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## BIOLOGICAL RHYTHMS AND MEDICATIONS

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# CIRCADIAN VARIATION IN THE EXPRESSION OF $\beta_2$ -ADRENOCEPTOR SITES IN MALE ASTHMATIC PATIENTS

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## KEY WORDS

circadian variation,  $\beta_2$ -adrenoceptors, peripheral mononuclear leucocytes (MNL), nocturnal asthma

## INTRODUCTION

We recently described a circadian variation in the expression of  $\beta_2$ -adrenoceptor sites on peripheral mononuclear leucocytes (MNL) from healthy subjects (Pangerl et al 1986, Haen 1987). At night  $\beta_2$ -adrenoceptor density was found to be minimal. This coincides with the time of lowest respiratory function in both healthy and asthmatic persons (Reinberg et al 1963, Barnes et al 1980). In asthmatics respiratory function decreases so much at night that patients are most endangered by attacks at that time of day ("nocturnal asthma", "nocturnal dip", Hetzel & Clark 1980). In 1968 Szentivanyi suggested that the atopic abnormalities in asthmatic disease are related to a malfunction of  $\beta_2$ -adrenoceptors, i.e. either a decreased adrenoceptor density or an impaired sensitivity of these hormone receptors to  $\beta$ -adrenergic stimuli (Szentivanyi 1968). We therefore studied the circadian variation of  $\beta_2$ -adrenoceptor density and function in asthmatic patients with predominantly nocturnal complaints.

## MATERIALS AND METHODS

At 14h00, 18h00, 22h00, 02h00, 06h00, 10h00, and again at 14h00 venous blood was drawn from 4 male asthmatic patients, 19-27 years of age. Two of them demonstrated normal or low normal respiratory function during daytime (24h-mean of peak expiratory flow  $\pm$  SE: 597 $\pm$ 32.6 l/min and 497 $\pm$ 29.4 l/min) with a marked nocturnal dip (30.1 and 26.0 % of 24h-mean, respectively) between 02h00 and 06h00. The other two patients showed a similar nocturnal dip (29.8 and 26.7 % of 24h-mean) from an overall decreased respiratory function (24h-mean of peak expiratory flow  $\pm$  SE: 335 $\pm$ 21.0 l/min and 434 $\pm$ 45.8 l/min, Fig. 1). All four men were without any bronchodilator therapy before the study. 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 hospital. They continued to follow their normal daily routine. Subjects were asked to record meal times, the consumption of alcohol and coffee. All were non-smokers.

The blood specimen were immediately assayed for the number of high affinity  $\beta$ -adrenergic

binding sites (B-max) on intact lymphocytes, using a receptor binding assay (Anhäupl et al 1988) with  $^{125}I$ -cyanopindolol, a  $\beta$ -antagonist.  $\beta_2$ -adrenoceptor coupled adenylate cyclase was stimulated by incubating the intact cells with  $10^{-7}$  mol/l isoprenaline for 5 minutes at  $37^\circ C$ ; the increase of intracellular cAMP above basal values was determined by radio-immunoassay after cell disruption.

Directly after venopuncture respiratory function was assessed using a computer based, room-restricted spirometer. Among other variables the best of three peak expiratory flow (PEF) readings was recorded.

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

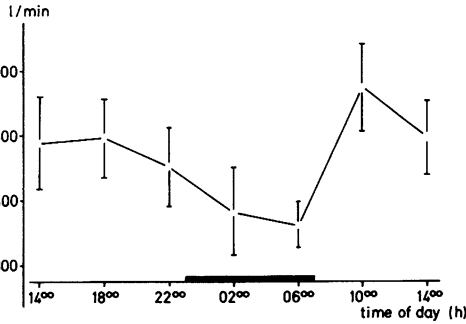


Fig. 1. Peak expiratory flow of untreated male asthmatics ( $\bar{x} \pm SE$ ).

### RESULTS

When expressed as % of the 24h-mean the circadian variation in the expression of  $\beta_2$ -adrenoceptor sites on peripheral MNL from male asthmatic patients was significant with a  $p < 0.05$  (anova). The maximum was seen at 10h00 ( $1575 \pm 462$  sites/cell,  $\bar{x} \pm SE$ ), the minimum at 02h00 ( $600 \pm 101$  sites/cell, Fig. 2). The circadian range was 59.1-155.2 % of the 24h-mean. Cosinor analyses approximated a circadian mesor of  $976 \pm 51$  sites/cell, a circadian amplitude of  $475 \pm 197$  sites/cell (equivalent to 48.7% of mesor), and a circadian acrophase of  $-198 \pm 34^\circ$  equivalent to 13h14+2h17 (all  $\bar{x} \pm SE$ ). The individual single cosinor analyses did not reach statistical significance.

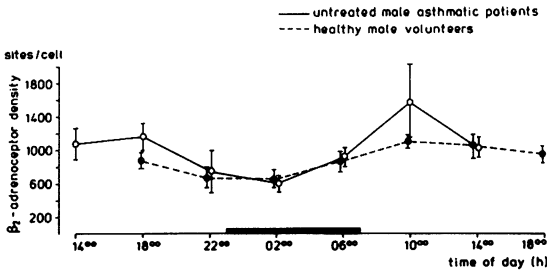


Fig. 2.  $\beta_2$ -Adrenoceptor density on peripheral mononuclear leucocytes of healthy men and of untreated male asthmatic patients.

Basal cAMP content of the cells closely paralleled the circadian variation in the expression of  $\beta_2$ -adrenoceptor sites. Maximal values were seen between 06h00 and 10h00 ( $6.0 \pm 1.12$  pmol/ $10^6$  cells,  $\bar{x} \pm \text{SE}$ ), minimal values at 22h00 ( $3.5 \pm 0.95$  pmol/ $10^6$  cells,  $\bar{x} \pm \text{SE}$ ) with a circadian range of 74.6-126.7 % of 24h-mean ( $4.8 \pm 0.36$  pmol/ $10^6$  cells, Fig. 3).

$\beta_2$ -adrenoceptor coupled adenylate cyclase could be stimulated by  $10^{-7}$  mol/l isoprenaline to  $6.8 \pm 0.52$  pmol/ $10^6$  cells resulting in a  $44 \pm 11$  % increase over basal cAMP values (24h-mean  $\pm$  SE, Fig. 3).

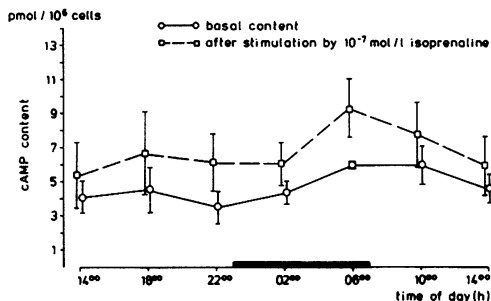


Fig. 3. Cyclic AMP content of peripheral mononuclear leucocytes from untreated male asthmatic patients before and after in vitro stimulation by  $10^{-7}$  mol/l isoprenaline.

## DISCUSSION

Studies trying to detect  $\beta$ -adrenoceptor malfunction in asthmatic patients are contradictory in their results (Conolly et al 1976, Scarpace et al 1982, Titinchi et al 1984). In general a difference in the expression of  $\beta_2$ -adrenoceptor sites and in their response to isoprenaline could not be clearly observed between healthy and asthmatic people. These studies, however, were not chronobiologically designed and were hampered with pretreatment of the subjects or with inter-individual differences in the pathophysiology of the disease.

The four patients in this study were clearly untreated. The severity of impairment of their respiratory function, however, differed a lot among the individuals (Fig. 1). A circadian variation in the expression of  $\beta_2$ -adrenoceptor sites could be observed in these patients that correlated well with the circadian variation in peak expiratory flow. Nevertheless, differences to our healthy control group (Pangerl et al 1986) are, if at all present, very shallow. Most of all the marked nocturnal dip in respiratory function is not paralleled by an equally enlarged decrease in  $\beta_2$ -adrenoceptor density compared to the healthy controls (Fig. 2). There is just a tendency towards an increased circadian amplitude in the expression of  $\beta_2$ -adrenoceptor sites among the asthmatics, which might still be obscured at that stage of our investigation by the small number of untreated subjects and their large inter-individual differences in respiratory function.

This study suggests that the expression and function of  $\beta_2$ -adrenoceptors is not critically linked to pathological abnormalities of peak expiratory flow measurements in nocturnal asthma. However, the results also raise the question of MNL being a useful tissue model for studies of receptor disturbances in humans. It is within reason to assume that data for receptors obtained from the study of MNL do represent the physiological situation in the body; the shielding of certain receptor populations from overall occurring influences (e.g. endocrine effects) constitutes an extraordinary and unnecessary biological expenditure. The same holds true for effects of systemically administered drugs. The results of this study, however, do not preclude isolated, pathological  $\beta_2$ -adrenoceptor disturbances in bronchial tissue of asthmatic patients.

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