

*Mechanisms of Disease*FRANKLIN H. EPSTEIN, M.D., *Editor***MELATONIN IN HUMANS**

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THREE centuries ago, the French philosopher René Descartes described the pineal gland as “the seat of the soul,” but it was not until the late 1950s that melatonin, the principal substance secreted by the pineal gland, was identified.¹ There is now evidence that melatonin may have a role in the biologic regulation of circadian rhythms, sleep, mood, and perhaps reproduction, tumor growth, and aging (Table 1). However, uncertainties and doubts still surround the role of melatonin in human physiology and pathophysiology. This review summarizes current knowledge about melatonin in humans and its clinical implications.

PHYSIOLOGY AND PHARMACOLOGY

In humans, the pineal gland lies in the center of the brain, behind the third ventricle (Fig. 1). The gland consists of two types of cells: pinealocytes, which predominate and produce both indolamines (mostly melatonin) and peptides (such as arginine vasotocin), and neuroglial cells. The gland is highly vascular.

Melatonin, or *N*-acetyl-5-methoxytryptamine, was first identified in bovine pineal extracts on the basis of its ability to aggregate melanin granules and thereby lighten the color of frog skin.¹ In the biosynthesis of melatonin, tryptophan is first converted by tryptophan hydroxylase to 5-hydroxytryptophan, which is decarboxylated to serotonin. The synthesis of melatonin from serotonin is catalyzed by two enzymes (arylalkylamine *N*-acetyltransferase and hydroxyindole-*O*-methyltransferase) that are largely confined to the pineal gland.^{2,3}

The mammalian pineal gland is a neuroendocrine

transducer. Photic information from the retina is transmitted to the pineal gland through the supra-chiasmatic nucleus of the hypothalamus and the sympathetic nervous system (Fig. 1). The neural input to the gland is norepinephrine, and the output is melatonin. The synthesis and release of melatonin are stimulated by darkness and inhibited by light. During daylight hours, the retinal photoreceptor cells are hyperpolarized, which inhibits the release of norepinephrine.⁴ The retinohypothalamic-pineal system is quiescent, and little melatonin is secreted. With the onset of darkness, the photoreceptors release norepinephrine, thereby activating the system, and the number of α_1 - and β_1 -adrenergic receptors in the gland increases.⁵ The activity of arylalkylamine *N*-acetyltransferase, the enzyme that regulates the rate of melatonin synthesis, is increased, initiating the synthesis and release of melatonin.

As the synthesis of melatonin increases, the hormone enters the bloodstream through passive diffusion. In humans, melatonin secretion increases soon after the onset of darkness, peaks in the middle of the night (between 2 and 4 a.m.), and gradually falls during the second half of the night. Serum melatonin concentrations vary considerably according to age. Infants younger than three months of age secrete very little melatonin. Melatonin secretion increases and becomes circadian in older infants, and the peak nocturnal concentrations are highest (average, 325 pg per milliliter [1400 pmol per liter]) at the age of one to three years, after which they decline gradually.⁶ In normal young adults, the average daytime and peak nighttime values are 10 and 60 pg per milliliter (40 and 260 pmol per liter), respectively. The daytime rhythm in serum melatonin concentrations parallels the day-night cycle.^{7,8} However, a rhythm of about 24 hours' duration also persists in normal subjects kept in continuous darkness.

The circadian rhythm of melatonin secretion is of endogenous origin, reflecting signals originating in the suprachiasmatic nucleus.⁹ Environmental lighting does not cause the rhythm but entrains it (alters its timing). Light has two effects on melatonin: day-night light cycles modify the rhythm of its secretion (Fig. 2), and brief pulses of light of sufficient intensity and duration abruptly suppress its production.¹⁰ In normal subjects, exposure to light inhibits melatonin secretion in a dose-dependent manner.¹¹ The threshold is 200 to 400 lux (equivalent to ordinary fluorescent light), and maximal inhibition occurs after exposure to intense light (600 lux or higher) for one hour. A longer exposure to light has no further suppressive effect on serum melatonin concentra-

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TABLE 1. BIOLOGIC FUNCTIONS AND PROCESSES THAT MAY BE AFFECTED BY MELATONIN AND SUGGESTED MECHANISMS OF ACTION IN HUMANS.

| FUNCTION OR PROCESS | EFFECT | SUGGESTED MECHANISM | TYPE OF EVIDENCE |
|------------------------------------|--|--|---|
| Sleep | Hypnotic effect and increased propensity for sleep | Hypothermic effect (at pharmacologic doses) Receptor-mediated action on limbic system | Placebo-controlled clinical trials |
| Circadian rhythm | Control of circadian rhythms and entrainment to light–dark cycle | Secretion of melatonin in response to neural input from the eyes and suprachiasmatic nucleus Receptor-mediated effects on neural and peripheral tissues Thermoregulation | Studies in animals and in humans on the effects of light and the light–dark cycle on the pattern of melatonin secretion |
| Mood | Possible role in cyclic mood disorders (seasonal affective disorder, depression) | Unknown | Comparative clinical studies of the pattern of melatonin secretion and studies of phototherapy for mood disorders |
| Sexual maturation and reproduction | Inhibition of reproductive process | Inhibition of hypothalamic–pituitary–gonadal axis Effect on ovarian steroidogenesis | Studies in animals and comparative clinical studies of the pattern of melatonin secretion (during puberty and in women with amenorrhea) |
| Cancer | Antiproliferative effects | Direct antiproliferative effect Enhanced immune response Scavenging of free radicals | In vitro and in vivo studies in animals, in vitro studies of human neoplastic cells and cell lines, and a few small clinical studies |
| Immune response | Enhanced immune response | Increased interleukin production by T-helper lymphocytes | Studies in animals and a few uncontrolled studies in humans |
| Aging | Possible protective effects and decreased cell damage | Scavenging of free radicals | In vitro and in vivo studies in animals |

tions. Some blind persons with no pupillary light reflexes and no conscious visual perception have light-induced suppression of melatonin secretion,¹² suggesting the existence of two photoreceptive systems: one mediating melatonin secretion and the other mediating the conscious perception of light.

Melatonin is rapidly metabolized, chiefly in the liver, by hydroxylation (to 6-hydroxymelatonin) and, after conjugation with sulfuric or glucuronic acid, is excreted in the urine. The urinary excretion of 6-sulfatoxymelatonin (the chief metabolite of melatonin) closely parallels serum melatonin concentrations.⁷ Intravenously administered melatonin is rapidly distributed (serum half-life, 0.5 to 5.6 minutes) and eliminated.¹³ The bioavailability of orally administered melatonin varies widely. For example, in normal subjects given 80 mg of melatonin in a gelatin capsule, serum melatonin concentrations were 350 to 10,000 times higher than the usual nighttime peak 60 to 150 minutes later, and these values remained stable for 90 minutes.¹⁴ Much lower oral doses (1 to 5 mg), which are now widely available in drugstores and food stores, result in serum melatonin concentrations that are 10 to 100 times higher than the usual nighttime peak within one hour after ingestion, followed by a decline to base-line values in four to eight hours. Very low oral doses (0.1 to 0.3 mg) given in the daytime result in peak serum concentrations that are within the normal nighttime range.¹⁵

No serious side effects or risks have been reported in association with the ingestion of melatonin. The

dose-dependent physiologic effects of the hormone, however (e.g., hypothermia, increased sleepiness, decreased alertness, and possibly reproductive effects), have not yet been properly evaluated in people who take large doses for prolonged periods of time. Despite the general absence of a marked endocrine action, decreased serum luteinizing-hormone concentrations and increased serum prolactin concentrations have been reported after the administration of pharmacologic doses of melatonin in normal subjects.^{16,17}

Numerous synthetic melatonin preparations are currently available at health-food stores and drugstores. The purity of some of these preparations is questionable. The consumer's only guarantee of purity is to purchase a preparation made by a company that follows good manufacturing practices (i.e., is able to pass an inspection by the Food and Drug Administration).

MECHANISMS OF ACTION

Receptors

Two membrane-bound melatonin-binding sites belonging to pharmacologically and kinetically distinct groups have been identified: ML1 (high-affinity [picomolar]) sites and ML2 (low-affinity [nanomolar]) sites.^{18,19} Activation of ML1 melatonin receptors, which belong to the family of guanosine triphosphate-binding proteins (G protein-coupled receptors),²⁰ results in the inhibition of adenylate cyclase activity in target cells. These receptors are probably involved in the regulation of retinal function, circa-

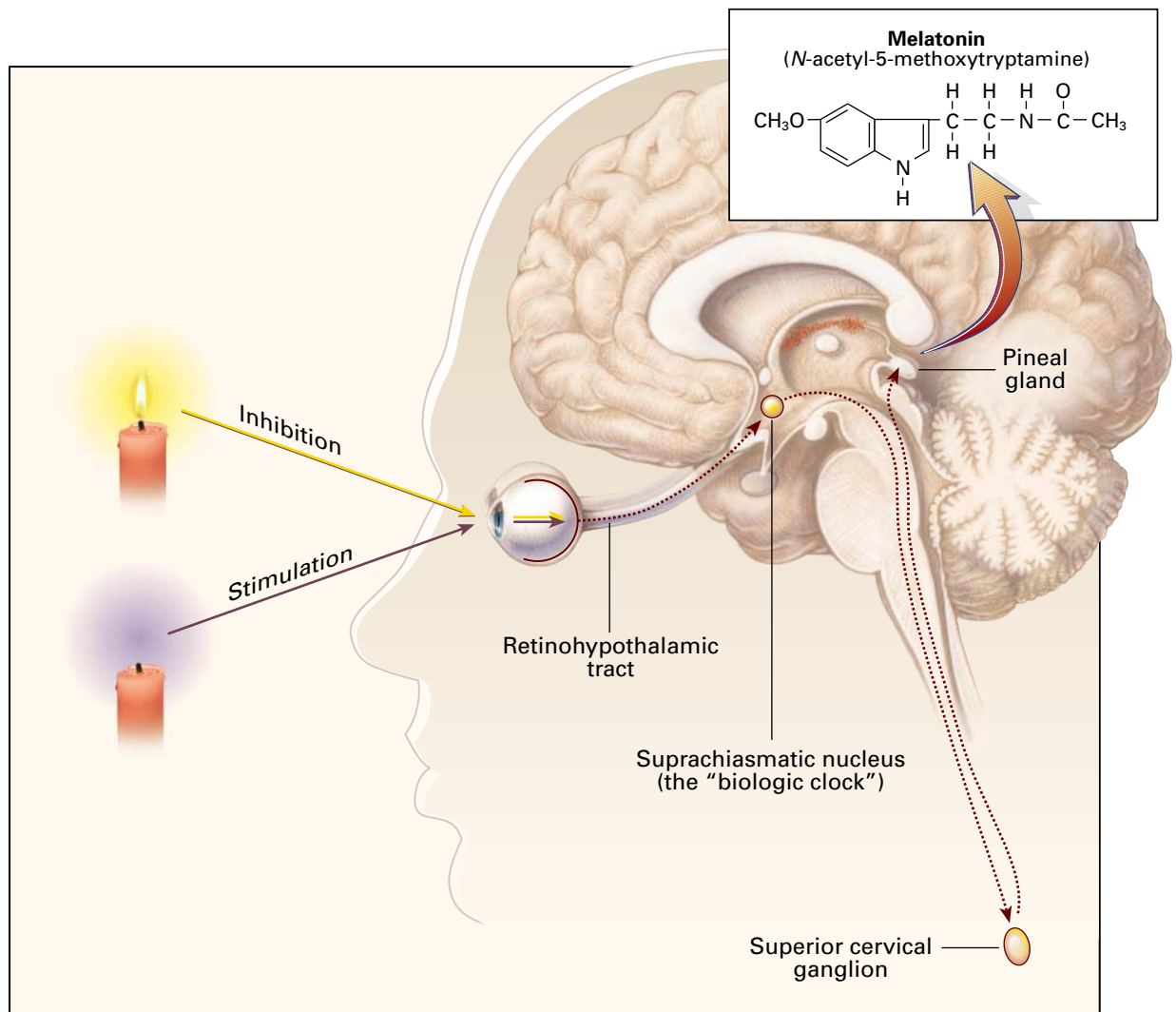


Figure 1. Physiology of Melatonin Secretion.

Melatonin (inset) is produced in the pineal gland. The production and secretion of melatonin are mediated largely by postganglionic retinal nerve fibers that pass through the retinohypothalamic tract to the suprachiasmatic nucleus, then to the superior cervical ganglion, and finally to the pineal gland. This neuronal system is activated by darkness and suppressed by light. The activation of α_1 - and β_1 -adrenergic receptors in the pineal gland raises cyclic AMP and calcium concentrations and activates arylalkylamine *N*-acetyltransferase, initiating the synthesis and release of melatonin. The daily rhythm of melatonin secretion is also controlled by an endogenous, free-running pacemaker located in the suprachiasmatic nucleus.

dian rhythms, and reproduction. The ML2 receptors are coupled to the stimulation of phosphoinositide hydrolysis, but their distribution has not been determined (Fig. 3). With the use of the polymerase chain reaction (PCR), two forms of a high-affinity melatonin receptor, which have been designated Mel1a and Mel1b, were cloned from several mammals, including humans.^{21,22} The Mel1a receptor is expressed in the hypophysial pars tuberalis and the suprachiasmatic nucleus (the presumed sites of the reproductive and circadian actions of melatonin, re-

spectively). The Mel1b melatonin receptor is expressed mainly in the retina and, to a lesser extent, in the brain.

Melatonin may also act at intracellular sites. Through binding to cytosolic calmodulin, the hormone may directly affect calcium signaling by interacting with target enzymes such as adenylate cyclase and phosphodiesterase, as well as with structural proteins.²³ Melatonin has recently been identified as a ligand for two orphan receptors (α and β) in the family of nuclear retinoid Z receptors.²⁴ The binding

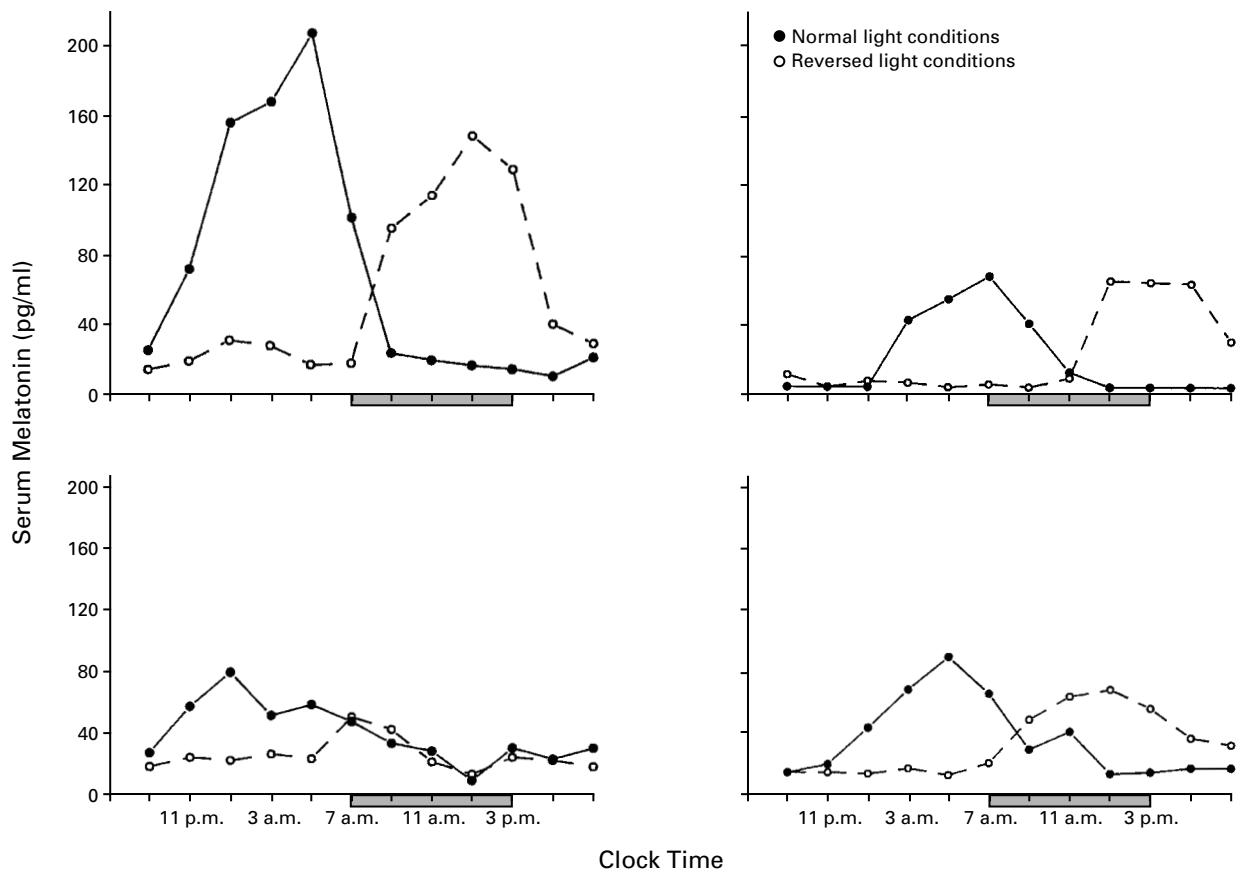


Figure 2. Serum Melatonin Concentrations in Four Normal Men (22 to 35 Years Old) Living under Normal Light Conditions (Solid Circles) and after Living under Reversed Light Conditions for Seven Days and Six Nights (Open Circles).

Under reversed light conditions, lights were out between 7 a.m. and 3 p.m. (shaded bars). The peak serum melatonin concentrations shifted from the nighttime, under normal conditions, to the daytime, under reversed light conditions. To convert values for serum melatonin to picomoles per liter, multiply by 4.31.

was in the low nanomolar range, suggesting that these receptors may be involved in nuclear signaling by the hormone.

Autoradiography and radioreceptor assays have demonstrated the presence of melatonin receptors in various regions of the human brain²⁵ and in the gut,²⁶ ovaries,²⁷ and blood vessels.²⁸ Neural receptors (e.g., those in the suprachiasmatic nucleus of the hypothalamus) are likely to regulate circadian rhythms. Non-neural melatonin receptors (such as those located in the pars tuberalis of the pituitary) probably regulate reproductive function, especially in seasonally breeding species, and receptors located in peripheral tissues (e.g., arteries) may be involved in the regulation of cardiovascular function and body temperature.

Free-Radical Scavenging

Both *in vitro* studies²⁹ and *in vivo* studies³⁰ have shown that melatonin is a potent scavenger of the

highly toxic hydroxyl radical and other oxygen-centered radicals, suggesting that it has actions not mediated by receptors.³¹ In one study, melatonin seemed to be more effective than other known antioxidants (e.g., mannitol, glutathione, and vitamin E) in protecting against oxidative damage.³¹ Therefore, melatonin may provide protection against diseases that cause degenerative or proliferative changes by shielding macromolecules, particularly DNA, from such injuries. However, these antioxidant effects require concentrations of melatonin that are much higher than peak nighttime serum concentrations. Thus, the antioxidant effects of melatonin in humans probably occur only at pharmacologic concentrations.

Enhancement of Immune Function

Melatonin may exert certain biologic effects (such as the inhibition of tumor growth and counteraction of stress-induced immunodepression) by augmenting

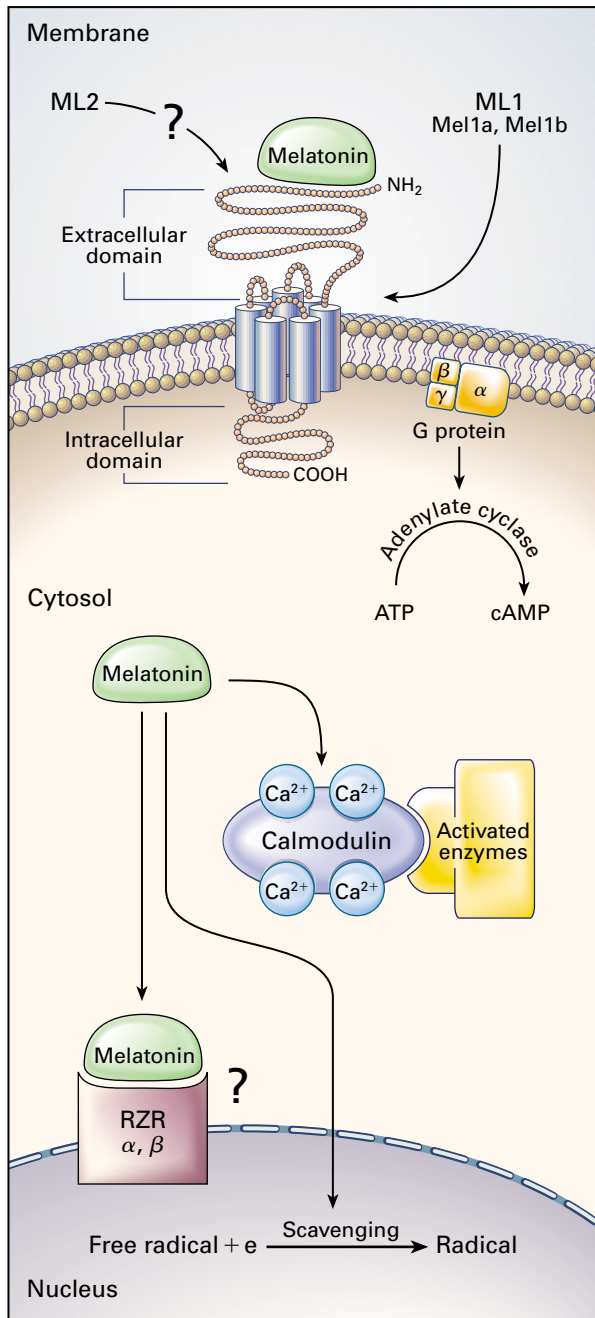


Figure 3. Suggested Sites and Mechanisms of Action of Melatonin at the Cellular Level.

Two membrane-bound melatonin receptors have been identified: ML1 (a high-affinity receptor) and ML2 (a low-affinity receptor). ML1 has two subtypes, designated Mel1a and Mel1b. By binding to its membrane-bound receptors, melatonin changes the conformation of the α subunit of specific intracellular G proteins, which then bind to adenylate cyclase and activate it. Cytosolic and nuclear binding sites have also been described. On binding to cytosolic calmodulin, melatonin may directly affect calcium signaling by interacting with target enzymes, such as adenylate cyclase and phosphodiesterase, and structural proteins. The nuclear binding sites are retinoid Z receptors (RZR) α and β . Melatonin scavenges oxygen-centered free radicals, especially the highly toxic hydroxyl radical, and neutralizes them by a single electron transfer (e^-), which results in detoxified radicals. The hormone may therefore protect macromolecules, particularly DNA, from oxidative damage. The question marks indicate mechanisms of action that have not been proved. cAMP denotes cyclic AMP.

SLEEP AND CIRCADIAN RHYTHMS

Sleep

In humans, the circadian rhythm for the release of melatonin from the pineal gland is closely synchronized with the habitual hours of sleep. Alterations in synchronization due to phase shifts (resulting from transmeridian airline flights across time zones or unusual working hours) or blindness are correlated with sleep disturbances. In the initial description of melatonin as a melanophore-lightening agent, its sedative effect in humans was noted.³⁶ More recently, serum melatonin concentrations were found to be significantly lower, with later peak nighttime concentrations, in elderly subjects with insomnia than in age-matched controls without insomnia.³⁷ Electrophysiologic recordings demonstrated that the timing of the steepest increase in nocturnal sleepiness (the "sleep gate") was significantly correlated with the rise in urinary 6-sulfatoxymelatonin excretion.³⁸

Ingestion of melatonin affects sleep propensity (the speed of falling asleep), as well as the duration and quality of sleep (Table 2), and has hypnotic effects.^{40,41} In young adults, oral administration of 5 mg of melatonin caused a significant increase in sleep propensity and the duration of rapid-eye-movement (REM) sleep.⁴⁸ In other studies, sleep propensity was increased in normal subjects given much lower doses of melatonin (0.1, 0.3, or 1 mg), either in the daytime¹⁵ or in the evening,⁴⁶ and sleepiness in the morning was not increased. The time to the maximal hypnotic effect varies linearly from about three hours at noon to one hour at 9 p.m.⁴⁸ The administration of melatonin for three weeks in the form of sustained-release tablets (1 mg or 2 mg per day) may improve the quality and duration of sleep in elderly persons with insomnia.⁴⁴

These results indicate that increasing serum mela-

the immune response.³² Studies in mice have shown that melatonin stimulates the production of interleukin-4 in bone marrow T-helper cells and of granulocyte-macrophage colony-stimulating factor in stromal cells,³³ as well as protecting bone marrow cells from apoptosis induced by cytotoxic compounds.³⁴ The purported effect of melatonin on the immune system is supported by the finding of high-affinity (K_d , 0.27 nM) melatonin receptors in human T lymphocytes (CD4 cells) but not in B lymphocytes.³⁵

TABLE 2. SUMMARY OF STUDIES OF THE EFFECTS OF EXOGENOUS MELATONIN ON SLEEP VARIABLES AND SLEEP DISTURBANCES.*

| STUDY | YEAR | SUBJECTS | ADMINISTRATION OF MELATONIN | | EFFECTS |
|------------------------------------|------|--|---|------------------------------|---|
| | | | DOSE AND ROUTE | TIMING AND DURATION | |
| Cramer et al. ³⁹ | 1974 | 15 normal subjects | Single dose of 50 mg intravenously | At 9:30 p.m. | Decreased sleep-onset latency |
| Vollrath et al. ⁴⁰ | 1981 | 10 normal subjects | Single dose of 1.7 mg intranasally | During daytime | Induction of sleep |
| Lieberman et al. ⁴¹ | 1984 | 14 normal subjects | Total dose of 240 mg intravenously (80 mg given three times over a 2-hr period) | During daytime | Reduced alertness, increased fatigue and sleepiness |
| Dahlitz et al. ⁴² | 1991 | 8 patients with delayed-sleep-phase syndrome | Single dose of 5 mg orally | At 10 p.m., for 4 wk | Earlier onset of sleep and wake-up time |
| Haimov et al. ⁴³ | 1995 | 26 elderly subjects with insomnia | Single dose of 2 mg orally (sustained release in one group and fast release in another) | 2 Hr before bedtime for 1 wk | Increased efficiency and duration of sleep in sustained-release group, improved initiation of sleep in fast-release group |
| Garfinkel et al. ⁴⁴ | 1995 | 12 elderly subjects with insomnia | Single dose of 2 mg orally, controlled release | At night for 3 wk | Increased efficiency of sleep, no effect on total sleep time |
| Oldani et al. ⁴⁵ | 1994 | 6 patients with delayed-sleep-phase syndrome | Single dose of 5 mg orally | For 1 mo | Advanced onset of sleep |
| Dollins et al. ¹⁵ | 1994 | 20 young subjects | Single dose of 0.1 or 0.3 mg orally | At midday | Increased duration of sleep, decreased sleep-onset latency |
| Zhdanova et al. ⁴⁶ | 1995 | 6 young subjects | Single dose of 0.3 or 1.0 mg orally | At 6, 8, or 9 p.m. | Decreased sleep-onset latency, no effect on REM sleep |
| Wurtman and Zhdanova ⁴⁷ | 1995 | 9 elderly subjects with insomnia | Single dose of 0.3 mg orally | 30 min before bedtime | Increased efficiency of sleep, decreased sleep-onset latency |

*All studies except that by Oldani et al. were placebo-controlled. REM denotes rapid eye movement.

tonin concentrations (to normal nighttime values or pharmacologic values) can trigger the onset of sleep, regardless of the prevailing endogenous circadian rhythm. The hypnotic effect of melatonin may thus be independent of its synchronizing influence on the circadian rhythm and may be mediated by a lowering of the core body temperature.⁴⁹ This possibility is supported by the observations that the circadian cycle of body temperature is linked to the 24-hour cycle of subjective sleepiness and inversely related to serum melatonin concentrations and that pharmacologic doses of melatonin can induce a decrease in body temperature.^{50,51} However, physiologic, sleep-promoting doses of melatonin do not have any effect on body temperature.⁴⁷ Alternatively, melatonin may modify brain levels of monoamine neurotransmitters, thereby initiating a cascade of events culminating in the activation of sleep mechanisms.

Circadian Rhythms

A phase shift in endogenous melatonin secretion occurs in airplane passengers after flights across time zones,⁵² in night-shift workers,⁵³ and in patients with the delayed-sleep-phase syndrome (delayed onset of sleep and late waking up).⁴² Subjects kept under constant illumination and some blind subjects have a 25-hour cycle of melatonin secretion.⁵⁴

Bright light and ingestion of melatonin may alter the normal circadian rhythm of melatonin secretion,⁵⁵ but the reports on this effect are inconsistent, probably because of variations in the timing of the

exposure to bright light or the administration of melatonin in relation to the light-dark cycle. The onset of nocturnal melatonin secretion begins earlier when subjects are exposed to bright light in the morning and later when they are exposed to bright light in the evening. The administration of melatonin in the early evening results in an earlier increase in endogenous nighttime secretion.⁵⁵ In a study of subjects traveling eastward across eight time zones,⁵² 5 mg of melatonin given at 6 p.m. before their departure and at bedtime after their arrival apparently hastened their adaptation to sleep and alleviated self-reported symptoms of jet lag. In a study of flight-crew members on round-trip overseas flights,⁵⁶ those who took 5 mg of melatonin orally at bedtime on the day of the return to the point of origin and for the next five days reported fewer symptoms of jet lag and sleep disturbances, as well as lower levels of tiredness during the day, than those taking placebo. However, crew members who started to take melatonin three days before the day of arrival reported a poorer overall recovery from jet lag than the placebo group.

Exogenous melatonin thus appears to have some beneficial effects on the symptoms of jet lag, although the optimal dose and timing of ingestion have yet to be determined. It is also unclear whether the benefit of melatonin is derived primarily from a hypnotic effect or whether it actually promotes a resynchronization of the circadian rhythm.

Abnormal circadian rhythms have also been implicated in affective disorders, particularly in those char-

acterized by diurnal or seasonal patterns, such as endogenous depression and seasonal affective disorder (winter depression). Low nighttime serum melatonin concentrations have been reported in patients with depression,⁵⁷ and patients with seasonal affective disorder have phase-delayed melatonin secretion.⁵⁸ Although bright-light therapy reduced the depression scores of such patients in one study, a direct association with the phase-shifting effect of light on melatonin secretion was not substantiated.⁵⁹

SEXUAL MATURATION AND REPRODUCTION

There is abundant evidence that the pineal gland, acting through the release of melatonin, affects reproductive performance in a wide variety of species. The efficacy of exogenous melatonin in modifying particular reproductive functions varies markedly among species, according to age and the timing of its administration in relation to the prevailing light–dark cycle or the estrus cycle. In some species melatonin has antigonadotropic actions, and the responses to it are greater in those species with greater seasonal shifts in gonadal function. Changes in the number of hours of darkness each day, and therefore the number of hours that melatonin is secreted, mediate the link between reproductive activity and the seasons. For example, in hamsters (a seasonal-breeding species) the reproductive system is inhibited by long periods of darkness, when more melatonin is secreted, leading to testicular regression in males and anestrus in females.⁶⁰ Although humans are not seasonal breeders, epidemiologic studies in several geographic areas point to a seasonal distribution in conception and birth rates.⁶¹ Among people living in the Arctic, pituitary–gonadal function and conception rates are lower in the dark winter months than in the summer.^{61,62}

The idea that the pineal gland may affect puberty dates back to 1898, when Heubner⁶³ described a 4.5-year-old boy with precocious puberty and a nonparenchymal tumor that had destroyed the pineal gland. Many similar cases were subsequently described, most of which involved boys. These cases support the idea that a melatonin deficiency can activate pituitary–gonadal function. As noted earlier, peak nighttime serum melatonin concentrations decline progressively throughout childhood and adolescence. Whether this reduction is related to changes in the secretion rate⁶⁴ or to increasing body size, without changes in secretion, is not known. If melatonin inhibits the activity of the hypothalamic gonadotropin-releasing–hormone pulse generator (as in ewes) or attenuates the response of the pituitary gland to stimulation by a gonadotropin-releasing hormone (as in neonatal rats), the onset of puberty in humans may be related to the decline in melatonin secretion that occurs as children grow.

No data are available from studies in humans to support either of these mechanisms. However, some children with precocious puberty have low levels of melatonin secretion for their age.⁶⁵ There is also a report of a man with hypogonadotropic hypogonadism, delayed puberty, and high serum melatonin concentrations in whom gonadotropin secretion increased and pubertal development occurred after a spontaneous decrease in the secretion of melatonin.⁶⁶ These findings provide some support for the hypothesis that melatonin has a role in the timing of puberty. Longitudinal studies are needed to determine whether there is a causal relation between the decline in serum melatonin concentrations and the time at which puberty occurs, as well as its rate of progression.

Melatonin secretion does not change during the menstrual cycle in normal women.⁶⁷ Similarly, substantial increases in serum estradiol concentrations do not alter melatonin secretion in infertile women with normal cycles.⁶⁸ On the other hand, serum melatonin concentrations are increased in women with hypothalamic amenorrhea^{67,69,70} (Fig. 4). Men with hypogonadotropic hypogonadism also have increased serum melatonin concentrations, which decline in response to treatment with testosterone.⁷¹ These findings suggest that changes in melatonin secretion may affect the production of sex steroids, and the converse may also be true.

In both animals that breed seasonally and those that do not, melatonin inhibits pituitary responses to gonadotropin-releasing hormone or its pulsatile secretion.⁶⁰ Although there are no similar data in humans, the increase in serum melatonin concentrations in women with hypothalamic amenorrhea raises the possibility of a causal relation between high melatonin concentrations and hypothalamic–pituitary–gonadal hypofunction. Serum melatonin concentrations also increase in response to fasting and sustained exercise, both of which, if prolonged, may cause amenorrhea. However, the hypersecretion of melatonin may merely be coincidental. In a study of normal young women, a very large daily dose of melatonin (300 mg) given orally for four months suppressed the midcycle surge in luteinizing-hormone secretion and partially inhibited ovulation, and the effects were enhanced by concomitant administration of a progestin.⁷²

Melatonin may also modulate ovarian function directly. Ovarian follicular fluid contains substantial amounts of melatonin (average daytime concentration, 36 pg per milliliter [160 pmol per liter]),⁷³ and granulosa-cell membranes have melatonin receptors.²⁷ In addition, melatonin stimulates progesterone synthesis by granulosa–lutein cells *in vitro*.⁷⁴ Collectively, these findings suggest that melatonin plays a part in the intraovarian regulation of steroidogenesis.

AGING

The decrease in nighttime serum melatonin concentrations that occurs with aging, together with its multiple biologic effects, has led several investigators to suggest that melatonin has a role in aging and age-related diseases.^{75,76} Studies in rats⁷⁷ and mice⁷⁸ suggest that diminished melatonin secretion may be associated with an acceleration of the aging process. Melatonin may provide protection against aging through attenuation of the effects of cell damage induced by free radicals or through immunoenhancement. However, the age-related reduction in nighttime melatonin secretion could well be a consequence of the aging process rather than its cause, and there are no data supporting an antiaging effect of melatonin in humans.

CANCER

There is evidence from experimental studies that melatonin influences the growth of spontaneous and induced tumors in animals. Pinealectomy enhances tumor growth, and the administration of melatonin reverses this effect or inhibits tumorigenesis caused by carcinogens.⁷⁹

Data on the relation between melatonin and oncogenesis in humans are conflicting, but the majority of the reports point toward protective action. Low serum melatonin concentrations and low urinary excretion of melatonin metabolites have been reported in women with estrogen-receptor-positive breast cancer and men with prostatic cancer.⁸⁰⁻⁸²

The mechanism by which melatonin may inhibit tumor growth is not known. One possibility is that the hormone has antimitotic activity. Physiologic and pharmacologic concentrations of melatonin inhibit the proliferation of cultured epithelial breast-cancer cell lines (particularly MCF-7)⁸³ and malignant-melanoma cell lines (M-6) in a dose-dependent manner.⁸⁴ This effect may be the result of intranuclear down-regulation of gene expression or inhibition of the release and activity of stimulatory growth factors. Melatonin may also modulate the activity of various receptors in tumor cells. For example, it significantly decreased both estrogen-binding activity and the expression of estrogen receptors in a dose-specific and time-dependent manner in MCF-7 breast-cancer cells.⁸⁵ Another possibility is that melatonin has immunomodulatory activity. In studies in animals, melatonin enhanced the immune response by increasing the production of cytokines derived from T-helper cells (interleukin-2 and interleukin-4),³² and as noted earlier, in mice melatonin protects bone marrow cells from apoptosis by enhancing the production of colony-stimulating factor by granulocytes and macrophages.³⁴ Lastly, as a potent free-radical scavenger, melatonin may provide protection against tumor growth by shielding molecules, especially DNA, from oxidative damage.³¹ However, the

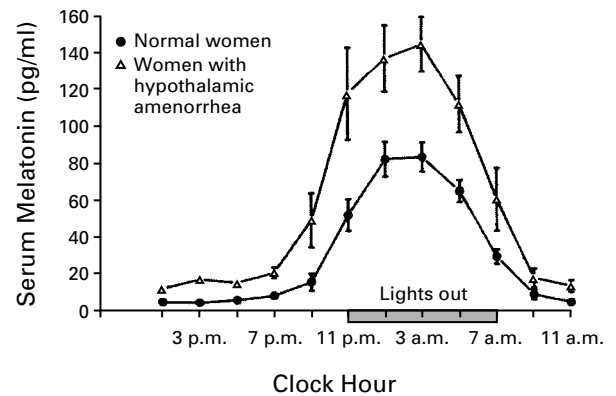


Figure 4. Mean (\pm SE) Serum Melatonin Concentrations Measured at 2-Hour Intervals for 24 Hours in 14 Normal Women (Circles) and 7 Women with Hypothalamic Amenorrhea (Triangles).

To convert values for serum melatonin to picomoles per liter, multiply by 4.31. Adapted from Brzezinski et al.⁶⁷ with the permission of the publisher.

antioxidant effects of melatonin occur only at very high concentrations.

The effects of melatonin have been studied in some patients with cancer, most of whom had advanced disease. In these studies, melatonin was generally given in large doses (20 to 40 mg per day orally) in combination with radiotherapy or chemotherapy. In a study of 30 patients with glioblastomas, the 16 patients treated with melatonin and radiotherapy lived longer than the 14 patients treated with radiation alone.⁸⁶ In another study by the same investigators, the addition of melatonin to tamoxifen in the treatment of 14 women with metastatic breast cancer appeared to slow the progression of the disease.⁸⁷ In a study of 40 patients with advanced malignant melanoma treated with high doses of melatonin (up to 700 mg per day), 6 had transient decreases in the size of some tumor masses.⁸⁸ It has been claimed that the addition of melatonin to chemotherapy or radiotherapy attenuates the damage to blood cells and thus makes the treatment more tolerable.⁸⁹ All these preliminary results must be confirmed in much larger groups followed for longer periods of time.

CONCLUSIONS

There is now evidence to support the contention that melatonin has a hypnotic effect in humans. Its peak serum concentrations coincide with sleep. Its administration in doses that raise the serum concentrations to levels that normally occur nocturnally can promote and sustain sleep. Higher doses also promote sleep, possibly by causing relative hypothermia. Exogenous melatonin can also influence circadian rhythms, thereby altering the timing of fatigue and sleep.

Abnormally high (or pharmacologic) concentrations of melatonin in women are associated with altered ovarian function and anovulation. It is tempting to speculate that the hormone also has antigonadal or antiovarulatory effects in humans, as it does in some seasonal and nonseasonal mammalian breeders, but this possibility has not been substantiated. The antiproliferative and antiaging effects of melatonin are even more problematic. Uncontrolled use of melatonin to obtain any of these effects is not justified.

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