16 The Pineal Hormone (Melatonin)

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CONTENTS

1. INTRODUCTION

The pineal gland, or epiphysis cerebri (Fig. 1), a neuroendocrine organ, is one of the major parts of the circadian system, which also includes the eyes and the suprachiasmatic nuclei of the hypothalamus. The pineal gland exerts important regulatory influences by secreting its hormone, melatonin (Fig. 2), in variable amounts, depending on the time of day; the animal's age; and, in some species, the time of year. The daily rhythm in circulating melatonin is characterized by very low concentrations during the day and high levels at night (Fig. 3). This rhythm persists in constant darkness but can be altered by nighttime light exposure, because light can acutely suppress melatonin production. Normal daily variations in melatonin secretion synchronize numerous body rhythms and, in diurnal species, probably are important for nighttime sleep initiation and maintenance. Since the onset and offset of melatonin production by the pineal gland occur at dusk and dawn, respectively, the length of time per 24-h period that plasma melatonin levels are elevated can synchronize physiologic processes to seasonal changes and, in seasonal animals, can affect season-dependent functions such as body temperature, locomotor activity, and reproductive behavior.

Lerner and colleagues first identified melatonin in 1958, as the constituent of bovine pineal glands that lightens isolated frog skin (by causing the melanin granules within the dermal melanophores to aggregate around the cell's nucleus). Initial studies on possible physiologic roles of melatonin focused on its effects on pigmentation (a phenomenon that is not observed in mammals) and on gonadal maturation. Kitay and Altschule had demonstrated that pinealectomy accelerated gonadal maturation in rats, and that administration of pineal extracts had the opposite effect. We then showed that melatonin was the constituent of bovine pineal extracts that was responsible for their antigonadal activity and suggested that melatonin thus is a hormone in mammals. On the basis of evidence that either removing a rat's pineal gland or exposing the maturing animal to continuous illumination caused equivalent—but not additive—increases in gonadal weight, we further proposed that light exposure suppressed the formation of the pineal gland's antigonadal hormone. Later results confirmed that light indeed suppresses melatonin synthesis, and that the rhythm in melatonin synthesis parallels the natural diurnal rhythm in environmental

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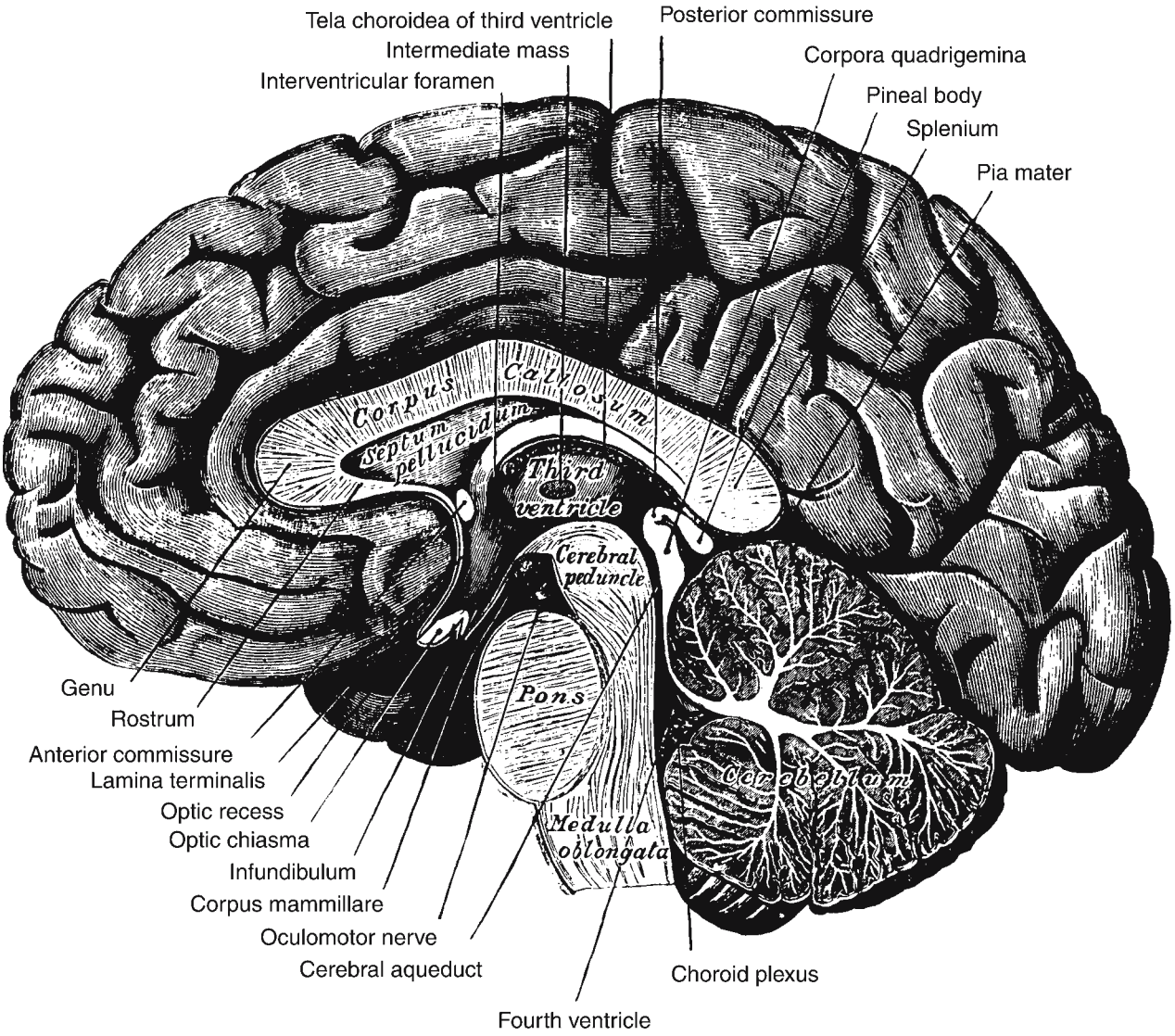

Fig. 1. Median sagittal section of brain. (Reproduced from Gray, 1985.)

illumination. Our laboratory also observed that serum melatonin levels in humans exhibit a characteristic daily pattern; levels are very low during the day (0.5–3 pg/mL), and can be as high as 200 pg/mL at night, with typical nighttime levels in adults of about 100 pg/mL. (Fig. 3).

The pineal gland and its hormone melatonin apparently are important components of the systems that organize rhythmic biochemical, physiologic and behavioral processes in living organisms. This chapter explores some of the fundamental mechanisms that control pineal function and that mediate melatonin's effects. It also considers possible clinical implications of impaired pineal function.

2. THE PINEAL GLAND

The pineal gland is a small unpaired organ located near the geometric center of the brain (Fig. 1). Its function has puzzled researchers for centuries. Postulates regarding this function have ranged from it being a mere vestigial appendage of the brain to Descartes' designation of the pineal gland as the "seat of the rational soul." Experimental investigation over the last half century has revealed that the pineal gland is indeed a biologically significant organ that has undergone profound changes in both form and cytologic differentiation during the course of evolution while retaining a functional role in the temporal organization of animal life.

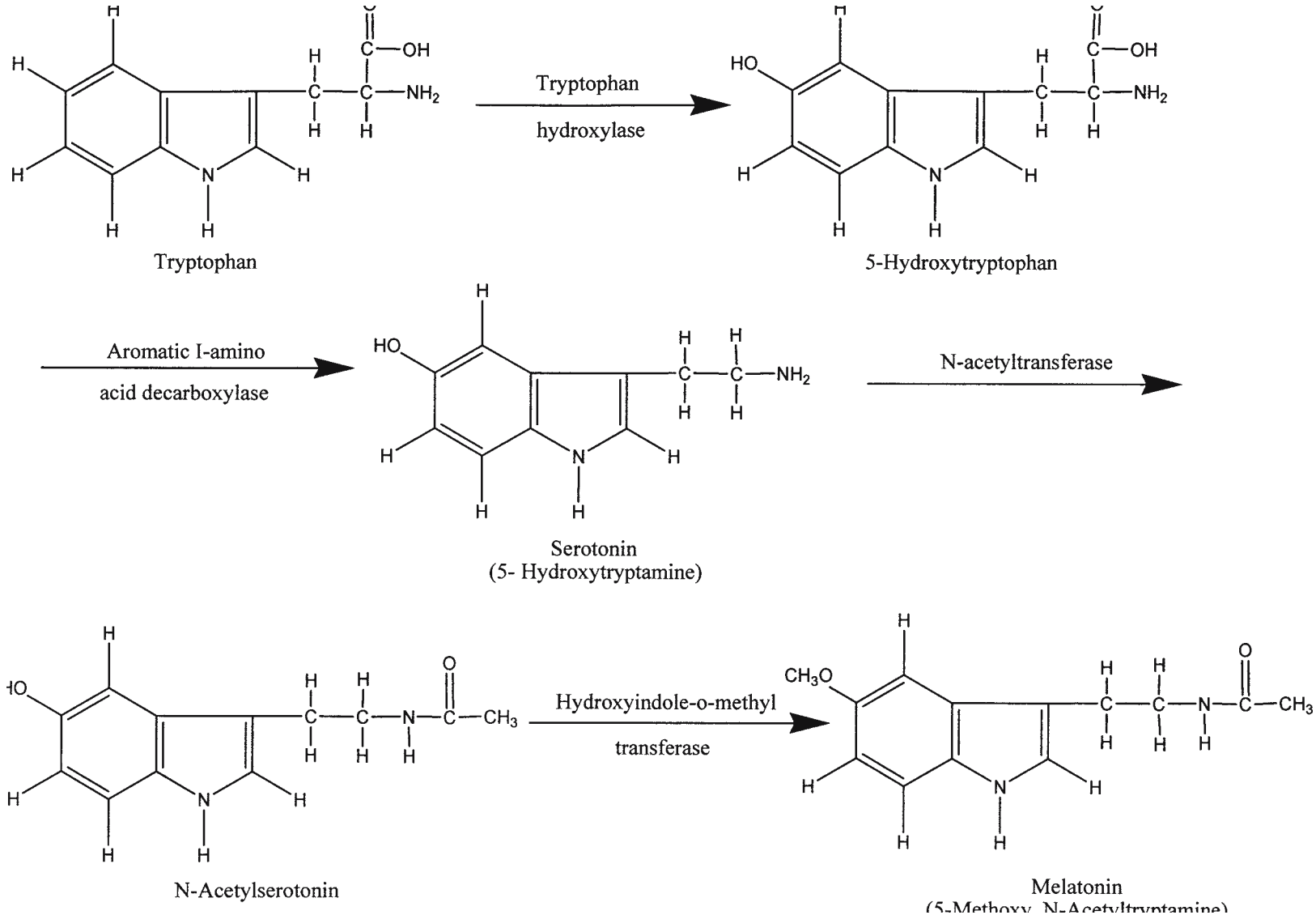

Fig. 2. Metabolism of tryptophan to melatonin in pineal gland.

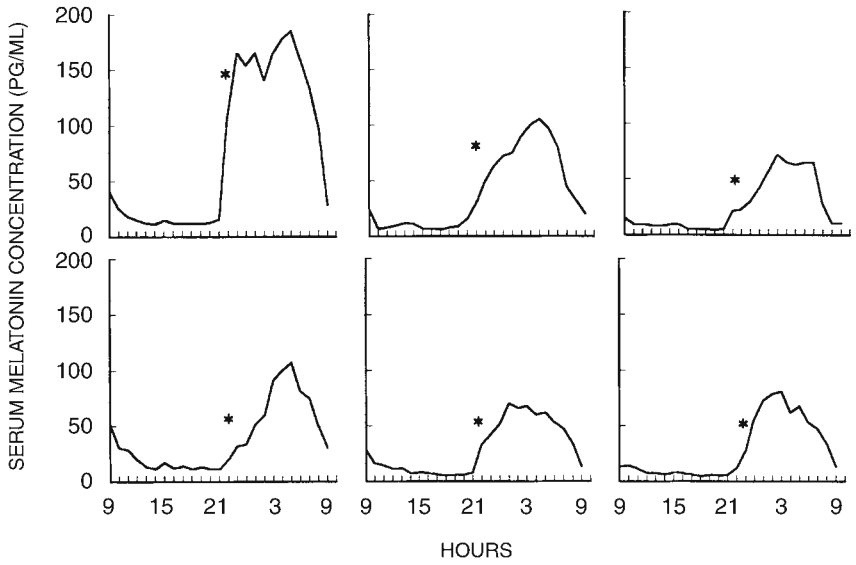

Fig. 3. Twenty-four-hour serum melatonin profiles measured from 9 AM to 9 AM in group of six young healthy males; *time of onset of habitual evening sleepiness.

Embryologically, the pineal organ arises as an evagination of the roof of the diencephalon. The diencephalon also gives rise to the lateral eyes and to the hypothalamus. This common embryologic origin is reflected in a common physiologic property—the capacity to respond to cyclic changes in environmental illumination. A fixed temporal pattern of photic input is an ubiquitous phenomenon, generated by Earth's daily rotation in reference to the sun. Viewed from an evolutionary perspective, the pineal origin is part of a sophisticated photoneuroendocrine system with photoreceptors represented both in the lateral eyes and, in some species (but not mammals), in the pineal organ itself. With development, this organ-system has acquired a unique feature: an endogenous, circadian (*circa* = around, *dian* = day) rhythmic pattern in its metabolic and/or neural activity. In mammals, a neuronal component of this neuroendocrine complex, the suprachiasmatic nuclei of the hypothalamus, displays a regular pattern of spontaneous neuronal discharges, entrained to the cyclic photic input, with a higher frequency during the daylight hours; this pattern persists in the absence of a day-night cycle. In vertebrate classes whose pineal organ possesses true photoreceptors (e.g., birds and reptiles), the pineal organ itself manifests a sustained circadian oscillation in melatonin biosynthesis. In the mammalian pineal organ, the absence of true photoreceptors is accompanied by the loss of this endogenous pace-setting capacity. Mammals thus rely on the suprachiasmatic nuclei for autonomous circadian stimulation. Under natural conditions, the environmental light-dark cycle and the suprachiasmatic nuclei's endogenous oscillator act in concert to produce the daily rhythm in melatonin production. A complex neural pathway has evolved that relays information regarding environmental illumination from the ganglion layer of the retina to pinealocytes via the optic nerve, the suprachiasmatic nuclei, the lateral hypothalamus, and through the spinal cord by preganglionic fibers synapsing in the superior cervical ganglion. Postganglionic fibers reaching the pineal organ via the nervi conarii release norepinephrine at night. This neurotransmitter then activates adenylate cyclase, stimulating production of the second messenger cyclic adenosine monophosphate (cAMP), which accelerates melatonin synthesis. Exposure to sufficiently bright light qiuckly suppresses melatonin synthesis; however, under conditions of constant darkness a circadian rhythm in melatonin production persists, generated by the cyclic suprachiasmatic nuclei output.

3. MELATONIN SYNTHESIS AND SECRETION

The circulating amino acid L-tryptophan is the precursor of melatonin. Within pineal cells, it is converted to serotonin by a two-step process, catalyzed by the enzymes tryptophan hydroxylase and 5-hydroxytryptophan decarboxylase. Pineal serotonin concentrations in mammals are high during the daily light phase and

decrease during the dark phase, when much of this indoleamine is converted into melatonin. This process, which occurs principally but not exclusively in the pineal gland (e.g., also in retina), involves serotonin's N-acetylation, catalyzed by an *N*-acetyltransferase enzyme, and its subsequent methylation by hydroxyindole-*O*-methyltransferase gland (Fig. 2).

There is no evidence that melatonin is stored in the pineal gland; rather, the hormone is thought to be released directly into the bloodstream and the cerebrospinal fluid as it is synthesized. The pattern of melatonin secretion in humans is characterized by a gradual nocturnal increase, starting about 2 h prior to habitual bedtime, and a morning decrease in serum concentrations of the hormone (Fig. 3). About 50–70% of circulating melatonin is reportedly bound to plasma albumin; the physiologic significance of this binding remains unknown. Inactivation of melatonin occurs in the liver, where it is converted into 6-hydroxymelatonin by the P-450-dependent microsomal mixed-function oxidase enzyme system. Most of the 6-hydroxymelatonin is excreted into the urine and feces as a sulfate conjugate (6-sulfatoxymelatonin), and a much smaller amount as a glucuronide. Some melatonin may be converted into *N*-acetyl-5-methoxykynurenamine in the central nervous system. About 2 to 3% of the melatonin produced is excreted unchanged in the urine.

4. ONTOGENY OF MELATONIN SECRETION

Lower vertebrates start secreting melatonin at an early embryonic age. However, in mammals, including humans, the fetus and the newborn infant do not produce their own melatonin but rely on the hormone supplied via the placental blood and, postnatally, via the mother's milk. The few studies of the development of circadian functions in full-term human infants, including the melatonin secretory rhythm, the sleep-wake rhythm, and the body temperature rhythm, reveal an absence of circadian variation neonatally until 9–12 wk. Preterm babies display a substantial delay in the appearance of rhythmic melatonin production. Total melatonin production rapidly increases during the first year of life, with highest nighttime melatonin levels observed in children ages 1–3 yr. These high levels start to fall around the time of onset of puberty, decreasing substantially with physiologic aging (Fig. 4). Marked, unexplained interindividual variations in "normal" melatonin levels are observed in all age groups, so some elderly people do still exhibit relatively high serum melatonin levels. Several factors may explain the decline in melatonin concentration during the life-span, such as the increase in body mass from infancy to adulthood (which results in a greater volume of distribution and, therefore, a decline in the melatonin concentration in body fluids even if melatonin production is almost constant); the calcification of the pineal gland with advancing age (which may suppress melatonin production); or a reduction in the sympathetic innervation of the pineal gland, which is essential for melatonin's nocturnal secretion (which may result in diminished melatonin production). High variability in melatonin production among individuals of the same age group could reflect, among other things, genetic predisposition, general health, and particular environmental lighting conditions. Determining the sources of this variability requires further investigation.

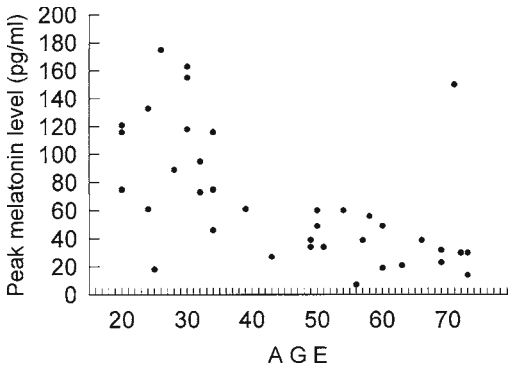

Fig. 4. Nighttime peak serum melatonin levels in subjects of different age (years).

5. EFFECTS OF MELATONIN ON CELLULAR METABOLISM

Melatonin is a highly lipophilic hormone, permitting its ready penetration of biologic membranes and its ability to reach each cell in the body. The effects of melatonin appear to be mediated via specific melatonin receptors, two of which (MT1 and MT2) have been cloned and characterized in mammals. These G protein–coupled receptors are present in various body tissues, such as brain, retina, gonads, spleen, liver, thymus, and gastrointestinal tract, and inhibit the formation of two second messengers, cAMP (both MT1 and MT2) or cyclic guanosine 5´-monophosphate (MT2). In mammals, high-affinity melatonin receptors are consistently found in the pars tuberalis of the pituitary gland; such labeling is especially intensive in seasonal breeders and is believed to mediate the seasonal reproductive effects of melatonin. The suprachiasmatic nucleus (SCN) is another brain region rich in melatonin receptors. Animal-based studies suggest that its receptors allow melatonin to inhibit SCN neuronal firing and metabolism at nighttime. This effect, presumably mediated via MT1

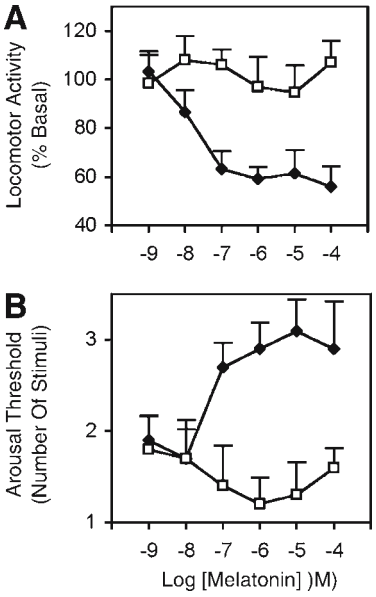

Fig. 5. Melatonin significantly and dose dependently reduces zebrafish locomotor activity **(A)** and increases arousal threshold **(B)** in larval zebrafish. Each data point represents the mean ± SEM group changes in a 2-h locomotor activity relative to basal activity, measured in each treatment or control group for 2 h prior to administration of treatment. Arousal threshold data are expressed as the mean ± SEM group number of stimuli necessary to initiate locomotion in a resting fish. (◆) treatment; (□) – vehicle control (n = 20 for each group). (Reproduced from Zhdanova et al., 2002.)

receptors, may contribute to the sleep-promoting effects of melatonin in diurnal species. On the other hand, MT2 receptors in the SCN can affect the circadian phase of SCN activity, either advancing or delaying it, depending on when in the cycle the melatonin is administered. These effects of melatonin might be important among lower vertebrates, in which the pineal gland responds directly to light.

Melatonin receptors are saturated at close-to-physiologic nocturnal melatonin concentrations; thus, their capacity to exhibit dose dependency is limited. One example of limited dose dependency, documented in both humans and diurnally active animals, is melatonin's sleep-promoting and activity-inhibiting effects. These behavioral effects in humans are initiated at melatonin levels close to those normally observed at the beginning of the night (about 50 pg/mL in blood plasma) but are not significantly enhanced when circulating levels are increased to substantially higher values (about 150 pg/mL). We found similar melatonin dose dependencies in macaques and zebrafish (Fig. 5). Furthermore, melatonin's effects depend on diurnal variations in the sensitivity of the melatonin receptors. Typically, melatonin receptors are more sensitive during the daytime—i.e., at the time endogenous melatonin is not secreted—perhaps reflecting receptor upregulation in the absence of endogenous ligand. Augmented sensitivity to melatonin in the morning or in the evening hours may facilitate circadian phase shifts in response to small increases in melatonin secretion.

6. MELATONIN AND PHYSIOLOGIC FUNCTIONS

Diversity in the adaptive strategies employed by particular mammalian species may dictate how each species responds to the circadian signal provided by the release of melatonin. In both laboratory animals and humans, the effects of melatonin on behavioral rhythmicity, sleep, reproduction, and thermoregulation have been studied most extensively and are discussed in the following sections. Some investigators have also proposed that melatonin might affect immune function, intracellular antioxidative processes, aging, tumor growth, and certain psychiatric disorders.

6.1. Homeostatic and Circadian Regulation of Sleep

The concurrence of melatonin release from the pineal gland and the habitual hours of sleep in humans had led to the hypothesis that the former might be causally related to the latter. The effects of the administration of melatonin made it clear that melatonin can affect both homeostatic and circadian sleep regulation (i.e., the need to sleep after having been awake for a sufficient number of hours, and the desire to sleep at certain times of day or night), and that it does so at normal plasma melatonin levels. Although the acute sleep-promoting effect of doses of physiologic melatonin has been documented only in diurnal species (e.g., humans, fish, birds, monkeys), the circadian effects of melatonin appear to be similar in both nocturnal and diurnal species.

This phenomenon can be explained by temporal organization of the circadian system in diurnal and nocturnal species and its relation to habitual hours of sleep. Activation of the SCN and synthesis of melatonin in the pineal gland vary inversely in both nocturnal and diurnal species, with the metabolic and neuronal activity of the SCN high during the day, and the production of pineal melatonin low. This pattern is reversed during the night, when the SCN is relatively inactive and melatonin production is substantially increased. Acute exposure to light stimulation, mediated through the lateral eyes, produces an excitatory response in SCN neurons and inhibits melatonin production. On the other hand, melatonin itself exerts an acute inhibitory effect on SCN neuronal activity (Fig. 6). When environmental light

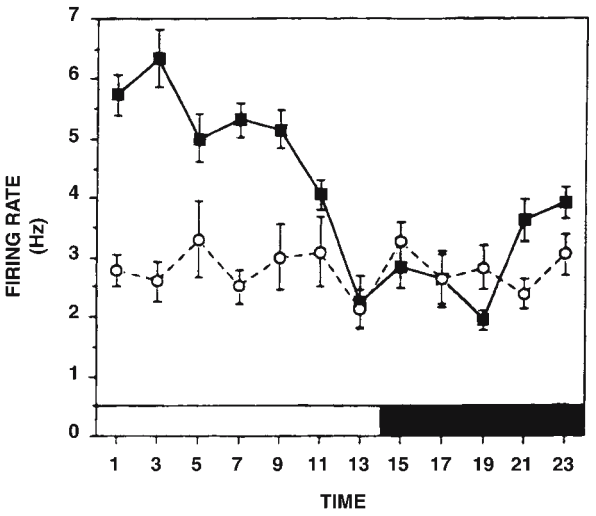

Fig. 6. Mean (± SEM) firing rates of SCN cells recorded in 2-h bins throughout daily cycle in slices from hamsters housed in a lighting cycle (■) or transferred to constant light for ~48 h before slice preparation (○). The lighting cycle for light:dark (LD) animals is illustrated at the bottom. (Reproduced from Guang-Di et al., 1993.)

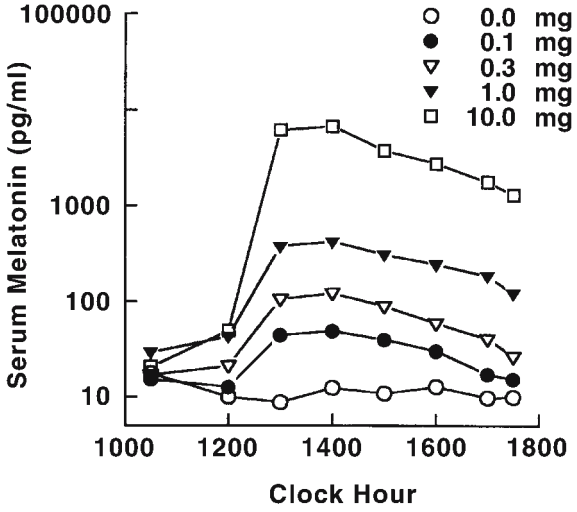

Fig. 7. Mean (± SEM) serum melatonin profiles of 20 subjects sampled at intervals after ingesting 0.1, 0.3, 1.0, and 10 mg of melatonin or placebo at 11:45 AM. (Reproduced from Dollins et al., 1994.)

or melatonin is applied at an unusual time of day, such as bright light at the beginning of the night or melatonin in the afternoon, the phase of the circadian activity of the SCN shifts and, thus, advances or delays other circadian rhythms. Such circadian effects are similar in nocturnal and diurnal species. By contrast, the temporal relationship between sleep and activation of the circadian system is different in diurnal and nocturnal species. Nocturnal melatonin secretion is concurrent with habitual hours of sleep in diurnal animals and with peak activity levels in nocturnal animals. As a result, melatonin is linked to sleep initiation and maintenance in diurnal but not nocturnal species. Indeed, physiologic melatonin levels promote sleep in humans, diurnal primates, birds and fish, but not in rats or mice.

Initial human studies regarding the acute effects of melatonin treatment utilized pharmacologic doses of the hormone (1 mg to 6 g, orally), which tended to induce sleepiness and sleep. These effects of the pineal hormone were commonly considered to be "side effects" of the pharmacologic concentrations of melatonin induced. We then showed that low melatonin doses (0.1–0.3 mg), which elevate daytime serum melatonin concentrations to those normally occurring nocturnally (50–120 pg/mL) (Fig. 7), also facilitate sleep induction in young healthy adults when administered at the time of low sleep propensity (Fig. 8). The response occurs within 1 h of administration of the hormone and is independent of the time of day that the treatment is administered.

Fig. 8. Effects of melatonin (0.3 or 1.0 mg, orally) on average (± SEM) latency to **(A)** sleep onset and **(B)** stage 2 sleep relative to placebo ($n = 11$). Treatment was administered at the time of low sleep propensity, 2–4 h before habitual bedtime ($^{*}p < 0.005$). (Reproduced from Zhdanova et al., 1996.)

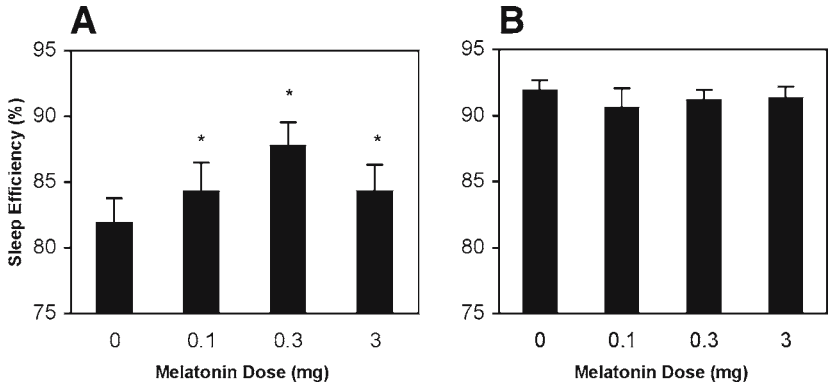

Fig. 9. Sleep efficiency in subjects with age-related insomnia **(A)** and normal sleep **(B)** following melatonin or placebo treatment ($^*p < 0.05$). (Reproduced from Zhdanova et al., 2001.)

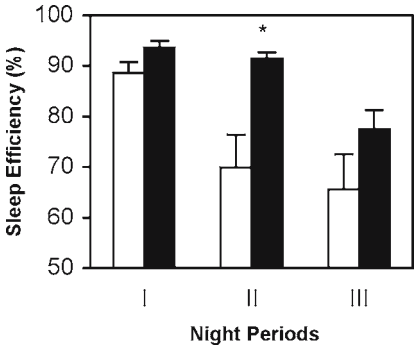

Fig. 10. Sleep efficiency in individuals with insomnia during three consecutive parts (I, II, III) of the night following placebo (□) or melatonin (0.3 mg, ■) treatment ($^*p < 0.05$). (Reproduced from Zhdanova et al., 2001.)

Elevation of circulating melatonin level within the physiologic range, although improving sleep in people who have insomnia, does not cause significant changes in nocturnal sleep structure in people who experience normal sleep, and it is without untoward side effects (i.e., drowsiness) on the morning following treatment.

These results support the idea that in humans melatonin secretion is physiologically related to normal sleep. This relationship would explain the high correlation between the onset of evening sleepiness or habitual bedtime in people and the onset of their melatonin release late in the evening. It might also partially explain the high incidence of insomnia in the elderly, whose circulating melatonin levels are, in general, significantly lower than those in young adults. This hypothesis is further supported by the fact that the sleep of aged people with insomnia was significantly improved by doses of both physiologic (e.g., 0.1–0.3 mg) and pharmacologic (e.g., 3 mg) oral melatonin administered 30 min before habitual bedtime (Fig. 9A). Such treatments increased overnight sleep efficiency, principally by increasing it during the middle portion of the nocturnal sleep period and, to a lesser extent, during the latter third of the night (Fig. 10). By contrast, bedtime melatonin treatment did not modify sleep efficiency in older people in whom sleep already was normal (Fig. 9B), affirming melatonin's physiologic mode of action. Furthermore, melatonin had no discernible effect on sleep architecture, such as latency to rapid eye movement sleep or percentage of time spent in any of the five sleep stages, among healthy individuals or aged individuals with insomnia. Such disturbances are common complications encountered with many of the existing hypnotics.

Desynchronization of daily rhythms of sleep and melatonin secretion could occur as a result of: (1) complete blindness, when the melatonin rhythm free-runs with a period either longer or shorter than 24 h; (2) pinealectomy or functional destruction of the pineal, resulting in a lack of melatonin production; (3) temporal displacement of the daylight period, as in transmeridian flight (the jet-lag syndrome) or shift work; or (4) the administration of drugs that block the release of norepinephrine from pineal sympathetic nerves, or the postsynaptic effects of the neurotransmitter. Such desynchronization might diminish the quantity and quality of sleep, a condition that then might be ameliorated by the timely administration of exogenous melatonin. If the goal is to entrain the circadian system to a specific time schedule (e.g., 24-h periodicity), it is critical to administer physiologic melatonin doses (0.1–0.3 mg, orally) at the same time, typically about 30 min prior to habitual bedtime. However, if the goal is to reentrain the circadian system to a new schedule (e.g., after a jet lag), the timing of melatonin treatment has to be carefully calculated in order to facilitate a phase shift,

rather than oppose it. Administration of the hormone in the morning causes a phase delay, whereas evening treatment results in a phase advance. In this case, it is also important not to exceed physiological melatonin levels. The reason is that the residual circulating melatonin left, e.g., after evening melatonin treatment (Fig. 11) designed to advance the circadian rhythms, would produce a phase delay if still acting during the morning hours, thus dampening the overall efficacy of melatonin.

Because sleep is under control of the circadian clock, changes in the circadian phase will either cause a delay in the onset of evening sleepiness or advance it to an earlier hour. This property of melatonin found a useful application in the treatment of blindness-related sleep disorders; sleep alterations related to jet lag after transmeridian flight; and sleep disruption experienced by workers on rotating shifts, whose endogenous circadian rhythms are not synchronized with their rest-activity cycle.

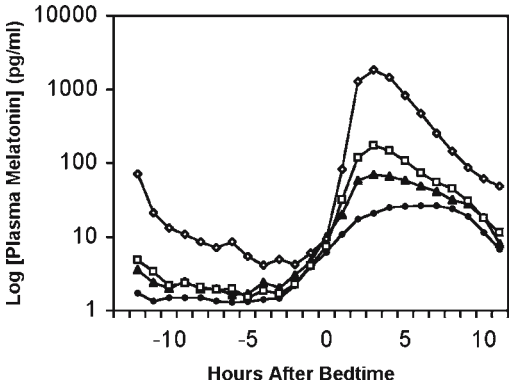

Fig. 11. Mean group (n = 30) plasma melatonin profiles during repeated melatonin or placebo treatment administered 30 min before bedtime. Daytime melatonin levels (i.e. before bedtime) reflect those after the previous night's treatment. (●) placebo; (▲) 0.1 mg; (□) 0.3 mg; (◆) 3 mg. (Reproduced from Zhdanova et al., 2001.)

6.2. Reproductive Physiology

The idea that pineal gland function in some way relates to gonadal expression originated with Heubner's 1898 description of a 4-yr-old boy who exhibited both precocious puberty and a nonparenchymal tumor that destroyed his pineal gland. The efficacy of the pineal hormone, melatonin, in modifying reproductive functions has been found to vary markedly, depending on the species and age of the animal tested, and the time of administration of melatonin relative to the prevailing light-dark schedule. Animal studies show that in seasonal breeders melatonin mediates the effects of changes in the photoperiod and, thus, the season of reproductive activity. Interestingly, the effects of exogenous melatonin on animals in which reproductive activity is inhibited during fall–winter (e.g., hamsters) are opposite from its effects on animals that are reproductively passive during spring–summer (e.g., sheep) (Fig. 12).

Whether pineal melatonin secretion influences reproductive activity in nonseasonal mammals such as humans is still unclear. Melatonin could normally affect sexual maturation; however, observations regarding the relation between circulating melatonin levels and the onset of puberty in humans are inconsistent. There also are conflicting observations regarding serum melatonin levels during normal menstrual cycles in women. Some investigators report a transient decrease in nocturnal melatonin levels during the preovulatory phase; others fail to document any association between circulating

Fig. 12. Opposite effects of seasonal variation in day length and melatonin secretion period on reproductive status in different species. (Reproduced from Goldman, 2001.)

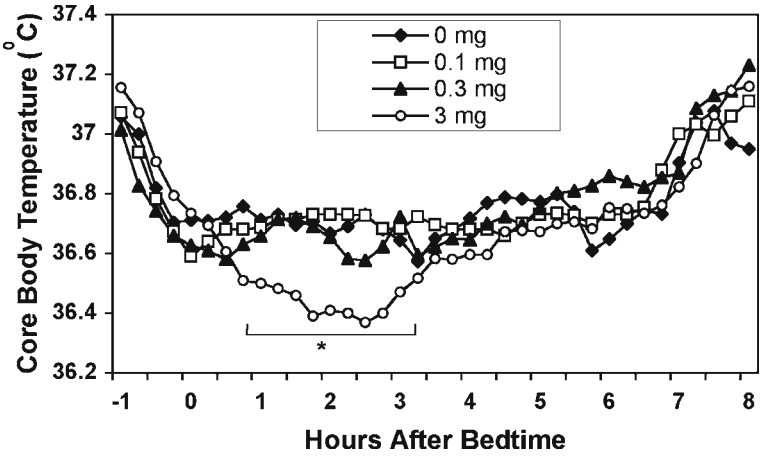

Fig. 13. Core body temperature profiles in adults over 50 yr of age following melatonin or placebo treatment ($^{*}p < 0.05$). (Reproduced from Zhdanova et al., 2001.)

melatonin and the phase of the menstrual cycle. Some patients with tumors involving pinealocytes, which result in an increased secretion of melatonin, reportedly displayed delayed puberty; nonparenchymal tumors, which presumably destroy pinealocytes and suppress melatonin production, have been associated with precocious puberty.

In women with amenorrhea whose estrogen levels are extremely low, serum melatonin concentrations are often substantially elevated. Exogenous estrogen also reportedly suppresses nocturnal melatonin secretion in women with secondary amenorrhea. Long-term suppression of estrogen synthesis in healthy women may lead to elevations in their circulating melatonin. Interestingly, in women with normal menstrual cycles and initially normal estrogen levels, treatment with conjugated estrogen did not suppress circulating melatonin levels. These findings suggest that there is an inhibitory feedback control of pineal function by estrogen, and that responses depend on the initial status of the organism. Other dysfunctions of the reproductive system may also be associated with abnormal melatonin levels: girls with central idiopathic precocious puberty may show diminished levels of circulating melatonin, and some cases of male primary hypogonadism are reportedly associated with elevated serum melatonin.

6.3. Thermoregulation

The daily decline in body temperature occurs 1 to 2 h prior to the onset of increased melatonin release from the pineal gland, and peak plasma melatonin concentrations precede the temperature minimum by about 2 h. Thus, although these two circadian rhythms have an inverse relationship, their extremes do not coincide and the decline in daytime temperature normally precedes the increase in melatonin production.

Animal studies reveal a hyperthermic effect of pinealectomy in some species (sparrows, chickens, rabbits, sheep), and an absence of effect or hypothermia in others (rats and hamsters). Exposure to bright light or administration of a β-adrenergic antagonist at night, which blocks sympathetic input to the pineal gland, suppresses melatonin production and increases core body temperature. Both pharmacologic and physiologic doses of melatonin are reported to be effective in reestablishing such experimentally modified temperature levels. By contrast, the administration of a physiologic melatonin dose (0.1–0.3 mg, orally) to human subjects whose core body temperature was not experimentally altered left temperature values unchanged, whereas a hypothermic effect of melatonin powerfully manifested after a pharmacologic dose (3 mg) of the hormone had been administered (Fig. 13). Indeed, human studies consistently show that pharmacologic doses of the hormone suppress daytime and nighttime core body temperature. It has been suggested, for some time, that sleep-promoting effects of melatonin in humans might be related to its hypothermic effects. Although a substantial reduction in body temperature following administration of high pharmacologic doses of melatonin might contribute to overall sedation, the clear dissociation between the doses required to produce hypnotic and hypothermic effects (compare the data in Figs. 9 and 13, collected in the same group of subjects) suggests that these two phenomena may not be related. Studies in fish and in birds showing dissociation between sleep and temperature-related effects of melatonin further confirm this notion.

7. CLINICAL IMPLICATIONS

The pineal gland, through the rhythmic secretion of its hormone, melatonin, is part of a complex neuroendocrine mechanism that controls the temporal organization of physiologic, biochemical, and behavioral processes within the organism and synchronizes the patterns of their activities to that of environmental cycles. The characteristic time course of nocturnal melatonin secretion, together with the somnogenic effect of exogenous melatonin in physiologic doses, underlies its involvement in processes that generate normal sleep and its potential use as a treatment for insomnias, including difficulty falling or remaining asleep.

A sleep-promoting effect of exogenous melatonin might be particularly important in elderly people with insomnia whose nocturnal serum melatonin levels tend to be diminished. The ability of "physiologic" doses of melatonin to shorten latency to sleep onset, or to improve sleep efficiency in elderly people with insomnia, suggests the potential use of melatonin as a hypnotic agent, with—at physiologic doses—an extremely low probability of untoward side effects. Administration of pharmacologic melatonin doses can lead to increased daytime melatonin levels (Fig. 11) and reduced nighttime core body temperature (Fig. 13).

Studies in children with various neurologic disorders, associated with severe insomnia, showed that administration of melatonin could substantially improve their sleep patterns and increase sleep duration. Similarly, our study of children with Angelman syndrome, a rare genetic disorder characterized by severe mental retardation, hyperactivity, and disturbed sleep, found that administration of low oral melatonin doses (0.3 mg) at bedtime both promoted sleep onset and increased the duration of nighttime sleep. In some patients—those with documented delays in the circadian rhythm of melatonin secretion—treatment with melatonin at bedtime advanced the circadian rhythm and synchronized it with the environmental light-dark cycle. Furthermore, some children with Angelman syndrome showed a reduction in daytime hyperactivity and enhanced attention. Whether these are consequences of improved nighttime sleep or represent additional results of melatonin treatment that could be beneficial to other populations suffering from attention deficits needs further investigation.

The phase shift–inducing effects of melatonin treatment on the activity pattern of the SCN can entrain sleep and other rhythmic functions to an altered time schedule. Thus, prudent administration of the pineal hormone can help ameliorate blindness-induced insomnia and jet-lag symptoms, and to assist shift workers in coping with their changing rest-activity schedule.

Manipulation of circulating melatonin levels may also prove useful in the clinical management of pathologic conditions of the reproductive system, such as amenorrhea in women or hypogonadism in men. The results of clinical and experimental investigations indicate that, with further study, melatonin may become a useful therapeutic tool for these disorders.

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