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Section 4 — General Chronopharmacology

Co-chairmen: P. BÉLANGER (Québec, Canada)
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S. NAKANO (Ehime, Japan)
R. STURTEVANT (Maywood, Illinois)

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Section 5 — Ulcerogenesis, H2-Antagonists, Diabetes and Nutrition

Co-chairmen: A. MARKIEWICZ (Katowice, Poland)
J. MOORE (Salt Lake City, Utah)
S. SZABO (Boston, Massachusetts)

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Section 6 — Cancer
Co-chairmen: I. ASHKENAZI (Tel Aviv, Israel) C. FOCAN (Liège, Belgium) R. VON ROEMELING (Lubbock, Texas) L. SCHEVING (Little Rock, Arkansas)

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Round Table — Drug Delivery Systems and Pumps for Timing Medications

Chairman: W. J. M. HRUSHESKY (Minneapolis, Minnesota)

Chronotherapy of patients with metastatic colorectal cancer with 5-fluorouracil (5-FU) and oxaliplatin (1-OHP), automatically delivered via a programmable external pump.
Preliminary results

J. P. CAUSSANEL, F. LÉVI, J. L. MISSET, A. DESCORPS DECLERE, R. ADAM, H. BISMUTH, A. REINBERG and G. MATHE

Time-modulating controlled delivery of peptide/protein drugs for possible applications in chronotherapy

Y. W. CHIEN

Circadian variations of vindesine serum concentrations during continuous infusion

C. FOCAN, V. MAZY, J. ZHOU, R. RAHMANI and J. P. CANO

Implantable therapeutic systems

J. KOST

Ambulatory 5-day chronotherapy of colorectal cancer with continuous venous infusion of 5-fluorouracil (5-FU) at circadian-modulated rate. Preliminary results


Pump delivered insulin and home monitored blood glucose in a diabetic patient: Retrospective and chronophysiologic evaluation of 3-year time series

A. REINBERG, P. DROUIN, M. KOLOPP, L. MÉJEAN, F. LÉVI, G. DEBRY, M. MECHKOURI, G. DI COSTANZO and A. BICAKOVA-ROCHER

Circadian timing and mode of fluoropyrimidine administration markedly impact organ-specific toxicity and maximal dose intensity

R. v. ROEMELING, J. RABATIN, M. TUCHMAN and W. J. M. HRUSHESKY
Feasibility, safety and accuracy of an automated drug delivery system suitable for chronochemotherapy in pediatric patients


Section 7 — Cardiovascular and Renal Systems

Co-chairmen: J. CAMBAR (Bordeaux, France)
H. DECOUSUS (St. Etienne, France)
B. LEMMER (Frankfurt, W. Germany)

Circadian variations in post ischemic acute renal failure in rats

P. CATROUX, C. DORIAN and J. CAMBAR

Role of renin angiotensin system in amikacin chrononephrotoxicity

C. DORIAN, P. CATROUX and J. CAMBAR

Does the circadian variation of $\beta_2$-adrenoceptor sites on peripheral mononuclear leucocytes (MNL) reflect the circadian variation of different MNL subsets?

E. HAEN, T. LEDERER, P. RIEBER, P. SCHLEICHER, I. LANGENMAYER, M. HALLEK and J. REMIEN

24-hour variations in the distribution of labeled microspheres to the intestine, liver and kidneys

G. LABRECQUE, P. M. BÉLANGER, F. DORÉ and M. LALANDE

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DOES THE CIRCADIAN VARIATION OF β²-ADRENOCEPTOR SITES ON PERIPHERAL MONONUCLEAR LEUCOCYTES (MNL) REFLECT THE CIRCADIAN VARIATION OF DIFFERENT MNL SUBSETS?

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ABSTRACT

The fractional distribution of lymphocyte subsets was determined in three male subjects. Its contribution to the circadian variation in the expression of β²-adrenoceptor sites on peripheral mononuclear leucocytes (MNL) was calculated to be 92.7-107.3 % of the 24h-mean. This strongly favors the idea that the actually observed circadian range of 74.5-124.9 % of the 24h-mean constitutes a circadian receptor down- and up-regulation.

KEY WORDS
circadian variation, β²-adrenoceptors, peripheral mononuclear leucocytes (MNL), lymphocyte subsets, humans

INTRODUCTION

MNL are widely used for clinical studies evaluating the expression and function of β²-adrenoceptors (Haen 1987, Brodde et al 1985, Middeke et al 1985). We recently described a circadian variation in the expression of β²-adrenoceptors on peripheral MNL (Pangerl et al 1986, Haen 1987). Since T-lymphocytes have been reported to bear less than half the number of β²-adrenoceptor sites as B-lymphocytes (Landmann et al 1984, Krawietz et al 1982), the circadian variation in the expression of β²-adrenoceptor sites may result from a circadian variation in the numerical distribution of these lymphocyte subsets.

MATERIALS AND METHODS

Venous blood was drawn at 14h00, 18h00, 22h00, 02h00, 06h00, 10h00, and again at 14h00 from three male subjects, 24-34 years of age. Peripheral mononuclear leucocytes were immediately harvested by Ficoll-Hypaque density gradient centrifugation. The cells were incubated with a set of mouse IgG monoclonal antibodies (CD 3, CD 4, CD 8, CD 37 specific for T-, T-helper*, T-suppressor*, and B-cells, respectively) and in a second step with a fluoresceinisothiocyanate (FITC)-labeled goat anti-mouse IgG monoclonal antibody. After washing out exceeding amounts of antibody the cells were fixed in 0.1% paraformaldehyde and stored at 4°C. Approximately one week after sampling the fixed cells were run in a fluorescence activated cell sorter (FACS) to count the percentage of labeled cells in a cell fraction gated to contain lymphocytes and monocytes. The distribution of lymphocyte
subsets was compared to the circadian variations in β2-adrenoceptor sites on peripheral MNL and in total lymphocyte count in another group of seven healthy men (Pangerl et al 1986).

The subjects were asked to follow a regular life-style for the two weeks preceding the study with bed rest between 23h00 and 07h00. On the day of the study the subjects stayed in the clinical pharmacological research unit of the institute. They continued to follow their normal daily routine. Subjects were asked to record meal times, the consumption of alcohol and caffeine. All were non-smokers.

Circadian variations were statistically validated by the cosinor method (Halberg et al 1967) and by analysis of variance (anova). Significance limit was \( p < 0.05 \).

RESULTS

The fractional distribution of T- and B-cells showed a large inter-individual variation and varied within 24 hours, but the circadian variation did not reach statistical significance (Fig. 1). The highest percentage of T-cells was observed at 18h00 (73.0±0.45 % of gated cells, \( \bar{x} \pm SE \)), the lowest percentage at 02h00 (56.4±9.7 % of gated cells, \( \bar{x} \pm SE \)). The highest percentage of B-cells occurred at 10h00 (11.2±6.9 % of gated cells, \( \bar{x} \pm SE \)), the lowest percentage was seen at 18h00 (6.3±3.0 % of gated cells, \( \bar{x} \pm SE \)). T helper- and T suppressor-cells also demonstrated a statistically insignificant variation with highest percentage of T helper at 06h00 (51.5±1.2 % of gated cells) and of T suppressor at 06h00 (22.0±1.0 % of gated cells). The lowest fraction was seen at 06h00 (34.6±4.2 % of gated cells) and at 22h00 (12.0±3.0 % of gated cells) for T helper and T suppressor, respectively (all \( \bar{x} \pm SE \)).

![Fig. 1. Fractional distribution of human lymphocyte subsets determined over 24 hours](image)

The total lymphocyte count demonstrated a circadian variation (\( p < 0.01 \) anova, \( p=0.07 / PR=61.3\% \) in population-mean cosinor analysis, Fig. 2 lower panel) with highest numbers at 02h00 (3367±236 cells) and lowest numbers at 10h00 (2175±262 cells, all \( \bar{x} \pm SE \)). Highest β2-adrenoceptor density occurred at the time of lowest lymphocyte count (10h00), the number of receptor sites decreased to a minimum at 02h00, when the total number of lymphocytes is highest. The circadian range was 74.5-124.9 % of 24h-mean for the expression of β2-adrenoceptor sites on peripheral MNL.
Circadian variation of $\beta_2$-adrenoceptor sites

Since the $\beta_2$-adrenoceptor density on MNL is expressed as sites/cell the circadian variation in the expression of these receptors is corrected for the circadian variation in total lymphocyte count. Landmann et al 1984, however, reported a different $\beta_2$-adrenoceptor density on T-cells (1400 sites/cell, irrespective of T\text{helper or T\text{suppressor}}) and on B-cells (3700 sites/cell). A circadian variation in the fractional distribution of lymphocyte subsets might account, therefore, for the circadian variation in the expression of $\beta_2$-adrenoceptor sites on peripheral MNL:

The total number of lymphocytes reaches a minimum at the time of highest $\beta_2$-adrenoceptor density (10h00). At that time the percentage of B-cells among peripheral MNL is highest (11.2%); approximately 243 cells of 2175 total lymphocytes may be B-cells bearing according to Landmann et al 1984 a total number of $8.99 \times 10^6$ sites; 60.5 % of the total lymphocytes are T-cells (1316 cells) that add another $1.84 \times 10^6$ $\beta_2$-adrenoceptor sites resulting in an average value for all lymphocytes at that time of day of 1259 sites/cell. At the trough of the circadian variation in the expression of $\beta_2$-adrenoceptor sites (02h00) the total number of lymphocytes is highest. At that time 8.1 % (273 cells) of the lymphocytes (3367 cells) are B-cells participating $1.00 \times 10^6$ $\beta_2$-adrenoceptor sites. The fraction of T-cells is minimal at that time: 56.4 % (1899 cells) of the lymphocytes bear $2.66 \times 10^6$ $\beta_2$-adrenoceptors. This results in an average value for all lymphocytes of 1087 sites/cell at 02h00.

According to this very rough calculation the circadian range of the variation in the expression of $\beta_2$-adrenoceptor sites on peripheral MNL would be 92.7-107.3 % of the 24h-mean, which is much less than the one actually observed (74.5-124.9 % of the 24h-mean). Quite a number of uncertainties are assumed in this calculation: It has not yet been established, how the extensive handling with antibody labelling and FACS-analysis affects the expression of $\beta_1$-adrenoceptor sites on MNL. In this context the data reported by Landmann et al 1984 have to be regarded as preliminary. Also our data on the fractional distribution of lymphocyte subsets are rather preliminary due to the small number of subjects; some cell types such as monocytes were not included yet into the analysis but may express $\beta_2$-adrenoceptors as well. Nevertheless the calculation yielded reasonable
adrenoceptor densities, but it appears that the fractional distribution of lymphocyte subsets does not show a relevant circadian variation at all. This study does not preclude, however, that the lymphocyte subset composition may change in response to short acting stimuli such as physical exercise. According to this study different lymphocyte subset distributions may contribute (if at all) only little to the circadian variation in the expression of $\beta_2$-adrenoceptor sites on peripheral MNL. As outlined elsewhere (Haen 1987) the circadian variation in the expression of $\beta_2$-adrenoceptor sites on peripheral MNL rather constitutes a circadian receptor down- and up-regulation in response to hormonal stimuli, such as adrenaline and cortisol concentrations in blood, respectively.

REFERENCES


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