonin rhythm shifted from its usual relationship to sleep. It was also variable from worker to worker. On average, melatonin onset was about seven hours earlier than usual. Sleep was initiated about three hours after melatonin onset whereas in subjects who were active during the day, sleep onset preceded melatonin onset by about three hours. In a study done in Antarctica it was found that readaptation of the 6-sulphatoxymelatonin rhythm following the night shift was more rapid in summer than in winter and that morning and evening bright light treatment was effective in speeding up readaptation in winter time (Midwinter and Arendt 1991).

A relationship of beta-blocker-induced CNS side-effects and reduced melatonin secretion has been reported (Brismar et al 1988). In patients receiving metoprolol there was a significant relationship between the fall in melatonin and sleep disturbance. Severe CNS side-effects such as nightmares were, in all cases, accompanied by low melatonin.

The circadian rhythm of core body temperature, with a maximum during the day and a minimum at night, has been widely used as a marker for circadian rhythms in man (Czeisler et al 1980; Weitzman et al 1981b; Moore-Ede et al 1983). It has been calculated that about 40% of the nocturnal temperature drop is secondary to the melatonin rise (Cagnacci et al 1992; 1993). These studies indicate that melatonin is a major modulator of core body temperature which interacts with other circadian factors in producing the circadian rhythm in temperature. Recent studies have established that this rhythm is closely associated with the circulating melatonin rhythm (Shanahan and Czeisler 1991; Strassman et al 1991; Cagnacci et al 1992). The fitted maximum of melatonin consistently precedes the minimum of temperature by 1.8 h and bright light exposure induces substantial and equivalent phase shifts of both rhythms (Shanahan and Czeisler 1991). Suppression of the nocturnal melatonin rise with atenolol attenuates the nocturnal decline in core body temperature and melatonin administration during the day causes a significant drop in core body temperature (Cagnacci et al 1992). Exposure to bright light at night reduces the nocturnal fall in core body temperature in both men (Strassman et al 1991) and women (Cagnacci et al 1993) and this effect is reversed by concomitant melatonin administration. These studies indicate that the nocturnal melatonin rise is a major regulator of core body temperature in man.

CONCLUSION

Melatonin, the pineal hormone which is regulated by the photoperiod and which has a role in regulating other body rhythms such as that of temperature, has been the subject of numerous investigations. One topic of considerable interest is melatonin's relationship to the circadian pacemaker. Melatonin is not only regulated by that circadian oscillator but also acts as a darkness signal providing feedback to the oscillator. Melatonin shows pronounced synchronizing activity in and around the time of both dusk and dawn, causing phase shifts opposite in direction to those caused by light. Moreover, acute suppression of melatonin secretion by light tends to reinforce the phase-shifting effects of light by eliminating the melatonin signal which opposes the phase-shifting action of light. Melatonin rhythms are altered in a variety of circadian rhythm disorders (Moore 1991) and melatonin has been of use in treatment of such disorders both because of its ability to entrain the sleep-wake rhythm and because of its sleep-inducing and sleep-maintaining effect. Among transient disorders of the sleep-wake cycle, melatonin treatment has been used in jet lag but not, as yet, in shift work disorder. Among persistent disorders there is some evidence that melatonin treatment may have a role to play in delayed sleep-phase syndrome and in the non-24-hour sleep-wake syndrome, while studies remain to be done in advanced sleep-phase disorders, and in those with irregular sleep-wake patterns. The use of melatonin in treatment of chronic insomnia is less well documented but clearly warrants further study. Abnormalities in the pattern of melatonin secretion are reported in affective disorder (Brown 1992) including both seasonal affective disorder and major depressive disorder as well as in aging. The role of light treatment in seasonal affective disorder is well established although participation of the pineal in the treatment response is not clearly established. It remains to be determined whether or not alterations which occur in pineal function in major affective disorder and in aging may be of pathophysiological significance.

ACKNOWLEDGEMENT

Dr. Gregory M. Brown is an Ontario Mental Health Foundation Research Associate.

REFERENCES

Andlauer P, Reinberg A, Fourre L, Battle W, Duverneuil G (1979) Amplitude of the oral temperature circadian rhythm and the tolerance to shift-work. J Physiol 75:507-512.

Anton-Tay F (1974) Melatonin: effects on brain function. Adv Biochem Psychopharmacol 11:315-324.

Arendt J, Marks V (1982) Physiological changes underlying jet lag. Br Med J 284:144-146.

Arendt J, Marks V (1983) Can melatonin alleviate jet lag? Br Med J 287:426.

Arendt J, Bojkowski C, Folkard S, Franey C, Marks V, Minors D, Waterhouse J, Wever RA, Wildgruber C, Wright J (1985) Some effects of melatonin and the control of its secretion in humans. Ciba Found Symp 117:266-283.

Arendt J, Aldhous M, English J, Marks V, Arendt JH (1987) Some effects of jet-lag and their alleviation by melatonin. Ergonomics 30:1379-1393.

Arendt J, Aldhous M, Wright J (1988) Synchronisation of a disturbed sleep-wake cycle in a blind man by melatonin treatment [letter]. Lancet 1:772-773.

Armstrong SM (1989) Melatonin and circadian control in mammals. Experientia 45:932-938.

Berga SL, Yen SS (1990) Circadian pattern of plasma melatonin concentrations during four phases of the human menstrual cycle. Neuroendocrinology 51:606-612.

Bojkowski CJ, Arendt J (1988) Annual changes in 6-sulphatoxymelatonin excretion in man. Acta Endocrinol 117:470-476.

Bojkowski CJ, Arendt J (1990) Factors influencing urinary 6sulphatoxymelatonin, a major melatonin metabolite, in normal human subjects. Clin Endocrinol 33:435-444.

Brismar K, Hylander B, Eliasson K, Rossner S, Wetterberg L (1988) Melatonin secretion related to side-effects of beta-blockers from the central nervous system. Acta Med Scand 223:525-530.

Brown GM (1992) Day-night rhythm disturbance, pineal function and human disease. Horm Res 3(Suppl 37):105-111.

Brzezinski A, Lynch HJ, Seibel MM, Deng MH, Nader TM, Wurtman RJ (1988) The circadian rhythm of plasma melatonin during the normal menstrual cycle and in amenorrheic women. J Clin Endocrinol Metab 66:891-895.

Cagnacci A, Elliott JA, Yen SS (1992) Melatonin: a major regulator of the circadian rhythm of core temperature in humans. J Clin Endocrinol Metab 75:447-452.

Cagnacci A, Soldani R, Yen SS (1993) The effect of light on core body temperature is mediated by melatonin in women. J Clin Endocrinol Metab 76:1036-1038.

Cassone VM (1990) Effects of melatonin on vertebrate circadian systems. Trends Neurosci 13:457-464.

Cassone VM (1992) The pineal gland influences rat circadian activity rhythms in constant light. J Biol Rhythms

Cassone VM, Speh JC, Card JP, Moore RY (1988) Comparative anatomy of the mammalian hypothalamic suprachiasmatic nucleus. J Biol Rhythms 3:71-91.

Chik CL, Ho AK, Klein DC (1988) Dual receptor regulation of cyclic nucleotides: al-adrenergic potentiation of casoactive intestinal peptide stimulation of pinealocyte adenosine 3', 5'- monophosphate. Endocrinology 122:1646-1651.

Claustrat B, Brun J, David M, Sassolas G, Chazot G (1992) Melatonin and jet lag: confirmatory result using a simplified protocol. Biol Psychiatry 32:705-711.

Cramer H, Rudolph J, Consbruch U, Kendel K (1974) On the effects of melatonin on sleep and behavior in man. Adv Biochem Psychopharmacol 11:187-191.

Czeisler CA, Kronauer RE, Allan JS, Duffy JF, Jewett ME, Brown EN, Ronda JM (1989) Bright light induction of strong (type 0) resetting of the human circadian pacemaker. Science 244:1328-1333.

Czeisler CA, Zimmerman JC, Ronda JM, Moore-Ede MC, Weitzman ED (1980) Timing of REM sleep is coupled to the circadian rhythm of body temperature in man. Sleep 2:329-346.

Dahlitz M, Alvarez B, Vignau J, English J, Arendt J, Parkes JD (1991) Delayed sleep phase syndrome response to melatonin. Lancet 337:1121-1124.

David M, Harthe C, Brun J, Mouren P, Veillas G, Claustrat B (1987) Plasma catecholamines and melatonin levels during acute exercise in cardiac patients. Neuroendocrinol Lett 9:267-272.

Desir D, Van Cauter E, Fang VS, Martino E, Jadot C, Spire J-P, Noel P, Refetoff S, Copinschi G, Golstein J (1981) Effects of "jet lag" on hormonal patterns. I. Procedures, variations in total plasma proteins, and disruption of adrenocorticotropin-cortisol periodicity. J Clin Endocrinol Metab 52:628-641.

Desir D, Van Cauter E, L'Hermite M, Refetoff S, Jadot C, Caufriez A, Copinschi G, Robyn C (1982) Effects of "jet lag" on hormonal patterns. III. Demonstration of an intrinsic circadian rhythmicity in plasma prolactin. J Clin Endocrinol Metab 55:849-857.

Dollins AB, Zhdanova IV, Wurtmand RJ, Lynch HJ, Deng MH (1994) Effect of inducing nocturnal serum melatonin concentations in daytime on sleep, mood, body, temperature, and performance. Proc Natl Acad Sci, USA 91:1824-1828.

Dubocovich ML (1988) Pharmacology and function of melatonin receptors. [Review]. Faseb J 2:2765-2773.

Duncan MJ, Takahashi JS, Dubocovich ML (1988) 2-[125I]iodomelatonin binding sites in hamster brain membranes: pharmacological characteristics and regional distribution. Endocrinology 122:1825-1833.

Fevre-Montange M, Van Cauter E, Refetoff S, Desir D, Tourniaire J, Copinschi G (1981) Effects of "jet lag" on hormonal patterns. II. Adaptation of melatonin circadian periodicity. J Clin Endocrinol Metab 52:642-649.

Folkard S, Arendt J, Aldhous M, Kennett H (1990) Melatonin stabilises sleep onset time in a blind man without entrainment of cortisol or temperature rhythms. Neurosci Letters 113:193-198.

Gillette MU, DeMarco SJ, Ding JM, Gallman EA, Faiman LE, Liu C, McArthur AJ, Medanic M, Richard D, Tcheng TK, Weber ET (1993) The organization of the suprachiasmatic nucleus of the rat and its regulation by neurotransmitters and modulators. J Biol Rhythms (8 Suppl):S53-S58.

Golstein J, Van Cauter E, Desir D, Noel P, Spire JP, Refetoff S, Copinschi G (1983) Effects of "jet lag" on hormonal patterns. IV. Time shifts increase growth hormone release. J Clin Endocrinol Metab 56:433-440.

Gunby P (1981) Piloting when you 'should' be sleeping: what effects? J Am Med Assoc 245:940-905.

Gundel A, Wegmann HM (1989) Transition between advance and delay responses to eastbound transmeridian flights. Chronobiol Int 6:147-156.

Haimov I, Schlitner A, Tzischinsky O, Sadeh A, Zisapel N, Lauden M, Lavie P (1993a) Circadian melatonin rhythms in the elderly: relation to sleep disorders and light expo-

sure. In: Programme and Abstracts, 6th Colloquium of the European Pineal Society, p.E2.

Haimov I, Zisapel N, Tzischinsky 0, Lauden M, Lavie P (1993b) Melatonin treatment of sleep onset insomnia in the elderly. In: Programme and Abstracts, 6th Colloquium of the European Pineal Society.

Horne JA, Donlon J, Arendt J (1991) Green light attenuates melatonin output and sleepiness during sleep deprivation. Sleep 14:233-240.

Illnerova H (1991) The suprachiasmatic nucleus and rhythmic pineal melatonin production. In: Klein DC, Moore RY, Reppert SM, eds. Suprachiasmatic nucleus: the mind's clock. New York, Oxford University Press, 197-216.

Jan JE, Abroms IF, Freeman RD, Brown GM, Espezel H, Connolly MB (1994a) Rapid cycling in severe multidisables children: a form of bipolar affective disorder. Pediatr Neurol 10:34-39.

Jan JE, Espezel H, Appleton RE (1994b) The treatment of sleep disorders with melatonin. Dev Med Child Neurol 36:97-107.

Joffe RT, Moul DE, Lam RW, Levitt AJ, Teicher MH, Lebegue B, Oren DA, Buchanan A, Glod CA, Murray MG, Brown J, Schwartz P (1993) Light visor treatment for seasonal affective disorder: a multicenter study. Psychiatry Res 46:29-39.

Karsch FJ, Woodfill CJI, Malpaux B, Robinson JE, Wayne NL (1991) Melatonin and mammalian photoperiodism: synchronization of annual reproductive cycles. In: Klein DC, Moore RY, Reppert SM, eds. Suprachiasmatic nucleus: the mind's clock. New York, Oxford University Press, 217-232.

Kennaway DJ, Van Dorp CF (1991) Free-running rhythms of melatonin, cortisol, electrolytes, and sleep in humans in Antarctica. Am J Physiol 260:R1137-R1144.

Klein DC, Smoot R, Weller JL, Higa S, Markey SP, Creed GJ, Jacobowitz DM (1983) Lesions of the paraventricular nucleus area of the hypothalamus disrupt the suprachiasmatic leads to spinal cord circuit in the melatonin rhythm generating system. Brain Res Bull 10:647-652.

Lam RW, Goldner EM, Solyom L, Remick RA (1994) A controlled study of light therapy for bulimia nervosa. Am J Psychiatry 151:744-750.

Levitt AJ, Joffe RT, Kennedy SH (1991) Bright light augmentation in antidepressant nonresponders. J Clin Psychiatry 52:336-337.

Lewy AJ, Ahmed S, Jackson JM, Sack RL (1992) Melatonin shifts human circadian rhythms according to a phase-response curve. Chronobiol Int 9:380-392.

Lewy AJ, Newsome DA (1983) Different types of melatonin circadian secretory rhythms in some blind subjects. J Clin Endocrinol Metab 56:1103-1107.

Lieberman HR, Waldhauser F, Garfield G, Lynch HJ, Wurtman RJ (1984) Effects of melatonin on human mood and performance. Brain Res 323:201-207.

MacFarlane JG, Cleghorn JM, Brown GM, Streiner DL (1991) The effects of exogenous melatonin on the total sleep time and daytime alertness of chronic insomniacs: a preliminary study. Biol Psychiatry 30:371-376.

McIntyre IM, Morse C (1990) Urinary 6-sulphatoxy melatonin levels within the menstrual cycle and in patients with premenstrual syndrome. Psychoneuroendocrinology 15:233-236.

Midwinter MJ, Arendt J (1991) Adaptation of the melatonin rhythm in human subjects following night-shift work in Antarctica. Neurosci Lett 122:195-198.

Miles LE, Raynal DM, Wilson MA (1977) Blind man living in normal society has circadian rhythms of 24.9 hours. Science 198:421-423.

Monteleone P, Maj M, Fuschino A, Kemali D (1992) Physical stress in the middle of the dark phase does not affect light-depressed plasma melatonin levels in humans. Neuroendocrinology 55:367-371.

Monteleone P, Maj M, Fusco M, Orazzo C, Kemali D (1990) Physical exercise at night blunts the nocturnal increase of plasma melaton in healthy humans. Life Sci 47:1989-1995.

Moore RY (1993) Organization of the primate circadian systema. J Biol Rhythms 8(Suppl):S3-S9.

Moore RY (1991) Disorders of circadian function and the human circadian timing system. In: Klein DC, Moore RY, Reppert SM, eds. Suprachiasmatic nucleus. the mind's clock. New York, Oxford University Press, 429-441.

Moore RY, Card JP (1985) Visual pathways and the entrainment of circadian rhythms. Ann N Y Acad Sci 453:123-133.

Moore-Ede NC, Czeisler CA, Richardson GS (1983) Circadian timekeeping in health and disease. Part I. Basic properties of circadian pacemakers. N Engl J Med 309:469-476.

Nakagawa H, Isaki K, Sack RL, Lewy AJ (1992a) Free-running melatonin, sleep propensity, cortisol and temperature rhythms in a totally blind person. Jpn J Psychiatry Neurol 46:210-212.

Nakagawa H, Sack RL, Lewy AJ (1992b) Sleep propensity free-runs with the temperature, melatonin and cortisol rhythms in a totally blind person. Sleep 15:330-336.

Nickelsen T, Samel A, Maass H, Vejvoda M, Wegmann H, Schoffling K (1991) Circadian patterns of salivary melatonin and urinary 6-sulfatoxymelatonin before and after a 9 hour time-shift. Adv Exp Med Biol 294:493-496.

Redman J, Armstrong S, Ng KT (1983) Free-running activity rhythms in the rat: entrainment by melatonin. Science 219:1089-1090.

Reinberg A, Vieux N, Ghata J, Chaumont AJ, Laporte A (1978a) Circadian rhythm amplitude and individual ability to adjust to shift work. Ergonomics 21:763-766.

Reinberg A, Vieux N, Ghata J, Chaumont AJ, Laporte A (1978b) Is the rhythm amplitude related to the ability to phase-shift circadian rhythms of shift-workers? J Physiol 74:405-409.

Ronkainen H, Vakkuri 0, Kauppila A (1986) Effects of physical exercise on the serum concentration of melatonin in female runners. Acta Obstet Gynecol Scand 65:827-829.

Rosenthal NE, Joseph-Vanderpool JR, Levendosky AA, Johnston SH, Allen R, Kelly KA, Souetre E, Schultz PM, Starz KE (1990) Phase-shifting effects of bright morning light as treatment for delayed sleep phase syndrome. Sleep 13(4):354-361.

Rosenthal NE, Sack DA, Carpenter CJ, Parry BL, Mendelson WB, Wehr TA (1985) Antidepressant effects of light in seasonal affective disorder. Am J Psychiatry 142:163-170.

Rosenthal NE, Skwerer RG, Sack DA, Duncan CC, Jacobsen FM, Tamarkin L, Wehr TA (1987) Biological effects of morning-plus-evening bright light treatment of seasonal affective disorder. Psychopharmacol Bull 23:364-369.

Sack RL, Blood NL, Lewy AJ (1992a) Melatonin rhythms in night shift workers. Sleep 15:434-441.

Sack RL, Lewy AJ, Blood ML, Keith LD, Nakagawa H (1992b) Circadian rhythm abnormalities in totally blind people: incidence and clinical significance. J Clin Endocrinol Metab 75:127-134.

Sack RL, Lewy AJ, Blood ML, Stevenson J, Keith LD (1991) Melatonin administration to blind people: phase advances and entrainment. J Biol Rhythms 6:249-261.

Sack RL, Lewy AJ, White DM, Singer CM, Fireman MJ, Vandiver R (1990) Morning *versus* evening light treatment for winter depression. Evidence that the therapeutic effects of light are mediated by circadian phase shifts [published erratum appears in Arch Gen Psychiatry 1992 Aug:49(8):650]. Arch Gen Psychiatry 47:343-351.

Shanahan TL, Czeisler CA (1991) Light exposure induces equivalent phase shifts of the endogenous circadian rhythms of circulating plasma melatonin and core body temperature in men. J Clin Endocrinol Metab 73:227-235.

Smith JA, O'Hara J, Schiff AA (1981) Altered diurnal serum melatonin rhythm in blind men [letter]. Lancet 2:933.

Sonis WA, Yellin AM, Garfinkel BD, Hoberman HH (1987) The antidepressant effect of light in seasonal affective disorder of childhood and adolescence. Psychopharmacol Bull 23:360-363.

Strassman RJ, Appenzeller 0, Lewy AJ, Qualls CR, Peake GT (1989) Increase in plasma melatonin, beta-endorphin, and cortisol after a 28.5-mile mountain race: relationship to performance and lack of effect of naltrexone. J Clin Endocrinol Metab 69:540-545.

Strassman RJ, Qualls CR, Lisansky EJ, Peak GT (1991) Elevated rectal temperature produced by all-night bright light is reversed by melatonin infusion in men. J Appl Physiol 71:2178-2182.

Thompson C, Stinson D, Smith A (1990) Seasonal affective disorder and season-dependent abnormalities of melatonin suppression by light. Lancet 336:703-706.

Touitou Y, Fevre M, Lagoguey M, Carayon A, Bogdan A, Reinberg A, Beck H, Cesselin F, Touitou C (1981) Age- and mental health-related circadian rhythms of plasma levels of melatonin, prolactin, luteinizing hormone and follicle-stimulating hormone in man. J Endocrinol 91:467-475.

Touitou Y, Motohashi Y, Reinberg A, Touitou C, Bourdeleau P, Bogdan A, Auzeby A (1990) Effect of shift work on the night-time patterns of melatonin, prolactin, cortisol and testosterone. Eur J Appl Physiol 60:288-292.

Tzischinsky 0, Dagan Y, Lavie P (1993) The effects of melatonin on the liming of sleep in patients with delayes sleep phase syndrome. In: Touitou Y, Arendt J, Pevet P, eds. Melatonin and the pineal gland: from basic science to clinical application. International Congress, volume 1017. Amsterdam: Excerpta Medica, 351-354.

Tzischinsky O, Skene D, Epstein R, Lavie P (1991) Circadian rhythms in 6-sulphatoxymelatonin and nocturnal sleep in blind children. Chronobiol Int 8:168-175.

Tzischinsky O, Pal I, Epstein R, Dagan Y, Lavie P (1992) The importance of timing in melatonin administration in a blind man. J Pineal Res 12:105-108.

Utiger RD (1992) Melatonin - the hormone of darkness [editorial; comment]. N Engl J Med 327:13771379.

van den Pol AN (1993) Glutamate and GABA presence and action in the suprachiasmatic nucleus. J Biol Rhythms (8 Suppl):S11-S15.

Vaughan GM, McDonald SD, Jordan RM, Allen JP, Bohmfalk GL, AbouSamra M, Story JL (1978) Melatonin concentration in human blood and cerebrospinal fluid: relationship to stress. J Clin Endocrinol Metab 47:220-223.

Vaughan GM, Taylor TJ, Pruitt BA Jr, Mason AD Jr (1985) Pineal function in burns: melatonin is not a marker for general sympathetic activity. J Pineal Res 2:1-12.

Waldhauser F, Vierhapper H, Pirich K (1986) Abnormal circadian melatonin secretion in night-shift workers. N Engl J Med 315:1614.

Waldhauser F, Weiszenbacher G, Tatzer E, Gisinger B, Waldhauser M, Schemper M, Frisch H (1988) Alterations in nocturnal serum melatonin levels in humans with growth and aging. J Clin Endocrinol Metab 66:648-652.

Waldhauser P, Saletu B, Trinchard-Lugan I (1990) Sleep laboratory investigations on hypnotic properties of melatonin. Psychopharmacology 100:222-226.

Weaver DR, Rivkees SA, Carlson LL, Reppert SM (1991) Localization of melatonin receptors in mammalian brain. In: Klein DC, Moore RY, Reppert SM, eds. Suprachiasmatic nucleus: the mind's clock. New York, Oxford University Press, 289-308.

Weaver DR, Stehle JH, Stopa EG, Reppert SM (1993) Melatonin receptors in human hypothalamus and pituitary: implications for circadian and reproductive responses to melatonin. J Clin Endocrinol Metab 76(2):295-301.

Wehr TA (1991) The durations of human melatonin secretion and sleep respond to changes in daylength (photoperiod). J Clin Endocrinol Metab 73:1276-1280.

Weitzman ED, Czeisler CA, Coleman RM, Spielman AJ, Zimmerman JC, Dement W, Richardson G, Pollak CP (1981) Delayed sleep phase syndrome. A chronobiological disorder with sleep-onset insomnia. Arch Gen Psychiatry 38:737-746.

Winton F, Corn T, Huson LW, Franey C, Arendt J, Checkley SA (1989) Effects of light treatment upon mood and melatonin in patients with seasonal affective disorder. Psychol Med 19:585-590.

Wright JE, Vogel JA, Sampson JB, Knapik JJ, Patton JF, Daniels WL (1983) Effects of travel across time zones (jet-lag) on exercise capacity and performance. Aviat Space Environ Med 54:132-137.

Yanovski J, Witcher J, Adler N, Markey SP, Klein DC (1987) Stimulation of the paraventricular nucleus area of the hypothalamus elevates urinary 6-sulphatoxymelatonin during daytime. Brain Res Bull 19:129-133.

Zaidan R, Geoffriau M, Claustrat B, Brun J, Taillard J, Bureau C, Chazot G (1993) A single afternoon or evening melatonin infusion advances the endogenous melatonin secretion in man. In: Touitou Y, Arendt J, Pevet P, eds. Melatonin and the pineal gland - from basic science to clinical application. Internation Congress Series Edition, Volume 1017. Amsterdam: Excerpta Medical, 235-239.