Circadian Variations in the Effect of Propranolol on Parameters of Heart Rate Variability in Rats

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β-Adrenoblockers, widely used in cardiology, belong to a group of pharmacological agents whose action is strictly dependent on the time factor. On the one hand, biorhythms of various duration have a substantial impact on the manifestation of the cardiotropic properties of the drugs, while on the other hand, these themselves alter the temporal organization of cardiac activity [1,5,9].

Mathematical analysis of the heart rhythm in the form of variational pulsometry or cardiointervalography, making it possible to assess the state of the adaptational processes in the cardiovascular system and in the organism as a whole, has lately gained ground [2]. This method was used in the present study for assessing the diurnal variations in the efficiency of the β-blocker propranolol.

MATERIALS AND METHODS

The experiments were performed on 48 nonpedigree albino female rats weighing 150-200 g in November. All rats were kept under standard conditions and natural lighting. The experiments in the night hours were performed in a dark room under red illumination. For estimation of the cardiointervalogram (CIG), the heart rate data for 100 consecutive R-R intervals were subjected to mathematical analysis [3]. The variational span (ΔX), mode (Mo), and its amplitude (AMo) were determined. Spectral analysis of CIG included estimation of the strength of the respiratory waves (less than 10 sec), and of the slow waves of the first (10-30 sec) and second order (more than 30 sec), and determination of the centralization index (CI, the ratio between the strength of the slow waves of the first and second order and the strength of the respiratory waves). In addition, we calculated the tension index (TI, ratio between AMo and 2Mo ΔX) and the index of autonomic equilibrium (AEI, ratio between AMo and ΔX).

The animals were divided into four groups, 12 animals in each. Cardiointervalograms were recorded at certain time points: 00:00-02:00 h and 12:00-14:00 h, corresponding to the periods of maximal activity and rest, respectively, and at 06:00-08:00 h and 18:00-20:00 h, when a change of the light phases occurs. In turn, each group was subdivided into two subgroups of 6 animals (experimental and control). The experimental rats received propranolol in a dose of 5 mg/kg and 1 mg/kg under acute or chronic intraperitoneal administration, respectively. The control animals received physiological saline according to an analogous scheme.

The results were processed by the methods of variational statistics using the Student and Wilcoxon-Mann-Whitney tests.

RESULTS

The CIG readings demonstrated clear-cut variations during the 24-hour cycle. In the night hours (pe-

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riod of maximal activity) the sympathetic tone prevailed. The histograms of R-R intervals had the typical shape, with the distribution curve shifted leftward along the abscissa, a narrow variability span, and high AMo. The tension and autonomic equilibrium indexes reached maximal values.

On the other hand, in the daytime the influence of the parasympathetic nervous system dominated, as was evident from the broadened variability span and lower AMo. These shifts correlated with low TI and AEI values. According to the data of spectral analysis, the strength of the respiratory waves increased and CI dropped during this period. In the morning and in the evening, during the light/darkness transitions, we recorded intermediate (optimal) values of all indexes, as is typical for normotony (Fig.1).

Judging from the CIG readings, acute administration of propranolol at different periods of the 24-hour cycle had different impacts on the state of the cardiovascular system. Common features were the shift of the histograms rightward along the abscissa and elevation of the Mo value. However, only during the night hours were these changes accompanied by a broadening of the variational span and reduction of AMo that unambiguously testified to attenuation of sympatheticotony and destabilization of the heart rate. The data of spectral analysis also pointed to a statistically reliable reduction of CI and increasing strength of the respiratory waves (Fig.1).

In other periods of the cycle we observed discoordination of CIG parameters, when a rise of Mo (a sign of intensified vagal control over cardiac activity) was accompanied by a narrowing of the variational span and an increase of AMo (a sign of sympatheticotony). Such shifts, together with a tendency of TI to increase, are regarded as indications of disregulatory processes and amplification of the central circuit control over the heart rate [3].

Under chronic administration, propranolol had a more pronounced effect during the night hours. The mode indexes approached the values characteristic of normotony. The TI and AEI values decreased with a high degree of reliability. On the other hand, during the rest of the time completely the opposite phenomena were observed. We recorded all the signs of intensified sympathetic activity: a decrease in Mo and ΔX and an increase in AMo. Maximal centralization of control over the heart rate was established during the morning hours, when CI, AEI, and TI reached their maximal values (Fig. 2). In other words, the peak of sympathetic activity shifted from the night to the morning hours.

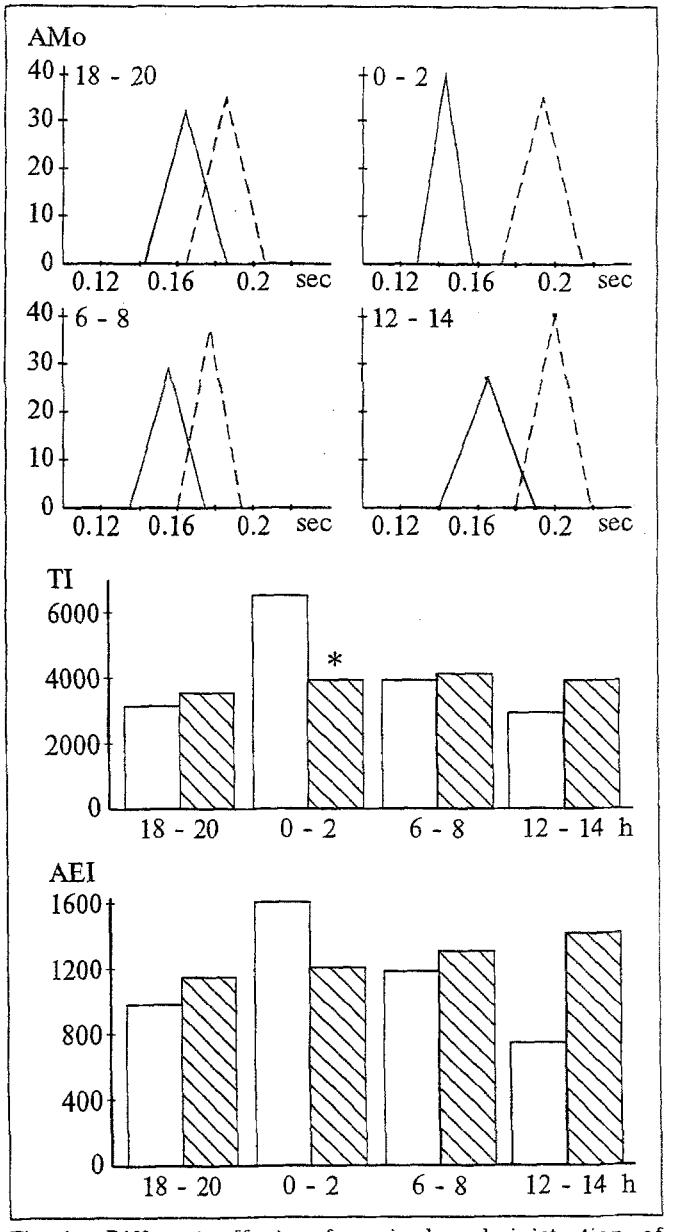

Fig. 1. Different effects of a single administration of propranolol on cardiointervalogram parameters during different periods of the 24-hour cycle in rats. Curves characterize the histographic profile of the cardiointervalograms. Continuous line refers to the results for the control group (after administration of physiological solution), dotted line refers to the experimental group after administration of propranolol. Abscissa: variational span (sec); ordinate: absolute value of AMo. Bars show tension index (TI) and autonomic equilibrium index (AEI) values in the control (light bars) and experimental (shaded bars) animals. Time of day (h) is indicated at bottom. * – statistically significant differences with respect to control ($p<0.05$).

Thus, for chronic administration of propranolol specific shifts indicating attenuation of sympatheticotony could be recorded only during the night hours. Single injections induced the gradual development of parasympathization and its further stabilization. At the same time, the disregulatory

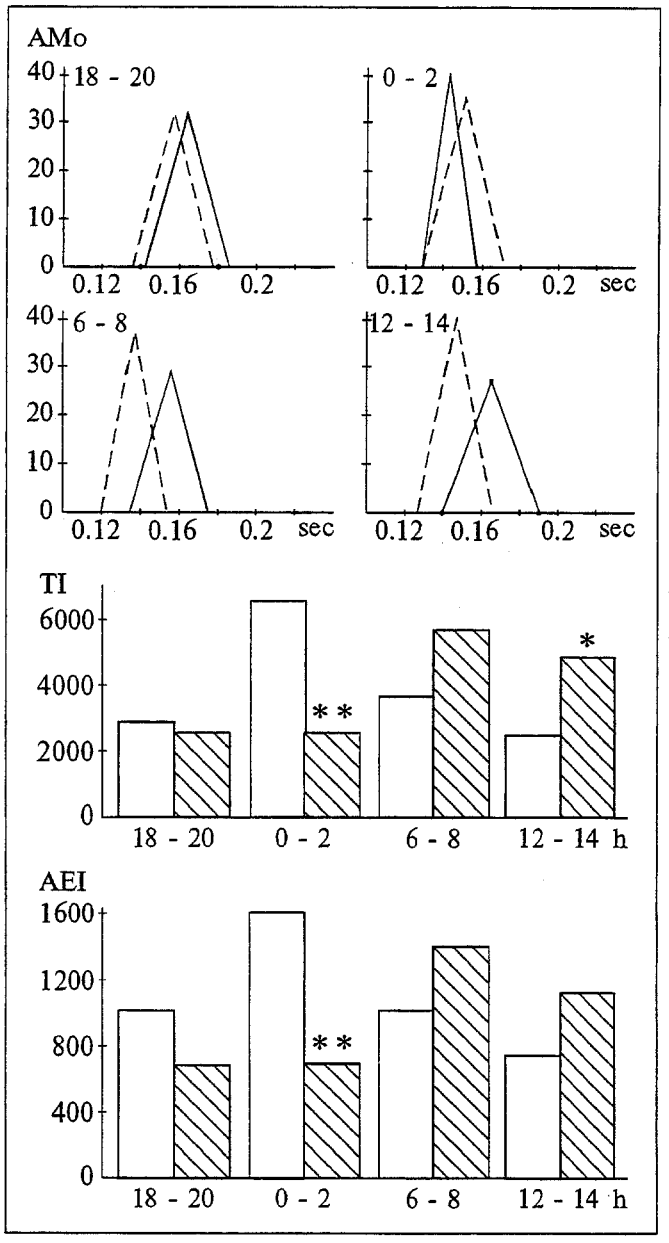

Fig. 2. Circadian fluctuations in the activity of propranolol according to data of cardiointervalography under chronic administration of the drug. All designations are the same as in Fig. 1.

phenomena observed for acute administration of the β-adrenoblocker were intensified during other periods of the 24-hour cycle and led to a stable increase in the sympathetic tone.

The revealed circadian variations in the autonomic status and the more pronounced effect of propranolol during the night hours (or during the day time for humans) support the data obtained from calculations of the number of cardiac contractions and measurements of arterial blood pressure [4,8,9]. However, cardiointervalography made it possible to reveal changes that could not be detected by traditional methods. We showed that a single injection of propranolol switches on the disregulatory processes during periods when the initial sympathetic tone is close to normal (during the morning and evening hours) or decreased (during the day time). This disregulation became aggravated after repeated treatment with the β-adrenoblocker and led to a stable increase in the sympathetic tone. Taken together, the findings demonstrate a broad spectrum of possibilities of cardiointervalography for predicting how the organism's response to the drug will evolve.

The different effects of propranolol during different periods of the diurnal cycle can hardly be explained by circadian variations in the drug pharmacokinetics, since the half-clearance period of β-adrenoblockers is shorter during the night hours, while their efficiency is higher. We believe that a more important factor here is fluctuation in the activity of β-adrenoblockers, the maximum activity being recorded during the night hours [7,10].

Special attention should be paid to the shift of the peak of sympathetic activity from night to morning hours and, to a lesser degree, to daytime hours after repeated treatment with propranolol. One of the reasons underlying this phenomenon may be interference of the drug in the functioning of the leading pacemakers of the circadian rhythms - the suprachiasmatic nuclei of the hypothalamus - which upsets the circadian organization of the physiological functions. The main factor is likely to be the blocking of the β-adrenoreceptors present in these and the adjacent hypothalamic formations of the brain [11]. Such an assumption seems to have a solid basis since, according to our preliminary data, the regular administration of propranolol facilitates reorganization of the round-the-clock mobility curve in rats with the shift of its acrophase to the morning hours.

At the same time, it is possible that reorganization of the autonomic status may occur without disturbing the functioning of the pacemaker structures in the brain. Sympathization during the morning and daytime hours may be a compensatory phenomenon, in which the balance between the components of the autonomic nervous system, compromised by the drug, is reestablished. In other words, this may be the organism's reaction to the propranolol-induced parasympathization during the night hours. Besides, as is known, repeated administration of propranolol leads to an increase in the density of β-adrenoreceptors [6]. According to CIG data, this shift is more easily revealed during that period of the diurnal cycle when the effect of the drug is more weakly expressed.

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Quantitative Pharmaco-Electroencephalographic Analysis of Bromantane

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Special attention in the field of pharmacology has been paid lately to derivatives of aminoadamantane, which is known to influence the monoaminergic processes in the brain [1,4,12,16,17]. Bromantane, a derivative of 2-aminoadamantane, exhibits immunostimulating activity and a pronounced stimulating effect on the central nervous system (CNS) [13,14]. Being a psychostimulator, bromantane significantly inhibits the development of fatigue in animals under conditions of prolonged operant activity and exerts a pronounced adaptogenic effect combined with an immunostimulating and detoxicating action. It is noteworthy that after just a single administration, bromantane manifests its protective effect under conditions of hypoxia, hypo- and hyperthermia, exhausting physical exercise, intoxication, etc. [7,13,14].

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The objective of the present study was to investigate the effect of bromantane on biopotentials of different structures of the brain of intact rats during free behavior, using quantitative spectral analysis of electroencephalograms (EEG) according to Fourier and to make a comparative evaluation of the effect of the drug on the CNS. This method was applied by us in earlier investigations on the effect of different psychotropic drugs such as neuroleptics, nootropics, antidepressants, tranquilizers, and psychic energizers on animals [2,5-7,9-11].

MATERIALS AND METHODS

The experiments were performed on 18 nonpedigree albino male rats weighing 180-250 g. Chronic implantation of Nichrome electrodes into the sensorimotor cortex of both hemispheres, dorsal hippocampus and lateral hypothalamus of the rat brain, the recording of biopotentials, processing of the experimental data, and quantitative spectral

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