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# CIRCACIAN RHYTHMS OF ADRENALIN AND NORADRENALIN EXCRETION IN MAN UNDER NORMAL CONDITIONS AND AFTER TAKING ALCOHOL

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UDC 612.452.018:577.175.522/523].014.46:547.262.]"52"

KEY WORDS: circadian rhythms; alcohol; adrenalin; noradrenalin.

The study of the effect of toxic substances on the body from the standpoint of chronobiology has led to the creation of a new discipline, namely chronotoxicology. Chronotoxicologic aspects of alcohol intoxication are only just beginning to be studied [3, 7].

The aim of this investigation was to study disturbances of biorhythms caused by alcohol in man, with special reference to circadian rhythms of adrenalin and noradrenalin, the principal parameters reflecting the state of function of the sympathicoadrenal system.

## EXPERIMENTAL METHOD

Adrenalin and noradrenalin were determined by a fluorometric method [5] in 20 healthy male volunteers aged 20-26 years, in samples of urine excreted during 4-hourly intervals at 7 and 11 p.m., 3, 7, and 11 a.m., and 3 p.m. in a 24-h period under normal conditions (control) and during 3-day cycles (72 h) after consumption of a single dose of 6.2 ml/kg body weight of 40° alcohol between 5 and 6 p.m. at the end of the control day. The maximal blood ethanol concentration was 3.9 ± 0.19 mM, which corresponds to an average degree of intoxication [6]. During the period of the investigation all subjects were kept under identical conditions of daily routine and on a standard diet. Irrelevant stress was reduced to the minimum. The investigation was conducted in March.

The results were subjected to statistical analysis by computer on a "Kosinor" program [1], with determination of mesors, amplitudes, and calculated acrophases of rhythms.

## EXPERIMENTAL RESULTS

It will be clear from Table 1 that normally the maximal excretion of adrenalin and noradrenalin is observed in the active period of the day (from 11 a.m. to 7 p.m.) and minimal during the period of sleep (from 11 p.m. to 7 a.m.), in agreement with data in the literature [2, 4]. The normal adrenalin/noradrenalin ratio (Table 2) has highest values at night (from 11 p.m. to 7 a.m.), and lowest during the first half of the day (from 7 a.m. to 3 p.m.).

Values of mesors, amplitudes, and calculated acrophases of adrenalin and noradrenalin after analysis of the data by the "Kosinor" program are given in Table 3.

Alcohol brings the sympathicoadrenal system into a state of strain, as shown by the considerable and sufficiently stable increase in catecholamine concentrations in the urine. In the first portion of urine after consumption of alcohol (7 p.m.) the adrenalin level was 10.6 times higher than normal ($P < 0.001$) and the noradrenalin level was 3.25 times higher ($P <$

Department of Biology, Tyumen' Medical Institute. (Presented by Academician of the Academy of Medical Sciences of the USSR G. N. Kryzhanovskii.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 99, No. 3, pp. 344-346, March, 1985. Original article submitted June 15, 1984.

 0007-4888/85/9903-0346$09.50 

TABLE 1. Dynamics of Adrenalin and Noradrenalin Excretion (in nanomoles/4 h intervals) under Normal Conditions and for 3 Days after Alcohol Consumption ($\bar{X} \pm S_{\bar{X}}$)

| Substance | 4-hourly interval | Normal | Days after taking alcohol | | |
|---|---|---|---|---|---|
| | | | 1 | 2 | 3 |
| Adrenalin | 15—19 | 14,9±2,45 | 159±22,9 | 47,3±5,31 | 19,5±3,1 |
| | 19—23 | 5,29±1,09 | 66,5±5,1 | 24,2±3,2 | 9,1±2,4 |
| | 23—3 | 3,61±0,37 | 43,4±6,0 | 25,1±1,54 | 5,1±1,32 |
| | 3—7 | 5,24±0,87 | 44,6±6,7 | 22,9±1,23 | 6,21±1,4 |
| | 7—11 | 5,96±0,62 | 40,5±4,7 | 28,1±2,18 | 7,54±1,63 |
| | 11—15 | 11,1±1,49 | 43,5±6,6 | 42,9±3,82 | 14,6±1,8 |
| Noradrenalin | 15—19 | 34,3±3,25 | 111,6±9,9 | 47,9±5,14 | 38,5±2,41 |
| | 19—23 | 13,8±1,12 | 77,4±8,51 | 45,5±5,91 | 20,1±2,26 |
| | 23—3 | 6,91±0,85 | 70,3±10,6 | 18,7±1,71 | 9,54±1,1 |
| | 3—7 | 10,1±1,18 | 57,2±9,1 | 18,0±1,59 | 10,8±1,24 |
| | 7—11 | 20,5±1,36 | 48,3±7,86 | 30,3±4,31 | 18,9±1,43 |
| | 11—15 | 32,6±1,89 | 48,2±3,48 | 41,0±2,18 | 30,6±1,92 |

TABLE 2. Dynamics of Adrenalin/Noradrenalin Ratio under Normal Conditions and during 3 Days after Taking Alcohol ($\bar{X} \pm S_{\bar{X}}$)

| 4-hourly interval | Normal | Days of taking alcohol | | |
|---|---|---|---|---|
| | | 1 | 2 | 3 |
| 15—19 | 0,43±0,12 | 1,42±0,31 | 0,98±0,19 | 0,50±0,08 |
| 19—23 | 0,38±0,08 | 0,86±0,17 | 0,53±0,09 | 0,45±0,09 |
| 23—3 | 0,52±0,07 | 0,61±0,10 | 1,34±0,27 | 0,53±0,09 |
| 3—7 | 0,51±0,11 | 0,77±0,14 | 1,27±0,22 | 0,57±0,12 |
| 7—11 | 0,29±0,04 | 0,83±0,15 | 0,92±0,18 | 0,39±0,05 |
| 11—15 | 0,34±0,07 | 0,90±0,16 | 1,04±0,20 | 0,47±0,06 |

TABLE 3. Parameters of Circadian Rhythms of Adrenalin and Noradrenalin Excretion in Man under Normal Conditions and during Three 24-Hourly Cycles after Alcohol Consumption

| Substance | Parameter | Normal | Period of taking alcohol, days | | |
|---|---|---|---|---|---|
| | | | 1 | 2 | 3 |
| Adrenalin | Mesor ($\bar{X} \pm S_{\bar{X}}$) | 7,68±0,65 | 66,2±6,9 | 31,7±1,7 | 10,3±0,87 |
| | Amplitude | 5,29(3,43—8,18) | 43,2(36,0—47,4) | 12,3(10,6—15,9) | 6,27(4,74—9,0) |
| | Acrophase | 16.36(13.48—18.46) | 19.39(18.55—20.28) | 16.54(15.28—18.16) | 16.57(13.23—18.00) |
| Noradrenalin | Mesor ($\bar{X} \pm S_{\bar{X}}$) | 19,7±1,47 | 68,8±4,31 | 33,5±2,12 | 21,4±1,68 |
| | Amplitude | 14,2(11,8—17,7) | 23,6(18,3—29,5) | 15,3(11,0—19,9) | 14,7(11,8—18,6) |
| | Acrophase | 16.19(15.09—17.46) | 21.33(20.00—22.47) | 18.43(17.16—20.48) | 16.39(15.15—18.04) |

Legend. Mesors and amplitudes given in nanomoles, acrophase, number before period in hours, number after period in minutes. [Decimals are here represented by commas — Publisher.] 95% confidence intervals shown in parentheses.

0.001). Catecholamine excretion remained high for 2 days (Table 1). As a result of a powerful release of hormones immediately after alcohol consumption the acrophases of adrenalin and noradrenalin were shifted by the time elapsing after alcohol consumption (Table 3). Amplitudes and mesors of the rhythms were significantly increased during the first day after alcohol consumption (Table 3). The adrenalin/noradrenalin ratio was 3.3 times higher in the portion of urine obtained at 7 p.m. ($P < 0.001$) and remained significantly raised for 48 h (Table 2). This indicates a more powerful response of the adrenal component of the sympathicoadrenal system to alcohol intake compared with its nervous (mediator) component, for the adrenalin in the urine is mainly adrenal in origin, whereas the noradrenalin is mediator in origin [2].

Alcohol, in the dose used, is oxidized in 12-15 h (method of gas chromatography). Despite complete elimination of ethanol, the chain of changes in biorhythms induced by it is not broken, and on the 2nd day after consumption the mesors of rhythms of adrenalin and noradrenalin still remained significantly raised; the amplitude of adrenalin also was signifi-

cantly higher than the control (Table 3). However, the amplitude of noradrenalin and acrophase of the rhythms returned within normal limits.

During 3 days after alcohol consumption the hourly adrenalin and noradrenalin levels returned to their initial values (Table 1), and parameters (mesors, amplitudes, acrophases) of the circadian rhythms also were indistinguishable from the control (Table 3).

In a dose inducing an average degree of intoxication, alcohol thus modifies the circadian temporal organization of normal functioning of the sympathicoadrenal system. During the 1st day after alcohol intake a shift of acrophases and an increase in mesors and amplitudes of the circadian rhythms of adrenalin and noradrenalin excretion were observed. On the 2nd day partial normalization of the rhythm parameters took place, with restoration of acrophases first of all. Restoration of the normal circadian rhythm was complete in the course of the third 24-hourly cycle after alcoholization.

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# CLONAL SUCCESSION OF HEMATOPOIETIC CELLS IN LONG-TERM BONE MARROW CULTURES


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UDC 612.419.014.2:612.119:612.6

KEY WORDS: hematopoietic stem cell; proliferation; self-maintenance; bone marrow; long-term culture; chromosomal markers.


To study self-maintenance of hematopoietic stem cells (CFU-c) from long-term bone marrow cultures it was found that no regular changes in proliferative potential of the CFU-c take place in the course of culture. Self-maintenance fluctuates within very wide limits from week to week [1]. Since the number of CFU-c in the cultures is maintained at a relatively stable level, fluctuations of self-maintenance cannot be explained by selection of CFU-c with high or low proliferative potential during culture. It has accordingly been suggested that clonal expansion of hematopoietic cells takes place in cultures with succession of functioning clones. This hypothesis was tested in the investigation described below.

## EXPERIMENTAL METHOD

CBA and CBAT6T6 mice of both sexes aged 8-12 weeks were used. The animals were irradiated with $^{137}Cs$ $\gamma$-rays on an IPK apparatus in a dose of 12 Gy, as described previously [1]. Self-maintenance of a CFU-c was characterized by the number of daughter CFU-c produced by it in irradiated mice during the formation of an 11-day splenic colony. Long-term bone marrow


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(Presented by Academician of the Academy of Medical Sciences of the USSR O. K. Gavrilov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 99, No. 3, pp. 346-348, March, 1985. Original article submitted April 13, 1984.




0007-4888/85/9903-0348$09.50