

General and unspecific damping by malignancy of the circadian amplitude of circulating human melatonin?

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Abstract

The circadian rhythm of serum melatonin of 39 cancer patients is compared with that of 28 healthy subjects matched by gender and age. Each subject provided 6 blood samples at 4-hour intervals for determination of melatonin by RIA. After \log_{10} -transformation, data series were analyzed by single and population-mean cosinor and compared between the two groups and among patients subgrouped by cancer site, stage and treatment. A circadian rhythm ($P < 0.001$) is demonstrated for both groups, with a contributing 12-hour harmonic ($P < 0.001$). In the absence of a difference in MESOR, the circadian amplitude of the cancer patients is smaller than that of the healthy subjects ($P = 0.003$). Numerically, nocturnal (00:00 and 04:00) melatonin concentrations are lower and daytime (08:00-20:00) melatonin concentrations are higher in the cancer patients than in the healthy subjects ($P = 0.032$ at 12:00 and $P = 0.058$ at 16:00). In the age ranges examined, no differences are found with age in either group or by gender in health. No differences are found among cancer patients subgrouped either by site, stage (localized vs. metastasized) or treatment. If these results are validated, other Janus-like (two-faced: stimulation or inhibition, depending on chronome stage) effects of malignancy should be taken into consideration for screening and for timing treatment.



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Introduction

As reviewed elsewhere (Halberg et al. 1988; Cornélissen and Halberg 1992; Ronco and Halberg 1996), with a resurgence of interest in the role of the pineal in cancer of the breast (Tamarkin et al. 1982), this gland has long been thought to be useful for oncotherapy. Engel (1934, 1935) reports that an aqueous-alkaline extract of the pineal, given daily subcutaneously, inhibits a transplanted Ehrlich carcinoma of mature albino mice. Most of the treated animals reportedly failed to show tumors, a result complicated by the concomitant administration of pituitary gonadotropic hormone, to which Engel attributes a cancer-promoting effect. His follow-up work on albino mice extends the scope of the first results, reported on the assumption that the pineal counteracts tumor promotion by the anterior lobe of the pituitary.

Melatonin, a main hormone produced by the pineal, among other sites, has been considered for oncochronotherapy (Bartsch et al. 1995b; cf. Ronco and Halberg, 1996). Even if the nocturnal peak in circulating melatonin may be decreased at certain stages and in certain kinds of cancer (Tamarkin et al. 1982; Bartsch et al. 1995b), it seems unlikely that a time-unqualified substitution therapy is appropriate, in view of different effects of the hormone and other agents at different rhythm stages (Halberg E. and Halberg F. 1980; Langevin et al. 1983; Wrba et al. 1986, 1990; Halberg et al. 1988; Cornélissen and Halberg 1992; Sánchez de la Peña 1993; Bartsch et al. 1995b; Ronco and Halberg 1996). Whether circulating melatonin “behaves” differently in various kinds of cancer and the two genders is here explored.

Subjects and Methods

The circadian rhythm of serum melatonin of 39 cancer patients (17 M + 22 F, 38-88 y; mean age \pm SD: 71.9 ± 11.2 y) was compared with that of 28 healthy subjects (11 M + 17 F; 39-91 y; mean age \pm SD: 64.8 ± 15.2 y) matched by gender and age, studied between March 1994 and May 1997. There were 9 patients with multiple myeloma and one patient with chronic lymphatic leukemia (i.e., 10 patients with a haematologic tumor), 9 patients with lung cancer, 3 patients with cancer of the prostate, 4 patients with breast cancer, 4 patients with colon cancer, 4 patients with cancer of the bladder or kidney and 5 patients with other miscellaneous malignancies. Of the 29 non-haematologic tumors, 8 were localized and the other 21 had metastasized. At the time of study, 26 patients were untreated and 5 were treated while the other 8 had been previously treated. Each subject provided blood samples at 4-hour intervals for 24

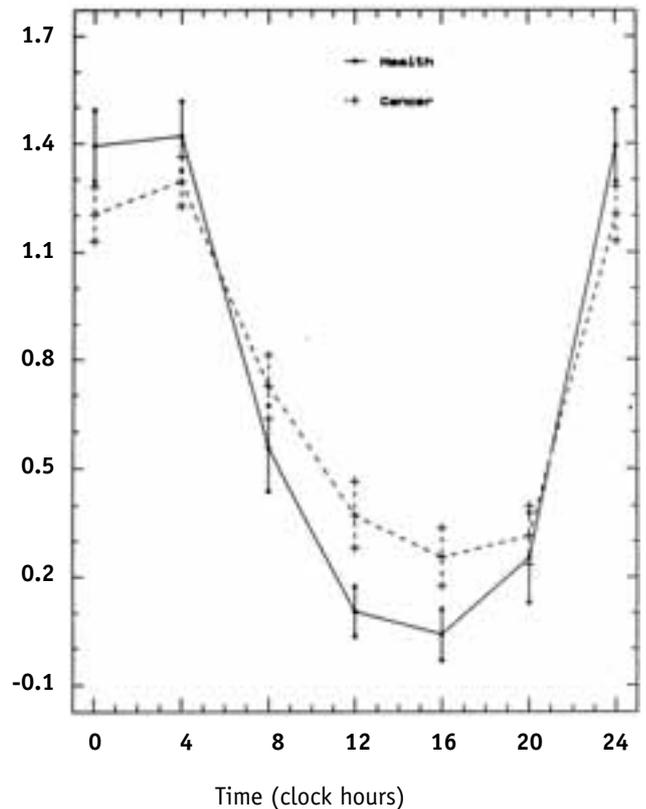


Figure 1. Circadian pattern of circulating melatonin in health and cancer. Timepoint means \pm 1 standard error.

hours (6 samples) for determination of melatonin by RIA. Each data series was \log_{10} -transformed in view of the skewed distribution of melatonin values and the \log_{10} -transformed data analyzed by single and population-mean cosinor (Halberg 1969). Circadian characteristics were compared between the two groups by parameter tests (Bingham et al. 1982) and by Student t-test (Sokal and Rohlf 1981), as were the \log_{10} -transformed mean values at each timepoint. Similar comparisons were made among patients grouped by cancer site, stage and treatment.

Results

A circadian rhythm is demonstrated for both cancer patients and for the healthy control group, as is the second harmonic with a trial period of 12 hours, Table 1. In the absence of a difference in MESOR (24-hour rhythm-adjusted mean), the circadian amplitude of the cancer patients is smaller than that of the healthy subjects ($P=0.003$). During the daytime (08:00-20:00), circulating melatonin concentrations are numerically higher in the cancer patients as compared to the control subjects, whereas at night (00:00 and 04:00), melatonin concentrations are lower in the patients as compared to the healthy subjects, Figure 1. The difference between the two groups is statistically significant at 12:00 ($P=0.032$) and is of borderline statistical significance at 16:00 ($P=0.058$).

Table 1. Circadian characteristics of circulating melatonin (\log_{10} -transformed) in health and cancer

Group (N)	Period	PR (h)	P	MESOR	Double amplitude		Acrophase (°)
					(pg/ml)		
Health (28)	24	83.8	<0.001	0.637	1.582	-39	
	12	14.3	<0.001		0.424	-53	
Cancer (39)	24	76.7	<0.001	0.695	1.132	-48	
	12	20.2	<0.001		0.344	-55	

PR=percent rhythm (proportion of variability accounted for by fitted cosine curve); P=P-values from zero amplitude (no rhythm) assumption; acrophase reference: local midnight (360 degrees equated to period length).

No differences are found as a function of age in either group or as a function of gender among the healthy subjects. A slight gender difference among the cancer patients is found at 12:00 ($P=0.078$) and 16:00 ($P=0.026$) when women have higher circulating concentrations of melatonin as compared to men. No difference is found in the MESOR, in the circadian amplitude and in timepoint mean values among cancer patients grouped either by site, stage (localized vs. metastasized) or treatment. Larger numbers of patients will be needed to validate the possibility that melatonin behavior in malignancy may be unspecific and not limited to a single site.

Discussion and Conclusion

The smaller circadian amplitude of circulating melatonin in cancer patients by comparison with healthy subjects in the absence of any MESOR difference may account for some of the results reported in the literature which appear to be discrepant until the circadian stage of blood sampling is specified. Higher melatonin concentrations are found between 07:30 and 09:30 in 46 patients with multiple myeloma by comparison to 31 age-matched healthy controls ($P<0.001$) (Tarquini et al. 1995). Higher serum melatonin concentrations are also reported at 08:00 and 00:00 for patients with advanced tumors of the breast, lung or gastrointestinal tract by comparison to healthy controls (Dogliotti et al. 1990). Patients with advanced breast cancer are also reported to have higher daytime plasma melatonin concentrations than patients receiving adjuvant treatment and patients with progressive disease reportedly have higher values than patients in remission or with stable disease (Falkson et al. 1990).

In venous blood samples collected between 08:00 and 09:00 after an overnight fast, serum melatonin concentrations are found to be higher in 74 untreated breast cancer patients as compared to 46 age-matched healthy women (Barni et al. 1989). While in blood samples collected at 08:00, plasma melatonin concen-

trations are reportedly higher in patients with prostatic carcinoma than in healthy subjects, they are lower in patients with breast cancer (Oosthuizen et al. 1989). Single samples around 08:00 may not be the optimal choice for determining melatonin concentrations in blood. At that time, the higher nightly values are dropping to lower daytime values. Slight changes in the daily activity routine may thus be associated with relatively large differences in melatonin concentration and hence with a larger uncertainty than that expected to characterize samples collected later in the day.

Lower nighttime circulating melatonin concentrations are also reported in patients with breast cancer vs. age-matched healthy controls by Bartsch et al. (1989), who also report a progressive lowering of nighttime values with increasing tumor size. A decreased nocturnal plasma melatonin peak is also reported for patients with estrogen-receptor-positive breast cancer (Tamarkin et al. 1982) while a lowered concentration of plasma melatonin is reported during the night for patients with colorectal carcinoma as compared to controls (Khoory and Stemme 1988). A decreased amplitude of the circadian rhythm in circulating melatonin is also reported by Bartsch et al. (1991, 1992) in patients with primary prostate cancer as well as in patients with breast cancer. A link between melatonin and cellular immunity has been suggested from animal studies (Bartsch et al. 1995a), with the further observation that there may be stimulation of the immune system and the pineal gland at early but inhibition at advanced stages of cancer.

The pineal has been hypothesized to be "hyperactive" at the outset, as a break to carcinogenesis, and to be "exhausted" thereafter, as the tumor grows (Relkin 1976). If the circadian amplitude is a gauge of hyperactivity when it is too large and of exhaustion when it is too small, the results herein fit exhaustion, and our earlier finding of an increased circadian amplitude in women at an elevated familial risk of breast cancer (Wetterberg et al. 1986) fits hyperactivity.

These chronobiologic considerations should be kept in mind in protocols aimed at using melatonin as adjuvant therapy for cancer patients (or otherwise), notably since in the experimental laboratory, immunomodulators such as melatonin have been found to be associated with differences as drastic as the enhancement vs. the inhibition of malignant growth solely as a function of chronome (notably circadian) stages at the time of their administration (Halberg E. and Halberg F. 1980; Langevin et al. 1983; Wrba et al. 1986, 1990; Sánchez de la Peña 1993; Bartsch et al. 1994). In summary, a chronobiologic inquiry reveals a consistent, seemingly unspecific reduction in the circadian amplitude of melatonin that remains undetected by conventional approaches and warrants further scrutiny as an endocrine chronome, almost certainly interacting with other chronomes of variables in and around us.

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