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POSSIBLE CONTRIBUTION OF MELATONIN TO THE TIMING OF THE LUTEINIZING HORMONE SURGE

To the Editor: Marshall and Kelch were asked during the discussion that followed their seminar (Dec. 4 issue)[1] about factors in the central nervous system that may contribute to the timing of the luteinizing hormone (LH) surge. Dr. Marshall replied that "some central mechanism in the rat clearly increases either the frequency or the amount of GnRH [gonadotropin-releasing hormone] secreted in the early evening. There is no evidence of such a daily signal in humans." On the contrary, such a factor has been clearly demonstrated in many mammals and may also apply to humans.

Melatonin, the hormone secreted by the pineal gland, has a marked endogenously driven daily rhythm. In all mammals studied thus far, including humans, plasma melatonin levels are 5- to 10-fold higher during the night than during the day.[2] Melatonin has been shown to be antigonadotropic in various mammals and to provide a link between photoperiodic information and reproduction

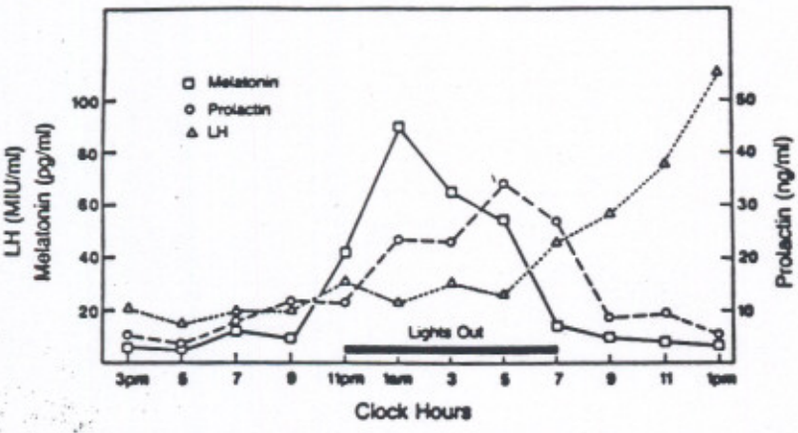

Figure 1. 24-Hour Levels of Melatonin, Prolactin, and Luteinizing Hormone (LH) at 2-Hour Intervals on Day 13 of the Menstrual Cycle of a Healthy 23-Year-Old Woman.

in animals that are seasonal breeders.[3] In female rats, melatonin contributes to the termination of phasic LH secretion and thereby participates in entraining the LH surge to the daily period of light.[4] Furthermore, late-afternoon injections of melatonin in female rats prevented the LH surge, blocked ovulation, and decreased circulating gonadotropin levels.[5]

The mode and site of action of melatonin are still incompletely understood, but most studies suggest that melatonin suppresses pituitary function either by suppressing the pituitary response to GnRH[6] or by inhibiting the frequency and amplitude of GnRH pulses.[7] Recent evidence suggests that the pineal gland and melatonin have a role in the timing of such human reproductive processes as puberty[8] and the menstrual cycle.[9]

To investigate possible relations between circulating melatonin levels and the human menstrual cycle, we identified daily patterns in serum melatonin levels during the early, follicular, periovulatory, and luteal phases of the menstrual cycle among 10 regularly menstruating volunteers. Subjects were exposed to light between 7 a.m. and 11 p.m. Blood samples were obtained through an indwelling cannula at two-hour intervals, and levels of melatonin, prolactin, and LH were measured.

Serum melatonin exhibited a diurnal rhythm in all the subjects, peaking around 2 a.m. Each subject's characteristic circadian pattern was remarkably similar during the early follicular, periovulatory, and luteal phases. The nighttime levels ranged from 56 to 161 pg per milliliter (mean + SE, 101 + 18). A diurnal rhythm in serum prolactin levels was also observed in each subject, peaking around 5 a.m. (mean + SE, 24 + 4 ng per milliliter). In two of the women, the preovulatory LH surge was detected, beginning in each case between 5 and 7 a.m., when serum melatonin levels were falling rapidly (Fig. 1). The reported early-morning onset of the LH surge[10] might thus be related to the concurrent decline in melatonin secretion (as in other mammals).

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