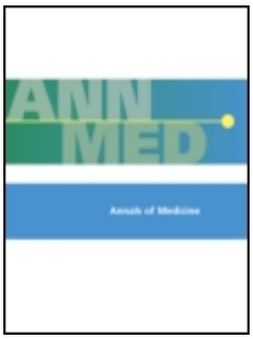

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Melatonin and human reproduction

Russel J Reiter

In photoperiodic nonhuman mammals the secretion of melatonin from the pineal gland plays a major role in regulating reproductive physiology; in humans these relationships are less clear. The melatonin rhythm changes throughout life with the first substantial change in nocturnal melatonin secretion being reportedly associated with puberty. The transition from Tanner stage 1 to Tanner stage 5 of sexual maturation is associated with a significant reduction in nocturnal melatonin levels, but a cause–effect relationship has not been established. Menstrual cyclicity has been reported to be associated with fluctuations in melatonin production but whether they are related to, eg ovulation or menstruation is not established. At high latitudes the quantity of melatonin produced by the pineal gland varies with season (changes in the light–dark cycle), and there is some evidence that this changes reproductive efficiency accordingly. Menopause is associated with a reduction in melatonin which may relate to the changing gonadotropin levels. In males of the same age melatonin levels also drop with no significant alteration in reproductive physiology. While correlations between melatonin and the status of the reproductive system in humans have been noted, whether they are functionally related remains to be determined.

Key words: menopause; pineal gland; puberty; seasonal reproduction.

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Introduction

While the structural identity of melatonin was uncovered because of its potential as an agent in influencing pigmentation of the skin of humans (1), following its isolation and chemical identification, research in mammals was primarily directed to its effects on the endocrine system, especially reproduction (2). This research proved highly rewarding because it established beyond a doubt that the organ of origin of melatonin, the pineal gland, was not a functional relic, as was previously assumed by most scientists, but rather a highly important organ of internal secretion. This research culminated in the finding that the seasonally fluctuating level of reproductive competence in photoperiodic species is regulated by melatonin produced in and secreted from the pineal gland (3). Although originally proposed to have exclusively an inhibitory effect on reproduction, it soon became apparent that both low or high melatonin levels could be associated with maximal reproductive potential in mammals depending on whether they were generally considered to be long-day (spring and summer) or short-day (autumn and winter) breeders (4). Thus, one of melatonin's primary effects in terms of the functional status of the reproductive organs in nonhuman mammals is to synchronize mating with the appropriate season to ensure that the young are born at the time that maximizes their survival, usually the spring (5). This important chronobiological feature of melatonin is readily apparent in animals that have been surgically pinealectomized, a situation in which seasonal breeders become essentially aseasonal.

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This brief review will consider melatonin in the light of human reproductive physiology. Unquestionably, the human pineal gland produces melatonin in a manner similar to that of other mammals but its effects on reproduction in both males and females have not always provided a clear picture of its specific functional niche.

Human pineal gland and the melatonin rhythm

The pineal gland in the human is located near the anatomical centre of the brain, and is on average of equal size in males and females although there are wide individual variations. The pineal gland is an end organ of the visual system, and it is the prevailing light–dark cycle, as perceived by the eyes, which regulates the quantity of melatonin produced. The neural connections between the eyes and the pineal gland have been identified, as have been many of the mechanisms whereby the innervation to the gland controls melatonin production (Fig 1) (6).

Melatonin has come to be known as the chemical expression of darkness because it is essentially uniquely produced in and secreted from the pineal gland at night leading to a circadian rhythm of melatonin in the blood with highest levels at night. In nonhuman mammals it is generally accepted that the duration of elevated melatonin, which is correlated with the duration of the daily dark period, is the key factor in determining seasonal reproductive patterns (7). This feature becomes progressively more important at higher latitudes where seasonal daylight fluctuations are more extreme. Despite the widespread use of artificial light sources in humans living at high latitudes, even within the Arctic circle, a seasonally changing pattern of melatonin secretion is evident (8), just as can be induced in humans living at low latitudes but maintained under artificially long or short nights (9). Although the nightly duration of melatonin elevation seems to be the predominant feature of the melatonin rhythm which impels seasonal reproductive cycles in nonhuman mammals, as seen below, it is usually an alteration of the amplitude of the night-time melatonin peak in humans that has been most critically assessed relative to reproductive pathophysiology (10).

Throughout the lifetime of an individual, the melatonin rhythm changes markedly. In fullterm newborn infants a melatonin rhythm is not apparent but it develops between the ninth and twelfth week

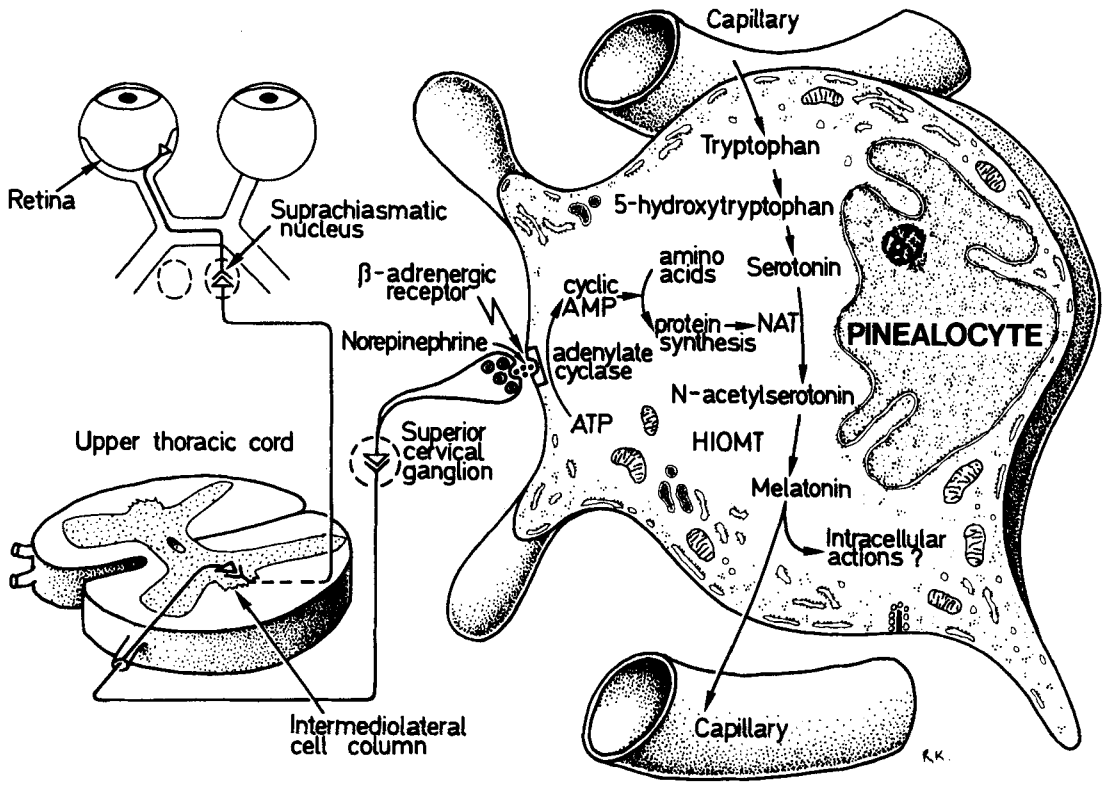

Figure 1. Neural connections between the eyes and the pineal gland along with the biosynthetic pathway of melatonin within the pineal gland. Light is normally inhibitory to melatonin secretion, whereas during darkness melatonin production is elevated. HIOMT; hydroxyindole-O-methyltransterase; NAT, *N*-acetyltransferase.

after birth (11). Infants born prematurely exhibit a 2–3 week delay in development of a melatonin rhythm even after correcting for gestational age. The pineal gland itself (12) as well as the associated melatonin cycle seem to be underdeveloped in children who die of sudden infant death syndrome, although a causal relationship has not been established. By the end of the first year of life, the day–night difference in circulating melatonin levels is marked, and throughout childhood a robust melatonin rhythm persists. During puberty, however, there has been reported to be a substantial reduction in the ratio of the day–night melatonin levels due to a decline in the nocturnal melatonin values (13). In prepubertal individuals and continuing into adulthood the melatonin rhythm persists albeit the amplitude of the rhythm varies widely even in individuals of the same age. Between the ages of 45 and 65 years, ie in the postreproductive period of females, but in males as well, nocturnal melatonin levels gradually drop so that in the elderly the day and night-time melatonin levels are equivalent (14).

Melatonin rhythm and puberty

In the late nineteenth century, Otto Huebner observed precocious puberty in a child associated with a pineal tumour and he therefore proposed that the pineal gland was an endocrine organ which, via a secretory product, influenced sexual maturation. It is now accepted that if indeed the pineal gland influences pubertal development it is via changes in the levels of melatonin (13, 15). As envisioned, during the interval associated with maturation of the neuroendocrine–reproductive axis, nocturnal melatonin levels decrease substantially. Because of the suppressive effect of melatonin on reproductive physiology, its decline, which coincides with the developmental phase of disinhibition of the gonadotrophin-releasing hormone pulse generator, is believed important in the eventual release of adult levels of pituitary follicle-stimulating hormone (FSH) and luteinizing hormone (LH) and the growth of the peripheral reproductive organs (16). In general, when night-time blood melatonin levels or the urinary excretion of melatonin metabolites are monitored at various Tanner stages of puberty, both are reported to drop between Tanner stages 1 and 5 (13, 16). While this association does not prove a causal relationship between melatonin and puberty, the findings are suggestive. Also, whether the reduction in blood melatonin values is merely a consequence of stable pineal melatonin secretion associated with a large increase in body weight or whether it actually represents a significant reduction in the biosynthetic activity of the human pineal gland during puberty is debated; recent data suggest that both these factors may account for the reduction in melatonin levels associated with puberty.

There is a recent report of a case in which a male subject in his third decade of life had not yet entered puberty and in whom very high melatonin levels were measured (Fig 2) (17). Of interest is that over a 7-year period, during which nocturnal melatonin levels dropped to normal adult values, the subject experienced sexual maturation and he fathered a child. While

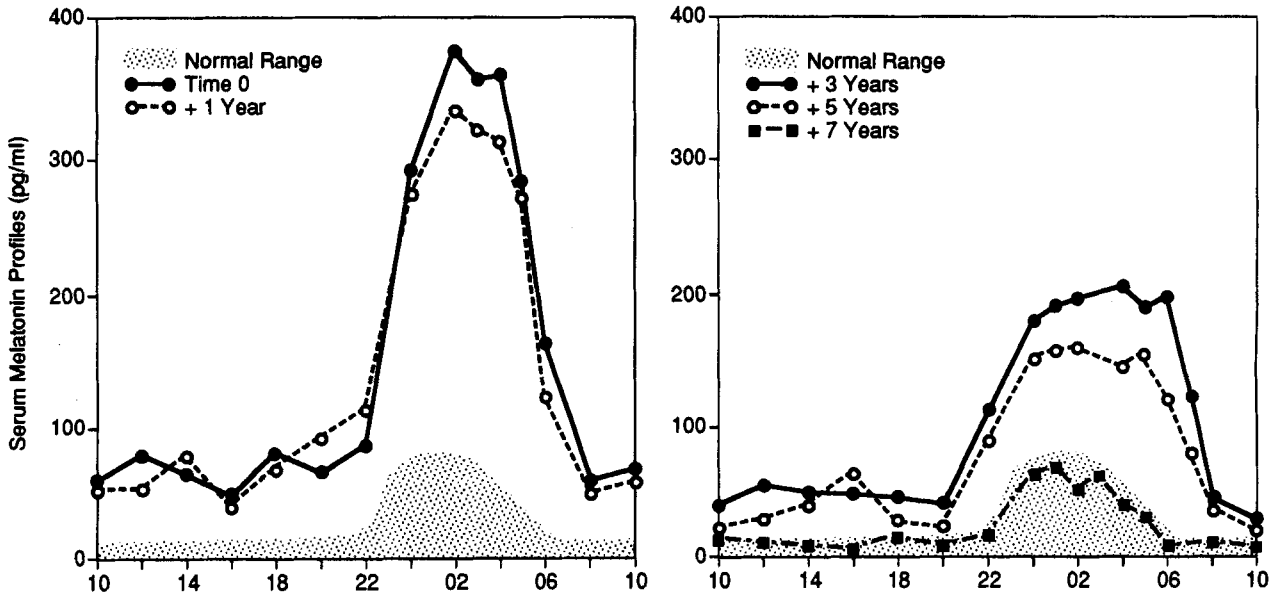

Figure 2. Blood melatonin levels in a prepubertal male in his third decade of life. When the subject was initially examined he had what would be considered to be abnormally high melatonin levels both during the day and night. As melatonin levels progressively dropped over a 7-year period, the subject experienced pubertal development and became sexually mature.

suggestive, this report does not constitute proof that the reduction of melatonin led to sexual maturation even though the events occurred concurrently.

Pineal tumours, which predominate in males and often occur before or at the time of puberty, have contributed little to our understanding of the pineal–puberty problem. Pineal tumours, possibly depending on their cell of origin, may either promote or delay sexual development (18). It has been assumed that the advancement of puberty due to pineal tumours occurs because the individuals have essentially been pinealectomized by the growing tumour, because of which melatonin levels have been reduced, while delayed puberty is a consequence of tumours of pinealocyte origin which secrete increased amounts of melatonin. There is, however, no clinical support for this assumption, because neither elevated nor depressed melatonin levels have ever been measured in individuals with various types of pineal tumours. As with tumours of the pineal gland, blindness at an early age, a condition that could maximize pineal melatonin synthesis, has provided no definitive evidence concerning the association of the pineal gland and melatonin with the transition from sexual immaturity to maturity (18).

Melatonin rhythm during the reproductively fertile period

After the attainment of sexual maturity until individuals are beyond middle age, the melatonin rhythm seems to change rather little. While there are no established limits as to what constitutes a normal melatonin rhythm in adult humans, it is usually assumed that circulating daytime levels of melatonin do not normally exceed 20 pg $\times$ mL^{-1} serum while night-time values may range from about 30–125 pg $\times$ mL^{-1}. A substantial amount of interest has been focused on the potential association of melatonin with the human menstrual cycle; conversely, there has been less interest in the adult male because males are normally continually fertile and generally lack overt signs of cyclicity.

During the ovarian cycle, gonadotrophic and steroid hormones change dramatically. Because melatonin has the capability of influencing the synthesis and secretion of reproductively active pituitary and gonadal hormones, a number of researchers have examined melatonin levels throughout the menstrual cycle but no clear consensus has emerged as to the changes that may occur. Some have claimed lowest levels of melatonin at the time of expected ovulation, which presumably permits maximal gonadotrophic hormone surges required for successful shedding of the ovum (19), while others have reported that the premenstrual syndrome in the late luteal phase is a result of an early offset of nocturnal melatonin secretion (20). Whether these associations exist and are causally related will only be proven with additional data. Large doses of melatonin (30–75 mg) in conjunction with progestin have been proposed as a novel oral contraceptive as well as a protection against breast cancer although proof of efficacy awaits the results of clinical trials (21).

What are considered abnormally high melatonin levels have been reported in women suffering from functional hypothalamic amenorrhoea (22) and in men with hypogonadotrophic hypogonadism (23). Likewise, oligospermia and aspermia in adult males are reportedly correlated with elevated nocturnal levels of melatonin (24). There is also some evidence that young females with anorexia nervosa (25) and adult females who exercise strenuously and experience menstrual acyclicity and anovulation have higher than usual levels of circulating melatonin (26). Collectively, the consistency of the findings summarized above suggests that elevated melatonin may account for some reproductive malfunctions; however, until it can be shown that pharmacologically lowering melatonin reverses these conditions, it will be difficult to prove definitive relationships.

Seasonal aspects of human reproduction

While humans are generally considered to reproduce continually, virtually all human populations exhibit some seasonality in terms of birth, owing primarily to seasonal fluctuations in conception (27). Considering the major impact of photoperiodically mediated changes in melatonin production in a number of nonhuman mammals (28), it was anticipated that annual fluctuations in reproductive competence in humans may also relate to changing day lengths and therefore to seasonally dependent melatonin alterations.

At high latitudes it is known that conception efficiency varies with day length and, in general, longer days (or shorter nights) are associated with increased fertility (29). Likewise, providing extra photic stimulation at the time of expected ovulation to women with highly irregular menstrual cycles regularizes their ovarian cycles and presumably permits ovulation at midcycle (30).

These observations led to important studies in which seasonal variations in melatonin secretion were investigated. In studies conducted in the northern hemisphere, when daytime levels of melatonin were estimated, two annual peaks (in May and December) were described with lowest values being measured in August (31). In humans living above 65°N, higher nocturnal melatonin levels have been reported in the winter months during the follicular phase of the menstrual cycle (32). These were found to be inversely related to serum levels of LH leading the authors to

speculate that seasonally elevated melatonin may be suppressing the secretion of this gonadotrophin from the pituitary gland. This speculation is certainly consistent with the observations that lengthening photoperiods in the spring are accompanied by increased levels of another gonadotrophin, namely FSH, and oestradiol as well as with an increase folliculogenesis (33). In similar studies, the darkest season of the year was found to be associated with an elevated melatonin index (integrated area under the curve of serum melatonin concentrations over a 24-hour period) and reduced ovarian and androgen activities (34). Besides melatonin levels in the blood, daytime concentrations of the indole in preovulatory follicular fluid also exhibit seasonal differences with the values being highest during the winter months (35). Collectively, these findings suggest that there may be residual rhythms in reproductive efficiency in humans living at high latitudes, and that these rhythms are driven by the prevailing photoperiod because of its action on either the amplitude and/or duration of nocturnal melatonin production.

Melatonin and menopause

It has already been mentioned that after middle age, night-time melatonin levels gradually decrease so that in some individuals beyond 60 years of age no day–night rhythm in this secretory constituent exists (14). From this it can be inferred that menopause in women is associated with the onset of a decline in melatonin production, but few studies have been conducted to test whether an alteration in the circadian melatonin rhythm relates either to the onset or to the progression of menopause. In one of the few studies designed to investigate these potential relationships, nocturnal urinary excretion of melatonin was found to decline significantly from premenopause to postmenopause (Fig 3) (36). During this interval urinary melatonin levels correlated negatively with FSH secretion. After considering these findings, it was the conclusion of the authors that the loss of melatonin during the perimenopausal period may be permissively linked to the onset of menopause.

Concluding remarks

It is well documented that in photoperiod-dependent species, the light–dark cycle, because of its marked influence on the function of the pineal gland and of the hypothalamic–pituitary–gonadal axis, has a major influence in controlling reproductive activity. The highest seasonal melatonin levels in nonhuman mammals may be associated with either decreased or elevated sexual competence, depending on the specific seasonal reproductive cycle of the species. In humans, the predominant effect of melatonin seems to be inhibitory although to date primarily correlative studies have been performed. With improved methodologies as well the availability of pharmacological agents which duplicate or antagonize melatonin's action, a clearer picture should emerge as to the precise role the circadian melatonin rhythm plays in controlling human reproductive physiology.

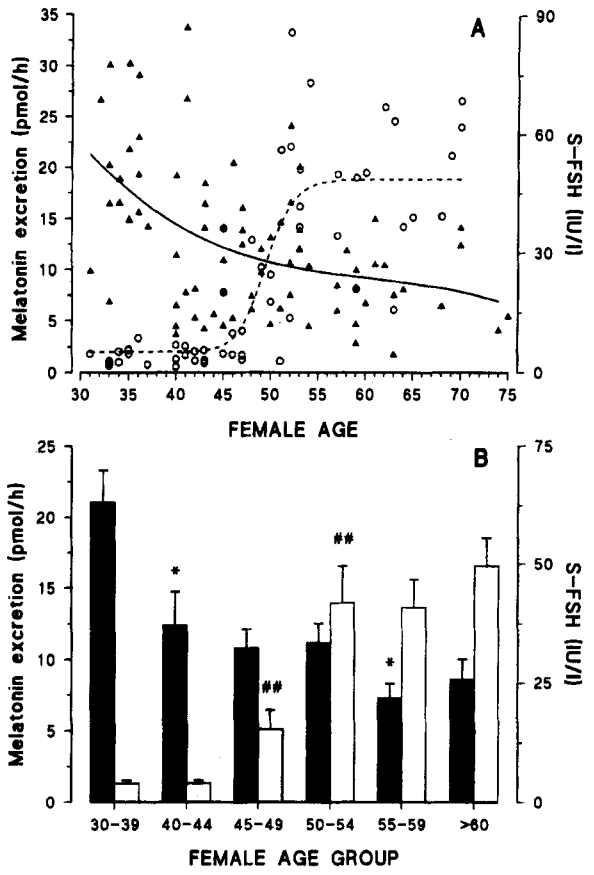

Figure 3. Age-related changes in urinary melatonin (▲) levels and serum FSH (O) levels in females at the time of menopause. Measurements were made on fluids collected at 09.00 h. (A) Scatter diagram with lines of best fit. (B) Means of values (± SE) during single decades. Solid bars, melatonin; open bars, follicle-stimulating hormone (FSH). *$P < 0.05$ for melatonin; ## $P < 0.01$ for FSH. (Reproduced from (36) with permission.)

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