EVIDENCE FOR A SEX-SPECIFIC FACILITATORY EFFECT OF MELATONIN ON PROLACTIN SECRETION. IS PINEAL-PROLACTIN INTERACTION RELEVANT TO THE CLINICAL COURSE OF BREAST CANCER?


Dipartimento di Scienze Cliniche e Biologiche, Università degli Studi di Torino, Cattedra di Medicina Interna, Ospedale S. Luigi, Orbassano (TO) and * Divisione di Ostetricia e Ginecologia, Ospedale Mauriziano Umberto I

In all mammals tested so far melatonin (MT), the main pineal hormone, is secreted according to a large-amplitude circadian rhythm. Its profile of secretion is characterized by a brisk surge during the period of darkness with the peak in the first hours after midnight and decline before dawn; during the day-light hours serum MT concentrations are persistently low (Preslock, 1984).

In seasonal breeding mammals this signal serves as a conveyer of the photoperiodic message to entrain the hypothalamic-pituitary-gonadal axis to environment (Tamarkin et al, 1985).

In human beings, it has been claimed that MT is a modulator of a number of endocrine functions, but its physiological role is still matter of debate (Arendt, 1988). The study of endocrine responses to exogenously administered MT was supposed to provide information but available data are controversial. Age, sex, menstrual stage of probands, dose, route and timing of administration are admittedly factors accounting for discrepancies (Brzezinski & Wurtman, 1988).

We have planned to systematically evaluate the effects of exogenous MT on some endocrine variables in humans. Since the inclusion of both female and male subjects in the proband group may yield equivocal results, we have considered separately the two sexes.

The first step was to study whether the acute administration was able to affect pituitary and adrenal responses to specific stimuli in the male. We carried out a double blind placebo-controlled protocol in six healthy adult subjects. They were randomly given on three separate occasions 100 mg and 1 mg of exogenous MT and placebo as gelatine capsules. One hour after the administration they underwent a combined stimulation test with Gn-RH (100 μg), TRH (200 μg) and the ACTH analogue, Alsactide (10 μg). LH, FSH, prolactin (PRL), TSH, cortisol, aldosterone and progesterone were measured on serial blood samples. The same protocol was performed at 08.00 and 20.00 hour with a one-month interval.

Either 100 or 1 mg of MT orally administered were able to raise the serum concentrations much over the physiological range for at least three hours, confirming previous observations (Arendt et al., 1984; Vakkuri et al., 1985; Role of Melatonin and Pineal Peptides in Neuroimmunomodulation Edited by F. Fraschini and R.J. Reiter, Plenum Press, New York, 1991 263}
Waldhauser et al., 1984). Despite interindividual variability, the absorption of MT is clearly effective. None of our volunteers complained of side effects apart from a moderate drowsiness. Exogenous MT did not cause appreciable changes in the release of gonadotropins after Gn-RH; TSH and PRL after TRH; cortisol, aldosterone and progesterone after the ACTH analogue. Hormonal responses were evaluated in terms of net and percent increment, and area of response. These findings were not surprising since in animal models MT had to be administered over a sustained period to elicit appreciable effects (Bittman et al., 1984). They could also be interpreted as compatible with the view that the hypothalamus is the most likely site of action of MT (Kamberi et al., 1971).

The second step was to investigate in 6 age-matched males the effects of long-term administration (2 mg MT per os at 18.00, daily for two months). Before and after MT, we evaluated the circadian rhythm of serum MT, cortisol, PRL and testosterone using chronobiological procedures. Blood sampling was at 4-h intervals for 24 h. LH, FSH, PRL, TSH, cortisol and aldosterone responses to the aforementioned stimuli, and the testosterone response to human Chorionic Gonadotropin (5000 IU; single im injection) were also evaluated.

In this area of research, previous studies have considered shorter courses of MT treatment (Wright et al., 1986; Mallo et al., 1988) or exceedingly high dosages (Nordlund and Lerner, 1977). Again, the only side effect of chronic MT was a moderate drowsiness. Serum MT raised as in the subjects studied by Wright et al. (1986). As a consequence of the evening administration, we found a clear-cut phase advance of the circadian rhythm of MT. The 24-h profiles of cortisol and PRL were not affected by treatment, whereas a significant phase-advance was documented for the testosterone rhythm. Responses to stimuli were unchanged as after acute administration.

From these results it is likely to think that MT plays a role in the control of circadian changes of the testicular function but does not play a similar role for cortisol, as previously reported by Vaughan et al. (1979), and PRL (Strassman et al., 1987).

As a third step, we have started to study female subjects. It is pertinent to say that recent data raise the questions whether MT mediates the effects of prolonged darkness to suppress the hypothalamic-pituitary-gonadal axis of women living in northern countries (Kauppila et al., 1987) and participates in the determination of the LH ovulatory surge (Brezinski et al., 1987).

We carried out two different protocols. In the first we evaluated LH, FSH, PRL, TSH and cortisol responses to the combined stimulation test with Gn-RH, TRH and Alsactide at 19.00, one hour after the oral intake of 2 mg of MT. Five normally cycling women were studied in the early follicular (5-7 day) and midluteal phases (22-24 day) of 4 different cycles with a double blind, placebo-controlled procedure.

In the second protocol we evaluated the pulsatile pattern of serum LH and PRL in five age-matched women in the late follicular phase (8-10 day) of two different cycles, baseline-placebo versus MT (2 mg at 16.00 and 20.00). Blood sampling was at 10-min intervals for 6 h from 18.00 to 24.00. A modified version of the peak detection algorithm of Santen and