

CIRCADIAN AND CIRCASEPTAN DEPENDENCE OF THE BETA-ATP PEAK OF FOUR DIFFERENT CANCER CELL CULTURES: IMPLICATIONS FOR CHRONORADIOTHERAPY

ULMER W.¹, CORNELISSEN G.², REVILLA M.³, SIEGELOVÁ J.⁴, DUŠEK J.⁴, HALBERG F.²

¹VARIAN International, Zug, Switzerland

²University of Minnesota, Minneapolis, Minnesota, USA

³University of Valladolid, Spain

⁴Department of Functional Diagnostics and Rehabilitation, Faculty of Medicine, Masaryk University, Brno

Abstract

The aim of the study was to examine the time-dependence of the beta-ATP peak of different tumor cells *in vitro* as a gauge of overall metabolism. In view of the large circaseptan-over-circadian prominence of the time-dependence of the beta-ATP peak, it is suggested to modulate the administration of radiotherapy according to a weekly schedule, to optimize treatment efficacy.

Key words

Circadian and circaseptan rhythm, Beta-ATP peak, Cancer cell cultures, Implications for chronoradiotherapy

INTRODUCTION

Multifrequency rhythms, chaotic-appearing changes, and trends in their characteristics are time structures within and around us. Interplanetary, planetary, hypothalamic and pineal intermodulations complement pineal, pituitary and adrenal interactions linked to periodic DNA and thus to growth, normal and abnormal. Sunshine by the day and geomagnetics by night with a yearly and half yearly variation modulate circulating human melatonin (*1*).

The present paper is aimed at studying the time-dependence of the beta-ATP peak of different tumor cells *in vitro* as a gauge of overall metabolism.

MATERIALS AND METHODS

Four different cell cultures were studied as tumor spheroids in the stationary phase: C3H-MA grown from a murine mammary adenocarcinoma; B14 cells from a Chinese hamster; 9L glioma cells of a rat, and a monolayer culture of mouse L1210 leukemia cells. All cell cultures were irradiated with 6 MeV electrons (VARIAN Clinac linear accelerator C/D 2300). The dishes containing the cell colonies and the nutrient medium were positioned between two foils in order to reach the maximal dose at the surface of the dishes; the second foil served as back scatter medium.

Cell cultures were grown in the cytological laboratory of the Max Planck Institute for Cell Biology, Goettingen, Germany. The ATP concentration was determined by ³¹-NMR Fourier spectroscopy with a Bruker spectrometer operating at 40.25 MHz. The internal reference system of the ³¹P peak was the resonance signal of phosphocreatine. Measurements were obtained around the clock for 44 days at 4.8-hour intervals (N=221). Each data series was detrended to compensate for the growth curve modelled nonlinearly as $M(1 - \exp(-t/T))$. Residuals from the stationary phase were analyzed by linear-nonlinear least squares and chronobiologic serial section at anticipated periods of 24 hours and 7 days.

RESULTS

All four cell cultures exhibited a prominent circaseptan component and a statistically significant if weaker circadian rhythm, *Table 1* and *Fig.1*. The circaseptan-to-circadian amplitude ratios are readily seen to vary between 2.5 and 4.

Nonlinear analyses yield period estimates with 95% confidence intervals covering 24 hours and 7 days, respectively. Chronobiologic serial sections exhibit a stable phase throughout the whole observation span.

Table 1

Circadian and circaseptan aspects of in vitro growth of cancer cells*

Cell culture	P	A ± SE	φ (95% CI)
Circadian			
B14	0.004	0.014 ± 0.004	-327 (-291; -3)
C3H	<0.001	0.024 ± 0.006	-328 (-297; -359)
Glioma	<0.001	0.023 ± 0.005	-328 (-305; -351)
L1210	<0.001	0.032 ± 0.006	-329 (-307; -351)
Circaseptan			
B14	<0.001	0.056 ± 0.002	-356 (-351; -360)
C3H	<0.001	0.088 ± 0.003	-356 (-353; -360)
Glioma	<0.001	0.060 ± 0.003	-355 (-350; -360)
L1210	<0.001	0.081 ± 0.003	-354 (-349; -358)

*P=P-value from zero-amplitude (no-rhythm) test; A=amplitude (arbitrary units, after normalization of growth curve); phi=acrophase, expressed in (negative) degrees, with 360 dg=period length and 0 dg=start of cell culture.

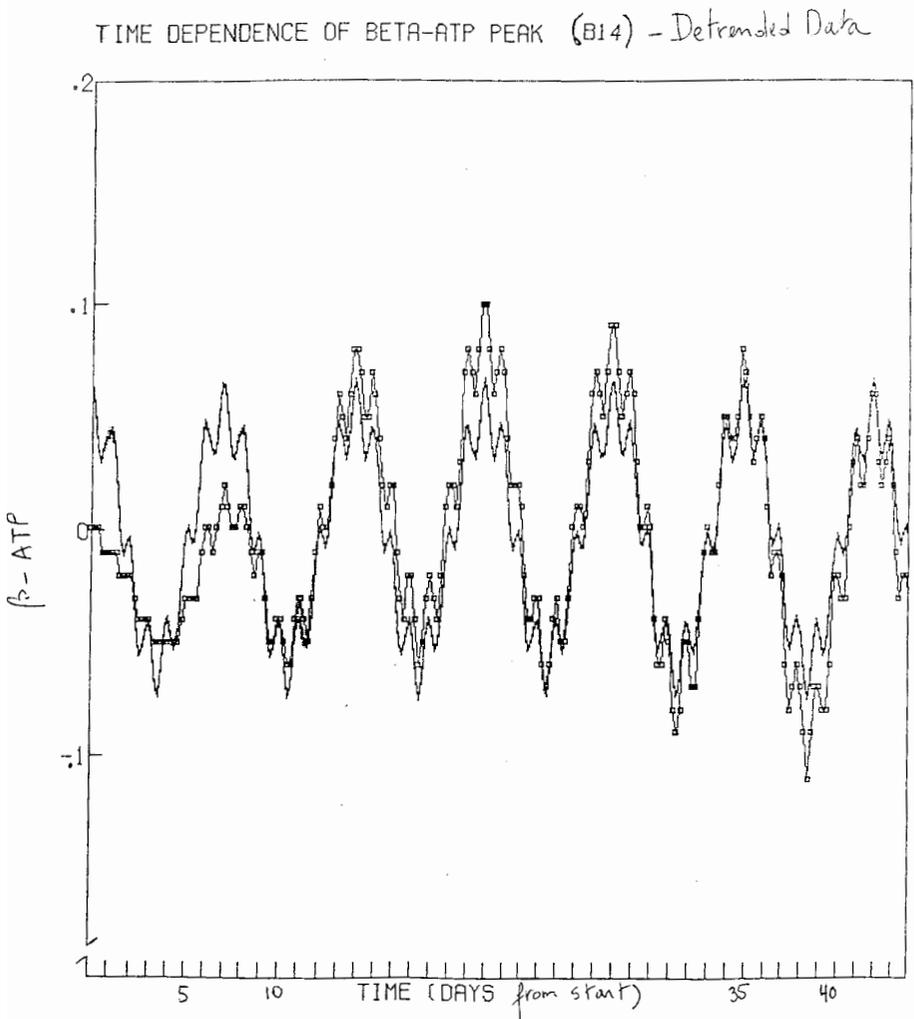


Fig. 1

Time dependence of beta-ATP peak (detrended data)

DISCUSSION

Circaseptan-to-circadian amplitude ratios of 4.0, 3.7, 2.6 and 2.5 suggest that under the conditions investigated, the weekly change was 2.5 to 4 times greater than the daily change, which latter has been demonstrated by an earlier NMR study to characterize high-energy phosphate metabolism in the human forearm (2). They are also in keeping with numerous reports of an amplified circaseptan component in the presence of malignant or regenerative and physiological growth (3,4).

There are changes in circulating melatonin in patients with different cancers in comparison to healthy controls (5). It seems that the study of the time-dependence of the beta-ATP peak of different tumor cells in vitro as a gauge of overall metabolism is an very important finding.

Disease-free survival of patients with large perioral tumors was doubled by timing radiotherapy according to the circadian rhythm in tumor temperature (6), another marker of overall metabolic activity. In view of the large circaseptan-over-circadian prominence of the time-dependence of the beta-ATP peak, it is suggested to modulate the administration of radiotherapy according to a weekly schedule, to optimize treatment efficacy.

A c k n o w l e d g e m e n t

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Ulmer W., Cornelissen G., Revilla M., Siegelová J., Dušek J., Halberg F.

CIRKADIÁNNÍ A CIRKASEPTÁNNÍ ZÁVISLOST VRCHOLU BETA-ATP ČTYŘ RŮZNÝCH TKÁŇOVÝCH KULTUR RAKOVINNÝCH BUNĚK: VÝZNAM V CHRONORADIOTERAPII

S o u h r n

Cílem studie bylo vyšetřit časovou závislost vrcholu beta-ATP různých nádorových buněk in vitro jako měřítka celkového metabolismu. Vzhledem k převládající asi týdenní rytmicitě nad cirkadiánní rytmicitou časové závislosti vrcholu beta-ATP se doporučuje upravit radioterapii podle týdenního programu s cílem optimalizovat účinnost léčby.

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