

The Pineal Gland: Its Possible Roles in Human Reproduction

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Until a few decades ago textbooks of physiology or endocrinology routinely dismissed the pineal gland as Descartes' "seat of the soul," or as a calcified vestige of a phylogenetically more primitive third eye whose only function, in humans, was as a landmark for neuroradiologists. However, since the end of the 1950s, rapid and continuing progress has been made in uncovering functions of the pineal and for its principal secretion, melatonin. The importance of this hormone in humans now appears to be well established.

Between 1959 and 1964, scientists working independently and using varied biomedical disciplines contributed observations which, taken together, provided the foundation for the general theory of pineal function which continues to underlie most research on this organ (90). This theory holds that the pineal is a "neuroendocrine transducer" which converts the neural signals that it receives from its sympathetic innervation to a hormonal output, the hormone melatonin (98).

In 1959 Lerner and his associates (42) described the chemical structure of melatonin, the compound in mammalian pineal extracts which had been shown, some decades earlier, to lighten frog skin *in vitro*. Soon thereafter one of us (RJW), Axelrod, and Chu proposed (91) that melatonin is also, in mammals, a hormone. The key enzymes that catalyze melatonin's

synthesis from its precursor amino acid, tryptophan, were characterized in 1960 by Axelrod and Weissbach (7). The most unusual of these appeared to be hydroxyindole-O-methyl transferase (HIOMT), the enzyme that catalyzes the last step in the biosynthetic sequence. Using this enzyme as an index of the rate at which the rat's pineal synthesizes melatonin, it was shown in 1963 to 1964 that this synthesis was suppressed when the animals were exposed continuously to light (92), and that the light acted not directly on the pineal itself but through the eyes, the brain, and the pineal's sympathetic nerves (94). Subsequent studies showed that the 24-hour cycle of daylight and darkness affects melatonin secretion from the human pineal; that nocturnal plasma (56) and urinary (45) melatonin levels are many-fold higher than those found during daylight hours, and that experimental shifts in the light-dark cycle cause, after a few days, parallel shifts in the melatonin secretory rhythm (44).

Three years before the discovery that melatonin synthesis is affected by light, Fiske and her associates (24) had already established the light-dependence of the mammalian pineal by showing that its weight was significantly reduced when rats were continuously exposed to light. A year later Wurtman et al. (96) proposed that this light-dependence allows the pineal to mediate light's well-known effects on gonadal maturation in various laboratory and domestic animals, light producing its progonadal effects in rodents by slowing the secretion of an antigonadotrophic pineal hormone. That the pineal produced such a hormone had first been suggested (Kitay and Altschule [36]) based on evidence that pinealectomy accelerates, and administration of bovine pineal extracts slows, gonadal growth in neonatal rats. The pineal extracts also blocked the acceleration in go-

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nadal maturation that occurred in rats exposed to supplemental light (96), as did melatonin itself (91).

Today, the role of the pineal in controlling mammalian reproduction, especially among seasonal breeders, is well established (60, 61). In these monoestrus animals, the time of the year at which reproductive activity occurs is synchronized by the number of hours per 24-hour day that the pineal secretes melatonin (10). In other polyestrus mammals, like humans and laboratory rodents, melatonin has been shown to influence the age of sexual maturation (i.e., puberty); the timing of the ovulatory cycle; gonadal steroidogenesis; and patterns of reproductive behaviors. Evidence describing actions on each of these processes is discussed below.

Pineal Physiology

As proposed above (90, 93, 98) the mammalian pineal is not a true gland: rather, like the adrenal medulla, it functions as a neuroendocrine transducer; converting a neural input, the neurotransmitter norepinephrine acting at synapses, to a hormonal output, circulating melatonin (5-methoxy-*N*-acetyltryptamine). When the pineal transmits information, it thus does so by changing the rate at which it secretes melatonin. Melatonin (Fig. 1) is a lipid-soluble derivative of 5-hydroxytryptamine (serotonin). Its synthesis from serotonin requires two enzymes, serotonin-*N*-acetyltransferase (SNAT) and HIOMT, which are characteristic of, and largely confined to,

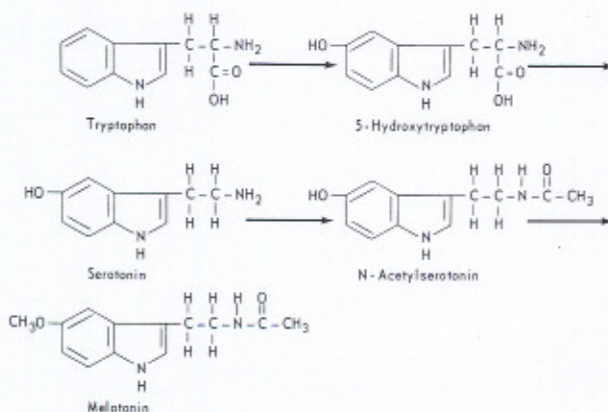


Fig. 1. Biosynthesis of melatonin (5-methoxy-*N*-acetyltryptamine). The essential amino acid tryptophan is converted to 5-hydroxytryptophan through the action of the enzyme tryptophan hydroxylase, and then to 5-hydroxytryptamine (serotonin). The conversion of serotonin to melatonin involves two enzymes that are characteristic of the Pineal: serotonin *N*-acetyltransferase, and hydroxyindole-*O*-methyltransferase. The activities of both enzymes rise with the onset of darkness (37, 90).

the pineal. Serotonin itself is synthesized in pineal cells, as well as in brain neurons, by the hydroxylation of the essential amino acid tryptophan to 5-hydroxytryptophan, followed by decarboxylation of this intermediate.

During the daylight hours the secretion of melatonin is minimal in humans and in all other mammals studied thus far (98). At that time, the flow of impulses along the pineal's sympathetic nerves is also minimal (73). However, with the onset of darkness these nerves become active, releasing norepinephrine onto the pineal's parenchymal cells and thereby initiating melatonin's synthesis and release. The catecholamine acts by combining with beta-noradrenergic receptors (97); this stimulates the synthesis of cyclic-AMP, which enhances melatonin synthesis (66) apparently by liberating 5-HT from its storage pool, and activating SNAT (37) (and perhaps HIOMT) (94). As pineal melatonin levels rise, the lipid-soluble hormone enters the blood stream via passive diffusion across a concentration gradient. The resulting daily rhythm in circulating melatonin levels normally is isomorphic with the day-night light-dark cycle (45, 56); however, a rhythm with a period that approximates 24 hours can be shown to persist when animals or humans are housed under continuous darkness or low-level illumination (44). This circadian rhythm requires about 4 days to become re-entrained to the new lighting cycle when humans are shifted westward through 12 time zones (i.e., when the daily dark period is abruptly changed from 11 PM-7 AM to 11 AM-7 PM) (44). This indicates that the ultimate source of the signal that turns on melatonin synthesis at nighttime is not simply the absence of light, but an endogenous circadian "clock," perhaps located within or acting through the suprachiasmatic brain nucleus (70).

Reproduction in Animals

The possible involvement of the pineal and melatonin in particular reproductive functions has usually been examined by 1) removing the pineal, which eliminates melatonin from the circulation (6); 2) administering exogenous melatonin at a particular period in the test animal's ovulatory or circadian cycles; or 3) looking for correlations between reproductive events and changes in plasma melatonin levels. Unfortunately, no pharmacologic tools like melatonin-blocking agents or drugs that selectively inhibit melatonin secretion, have been available to underlie additional tests.

Using these approaches, abundant evidence has been adduced that the pineal, acting via melatonin, affects reproductive performance in a wide variety of species (60, 98). The efficacy of exogenous melatonin in modifying particular reproductive functions has been found to vary markedly among species (60), depending also on the age of the tested animal (38), the time at which the melatonin is administered relative to the prevailing light-dark schedule (39, 72) or the phase of the animal's estrus cycle (99). Not surprisingly, species that exhibit major seasonal shifts in gonadal function also tend to exhibit greatest responses to exogenous melatonin.

In the rat, large doses of melatonin (1.25–5.0 mg) completely inhibited ovulation and prevented LH release when administered during the critical period of proestrus (99). Lower doses suppressed the ability of continuous light to accelerate ovarian growth and to cause persistent estrus (14). Implantation of melatonin into the median eminence or the mesencephalic reticular formation depressed pituitary and plasma LH levels (26, 27). The exogenous hormone also suppressed pituitary LH secretion in response to LH-RH stimulation, both *in vivo* (48) and *in vitro* (47), but apparently only in immature female rats. More recent studies (49, 82) have proposed that melatonin is involved in terminating phasic LH secretion, and thereby affects the timing of the LH surge and its coupling to the photoperiod. Perhaps in support of this hypothesis, pineal (55) and urinary (60) melatonin concentrations do vary with the rat's estrus cycle, decreasing with the approach of ovulation and increasing during the luteal phase.

Some seasonal-breeding animals (e.g., the ferret) breed during the spring and summer and are infertile during the fall and winter; others (e.g., sheep) display the opposite pattern. It has been proposed that the seasonal changes in the number of hours per day that melatonin is secreted mediate the temporal coupling of reproductive activity to seasonal changes in daylength. The hamster's reproductive system is inhibited by short photoperiods (i.e., fall-winter), leading to testicular regression in males and to anestrus in females; in contrast, long days produce and sustain the fertile state (13, 34, 59). The antigonadal effect of short photoperiod is prevented by pinealectomy (62); while gonadal inhibition can be achieved even during long days by daily injections of melatonin (69). As in the rat (39), the timing of these injections appears to be a critical factor in their reproductive consequences; optimal effects were observed when the hormone was injected in the late afternoon or

early morning (72) (i.e., at times of day when it extended the nocturnal elevations in plasma melatonin levels).

In the ewe, a monoestrus photoperiodic animal, the estrus cycle is suspended during the spring and summer (28) but fertility resumes in the fall and is maintained through the winter. Daylength is the major environmental variable governing these seasonal reproductive changes (9), probably acting via inverse changes in the number of hours per day that plasma melatonin levels are elevated (10). (In this species, melatonin apparently is progonadal.) It has been suggested that melatonin regulates the sensitivity of the ewe's brain to circulating estrogens, thus determining the extent to which a given estradiol level will suppress LH pulses (10).

There is also experimental evidence suggesting the involvement of environmental lighting in the control of gestation: Rodents exposed to continuous darkness or too-low light intensities throughout gestation had relatively short pregnancies (50). However, removal of the pineal did not abolish this effect, suggesting that it is mediated by factors other than the pineal and melatonin. Other studies have shown that chronic implants of melatonin depress serum and pituitary LH levels in pregnant rats, concurrently increasing serum prolactin and decreasing pituitary prolactin levels (53); opposite effects were observed in pinealectomized rats (52).

Reproduction in Humans

Puberty

Sexual maturation in humans, unlike that in most mammals, occurs many years after birth; a prolonged arrest in gonadal function occurs from late infancy to the onset of puberty. Each stage of sexual maturation is accompanied by a characteristic pattern in serum gonadotropin levels. During the first months of life, gonadotropin levels are high, resembling those of adults. By the end of the first year of life, these levels drop, remaining at low, prepubertal values until the onset of puberty (89). It was hypothesized (29) that this prolonged period of suppressed gonadotropin secretion resulted from an extreme sensitivity of the yet-immature hypothalamus to the low levels of estrogens and androgens in the plasma, allowing the gonadal steroids to suppress gonadotropin secretion via negative feedback mechanisms. However, this hypothesis failed to explain the absence of a similar supersensitivity early in infancy, nor why gonadotropin levels are low in prepubertal

subjects with gonadal dysgenesis (who are unable to produce estrogens and androgens) (17). This gap has led reproductive physiologists to search for another circulating substance or brain mechanism that could explain why plasma gonadotropin levels remain low between late infancy and the onset of puberty.

In view of melatonin's prominent antigonadotrophic effects in other mammals, the pineal hormone seems a serious candidate for the role of the non-gonadal hormone that normally postpones human puberty. A gradual and prolonged decrease in its secretion might be expected to trigger pubescence, just as the gradual decrease in the number of daylight hours during fall-winter triggers (sheep) or suppresses (ferrets) gonadal activity in monoestrous animals (i.e., by promoting melatonin secretion). The hypothesis that the human pineal affects (i.e., inhibits) gonadal growth is not new; its origin is usually dated from 1898, when Heubner (32) described a 4.5-year-old boy who exhibited both precocious puberty and a nonparenchymal tumor that had destroyed the pineal. In subsequent years many additional children, mostly boys, were described with advanced sexual maturation and similar pineal tumors. In 1954 Kitay (35) reviewed reports describing 178 cases of pineal tumors in children. More than 25 per cent of the children suffered from precocious puberty, and this abnormality occurred three times more frequently in patients with nonparenchymal than with parenchymal tumors. On the basis of these findings Kitay and Altschule (36) proposed that the human pineal has an antigonadotrophic effect on sexual maturation. Arguments against this hypothesis include the more recent finding that some pineal tumors are capable of producing hCG (68). This hormone, and not the lack of melatonin, might be stimulating the gonads in those particular cases. However, the hypothesis that the human pineal secretes an antigonadotrophic hormone has initiated a host of studies addressing the possibility that a decrease in melatonin secretion occurs prior to puberty.

Arendt et al. (3) noted a small decline in midnight plasma melatonin levels between prepuberty and puberty, in nine normal children. Wetterberg (87) found that significantly less melatonin was excreted during the day by six children (7-15 years) than by young adults (22-30 years). Silman et al. (67) measured serum daytime melatonin levels in 51 healthy boys and girls aged 11.5 to 14 years. Serum melatonin levels declined sharply during puberty in boys

but not in girls. Gupta et al. (30) reported that the amplitude of the nocturnal increment in plasma melatonin declined with pubertal development in 87 children sampled at noon and midnight. A significant decline in net increment was found between pubertal stages P1 (ages 6-10 years) and P2 (ages 9-12 years). More recently Waldhauser et al. (80, 81) measured morning and nighttime serum melatonin concentrations in 280 children, adolescents, and adults (Fig. 2). Morning levels were low in all subjects and did not change with age. However nighttime serum melatonin levels declined with progressing age. When subjects were grouped by age, melatonin concentrations dropped from 210 pg/ml in the youngest children (1-5 years) to 133 pg/ml in children 5 to 11 years, and to 46 pg/ml in young adults.

Differing results have been obtained in other studies. Lenko et al. (41) measured daytime plasma melatonin levels in 83 normal boys and 79 normal girls aged 7 years or older; no significant differences were found within different pubertal stages nor between the two sexes. In keeping with the findings of Waldhauser et al. (80, 81), but in contrast to those of Silman et al. (67), Ehrenkranz et al. (20) also failed to detect changes in daytime plasma melatonin levels during normal or precocious puberty in six children aged 9 to 13 years. Measurements of urinary melatonin in children also have resulted in discordant observations: Penny (57) found that urinary melatonin in 170 boys and girls increased through the first three stages of puberty (Tanner staging) then falling in girls with stage 4. Lemaître et al. (40) found significantly higher melatonin excretions among 58

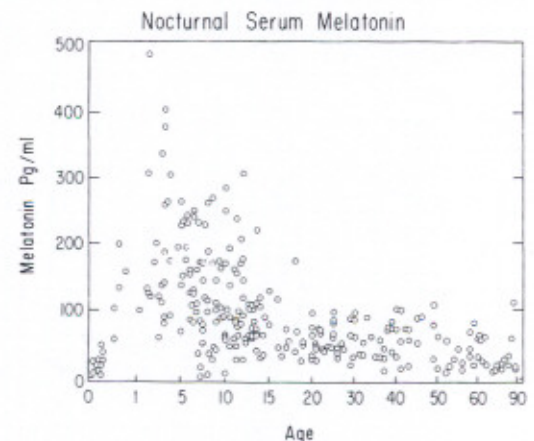


Fig. 2. Nighttime serum melatonin levels in 280 human subjects of all ages. When subjects were grouped according to their age, nocturnal melatonin concentrations declined by 75 per cent between childhood (1-5 years) and early adulthood (15-20 years). (Reprinted with permission of Waldhauser and Steger [80]).

children aged 4 to 15 years than in adults. Tetsuo et al. (75) found that urinary levels of the melatonin metabolite 6 OH-melatonin were similar in 101 children and 20 adults. Urinary 6 OH-melatonin levels may reflect the plasma melatonin concentrations (5), however, they also may depend on body weights: if small children excrete the same amount of 6 OH-melatonin as adults, it can be assumed that relative excretions per body weight, and perhaps plasma melatonin levels, are greater in the children.

It should be noted that most of the studies that examined large subject populations throughout childhood observed decreases in serum and urinary melatonin with pubescence. The negative correlation between melatonin secretion and sexual maturation is consistent with the hypothesis that melatonin is antigonadal in people; however it could merely be coincidental. It remains to be clarified, by longitudinal studies, whether plasma melatonin levels do, in fact, progressively decline in individuals undergoing puberty, or undergoing other particular stages of development (like adrenarche or gonadarche). A sudden fall in plasma melatonin, linked to a certain event in human maturation, could provide evidence for a causal connection.

The Menstrual Cycle

The menstrual cycle in humans and in other primates has long been associated anecdotally with moonlight and the lunar period (15). As early as 1842 Hille (33) described a monkey that allegedly menstruated with every full moon. The fact that the length of the human menstrual cycle is similar to that of the lunar month fed speculations that this similarity was not a mere coincidence (18). Light has been implicated as an ovulation-inducing factor. Artificial illumination during the night is well known to increase egg production in chickens. There is some evidence that light has similar progonadotrophic effects in humans; Suppressed pituitary-ovarian activity (63, 74) and reductions in the incidence of singleton and, especially, multiple pregnancies (64, 76) have been reported to occur during the dark winters to which populations near the Arctic Circle are exposed. An increased incidence of endometrial hyperplasia during the winter has also been described (77), and attributed to a greater incidence of anovulatory cycles during this darker time of the year.

One group of investigators (18, 19) examined possible effects of light on the human menstrual cycle by exposing 16 women with a history of menstrual irregularities and anovulation to continuous low-level

night light on days 14 through 17 of the menstrual cycle. Nine of the 11 subjects exposed to continuous nocturnal light for more than one cycle reportedly exhibited decreases in their cycle lengths; the cycles became regular, ranging from 29 to 31 days.

A number of investigators have used the sensitive and specific melatonin radioimmunoassays now available to look for changes in plasma or urinary melatonin during the human menstrual cycle (Table 1). An early study (88), using a single early-morning (every 2–3 days) time point, observed that plasma melatonin levels were lowest at the time of ovulation; increased during the following days; and peaked at the time of menstruation. Other investigators (3) using a more specific radioimmunoassay, found that plasma melatonin levels were low during the follicular phase and then rose to a peak coinciding with the midluteal progesterone peak. One study (8) reported that 24-hour mean serum melatonin levels were lowest on days 10 to 14 (preovulatory). Another study (57), presenting data from a single 28-year-old woman, described elevated urinary melatonin levels at the time of menstrual bleeding, with peak excretion 3 days before the gonadotropin surge. Similar results were also reported in a Russian study (51), i.e., higher urinary melatonin levels during the follicular phase than during the luteal phase. A study that used urinary 6-sulphatoxy-melatonin as an indicator of plasma melatonin levels failed to detect changes associated with the menstrual cycle (22).

The wide discrepancies among the above findings may reflect technical problems associated with early attempts to assay melatonin, and variable sampling approaches. Interindividual melatonin levels have large variations, however intraindividual variations are extremely small (4, 45). Thus, to detect subtle time-dependent changes in melatonin secretion, it is necessary to sample the same subject frequently through 24-hour periods, on different stages of the menstrual cycle. Two more recent studies have investigated circadian rhythms in plasma melatonin during the menstrual cycle by using such frequent blood sampling. One study (31) measured plasma melatonin every 2 hours, for 24 hours, in six normal young women, during the midcycle and the late luteal phases of their menstrual cycles. Total melatonin secretion (i.e., area under the curve) was found to be significantly higher during the late luteal phase than during the middle of the cycle (presumably preovulatory). Another study (84), using a 4-hour interval sampling procedure, determined the total exposure to melatonin during the 24-hour period (the

TABLE 1 Reports describing human plasma and urinary melatonin levels during the menstrual cycle

Publication	Subjects (N)	Sampling method	Follicular phase	Midcycle	Luteal phase
Wetterberg et al. (88)	5	One time-point; mean serum levels (3-day interval sampling)	100 pg/ml	90 pg/ml	180 pg/ml
Birau (8)	4	24-hr, mean serum levels	47 pg/ml	27.3 pg/ml	35.2 pg/ml
Hariharasubramanian (31)	6	Peak nighttime plasma levels (2-hr interval sampling for 24-hr)		79.2 pg/ml	125.0 pg/ml
Webley et al. (84)	10	24-hr mean plasma melatonin index*	0.75 nM/day		1.10 nM/day
Brzezinski et al. (12)	12	Peak nighttime plasma levels (2-hr interval sampling for 24-hr)	101 pg/ml	NSC†	NSC
Penny (57)	1	Overnight urine levels	15.0 ng/ml	15.5 ng/ml	2.5 ng/ml
Fellenberg et al. (22)	2	24-hr mean urine levels of 6-S-melatonin	19.3 µg/24-hr	NSC	NSC

* Melatonin index = Area under plasma melatonin curve.

† NSC, no significant change.

"melatonin index") for the follicular and luteal phases of 10 normal women. A significant increase in the melatonin index was found during the luteal phase as compared with that in the follicular phase. The same study also measured 24-hour melatonin profiles in eight women who were using contraceptive pills, and found an increase in the melatonin index relative to that in nonusers of the pill. The authors suggested that a positive relationship might exist between melatonin and progesterone and that changes in the circadian pattern of melatonin secretion—its rise during the luteal phase and a fall before ovulation—could modulate menstrual cyclicity.

In a study currently in progress we are examining the circadian patterns of plasma melatonin, prolactin, and gonadotropin during different stages of normal menstrual cycles. Our preliminary data (Fig. 3) suggest that the circadian rhythm in plasma melatonin is remarkably stable throughout the menstrual cycle. No significant preovulatory decrease in melatonin values has been evident in our subjects. However, in the two cases in which the onset of the LH surge could be detected, this onset occurred early in the morning (between 5 and 7 AM), at a time when melatonin levels were rapidly falling. This observation is consistent with other reports (65) that the onset

of the human's LH surge is an early-morning occurrence. A positive correlation existed between plasma melatonin and prolactin levels in all of our subjects.

Neuroendocrine Regulation of Pituitary Function

Only a few studies have attempted to correlate the circadian rhythm in plasma melatonin with changes in the levels of hormones secreted from the hypothalamo-pituitary-gonadal axis. Weinberg et al. (86) and Fideloff et al. (23) reported that, unlike the situation in rats (48), the acute administration of a pharmacological dose of melatonin did not suppress LH-RH-induced pituitary LH release in adult men or women. However, Aleen and her associates (1) found that intravenous melatonin infusions did suppress the elevated serum LH levels found in postmenopausal women. They postulated that melatonin acts by modulating the secretion of LH-RH, rather than by affecting the pituitary's response to the hypothalamic hormone. Chronic low-dose administration of melatonin does not seem to affect serum LH and FSH levels in humans (54).

There are indications that a positive correlation may exist between blood melatonin and prolactin levels. In rats, serum prolactin concentrations rise

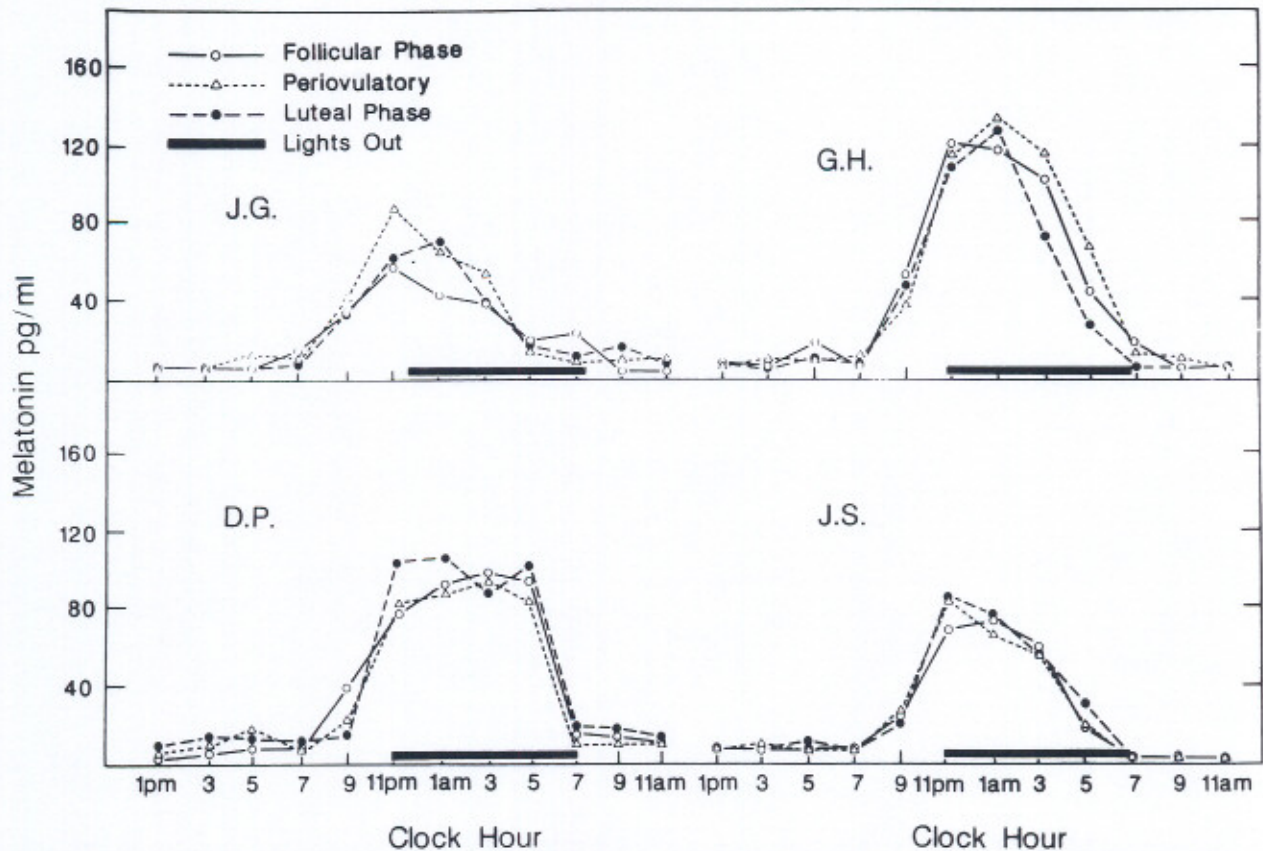


Fig. 3. Plasma melatonin 24-hour levels, sampled at 2-hour intervals, during the early follicular (days 3–6), periovulatory (days 13–16), and midluteal (days 21–25) phases of the menstrual cycle of four healthy young women. Melatonin's circadian rhythm revealed consistency for each individual throughout the menstrual cycle.

within 1 hour of the acute administration of melatonin (78). Similar effects have been described in humans (25, 79). Melatonin levels were reported to be high in several cases of hyperprolactinemia (87), however, reliable information is still lacking on exact relationships between pituitary prolactinomas and pineal activity. The mechanism by which melatonin might affect serum prolactin levels remains to be determined. Two possibilities might be considered: it could inhibit the release of hypothalamic dopamine (101), thus diminishing the inhibition by this neurotransmitter of prolactin secretion; or, it might act centrally by enhancing serotonin-mediated neurotransmission (2).

Recent reports suggest a link between the pineal gland and the secretion of opioid peptides. Exogenous opiates reportedly (43) increased serum melatonin levels in humans, and a decrease in plasma beta-endorphin levels was observed after melatonin was acutely administered to 10 normal men. These

observations suggest that a feedback system might exist between endogenous opiates and the pineal gland. (It should be noted that circulating opiates probably reflect secretion from peripheral organs rather than from the brain.)

Direct Pineal-Gonadal Relationships

Most studies support the idea that melatonin exerts its main reproductive effects at the level of the pituitary or the central nervous system, e.g., by suppressing pituitary responses to GnRH (47, 48), or by directly inhibiting hypothalamic GnRH pulses (10). However, melatonin could also exert direct effects on the gonads. The ovary takes up circulating 3H-melatonin, in cats and rats, more effectively than most other tissues (95). H3-melatonin binding has been demonstrated in hamster, rat, and human ovaries, in concentrations that exceeded those of other organs examined (16). A few studies report direct modulation by melatonin of ovarian steroidogenesis.

Melatonin reportedly stimulated progesterone synthesis *in vitro* by the human corpus luteum (46) in a dose-related manner, and increased the incorporation of acetate-1-¹⁴C into androstendione. More recent studies found that physiological concentrations of melatonin significantly stimulated progesterone production by human granulosa cells luteinized *in vitro* (85) and by corpus luteum of monkeys *in vivo* (83). Other investigators (100) reported that stimulation of rabbit ovarian follicles by hCG was blocked by melatonin. Inhibition of rat testicular androgen synthesis was achieved by adding melatonin to the culture medium (21). There is also some evidence to suggest that melatonin influences estrogen-dependent neoplastic growth (71). Physiological concentrations of melatonin (10^{-9} M– 10^{-11} M) were shown to inhibit the growth of human breast cancer cells in culture (11). Recently we discovered (12) substantial amounts of melatonin in fluids obtained from stimulated human preovulatory ovarian follicles. During daytime, when these samples were obtained, follicular concentrations of the hormone markedly exceeded (3- to 5-fold) those of serum samples obtained concurrently.

In view of these observations, melatonin could also affect ovarian function directly, by two possible modes of action. It could modulate steroid synthesis (by affecting enzyme systems in follicular granulosa cells), or it could inhibit follicular proliferation (in a manner similar to its reported effect on neoplastic cells). Further observations on melatonin's levels in follicular fluid during spontaneous (unstimulated) ovarian cycles, and its possible direct effects on ovarian steroidogenesis and oocyte maturation, may provide better insights into its significance in the control of ovarian function.

Conclusions

Prolonged and extreme diminution of the photoperiod (e.g., in northern countries) reportedly reduced reproductive function in humans suggesting a role for melatonin—which is secreted in darkness. However, attempts to demonstrate a functional link between the pineal gland and normal human reproductive processes have yielded equivocal and often confusing results. The apparent lack of dramatic effects of light or of exogenous melatonin on plasma LH and FSH levels has probably discouraged further investigations into the possible significance of the pineal for human reproduction. Nevertheless, in the hamster, it was not until studies were performed in

which melatonin was given at the right time (evening but not morning) that an antireproductive effect of the hormone could be demonstrated. Administration of melatonin with proper timing and dosage may be required to demonstrate its effect in humans. Evidence is accumulating that the human pineal gland does mediate the effects of photoperiodic information on the hypothalamo-pituitary-gonadal axis, and thus, the timing of reproductive processes like puberty and the menstrual cycle. In order to define this link further, a careful documentation of changes in melatonin's rhythm, phasing, mesor, and amplitude, will be required, using data obtained over a prolonged period of time.

Currently patterns of human melatonin secretion are being measured during various reproductive processes (like puberty, the menstrual cycle, menopause, and gestation). A closer investigation is needed of possible abnormal patterns of melatonin in pathological conditions like amenorrhea, anovulation, unexplained infertility, premature menopause, and habitual abortions.

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