PHYSIOLOGY

Effect of Atropine, Propranolol, and Atenolol on Wave Structure of Heart Rate Oscillations in Rats

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Were studied the effects of atropine and β-adrenoblockers on the power of very low (<0.25 Hz), low (0.25-0.70 Hz), and high frequency (0.7-1.8 Hz) waves of the heart rhythm in wakeful rats. Atropine reduced the power of all waves in 100% cases. Propranolol on average decreased the power of very low frequency waves and increased the power of low and high frequency waves, although opposite effects were observed in many cases. Atenolol produced similar effects. Some animals demonstrated spontaneous moderation of respiratory rate to a level corresponding to low-frequency oscillations of the heart rhythm accompanied by elevation of the relative power of low frequency waves. Inconsistency of the effects of β-adrenoblockers in rats can be related to variability of sympathetic tone and spontaneous deceleration of respiration with the corresponding changes of low frequency waves. Augmentation of the high frequency waves during application of β-adrenoblockers is not related to their action on CNS.

Key Words: *heart; autonomic nervous system; heart rhythm variability*

Pharmacological analysis is the most widespread method of evaluation of the mechanisms underlying the formation of the wave structure of the heart rhythm. However, the results of these studies are controversial, especially of those dealing with the effects of β-adrenoblockers (β-AB). While some researchers reported no changes in low-frequency (LF) waves after injection of β-AB [1,7], other authors consider the decrease in the spectrum power of these waves as the basic effect of β-AB [9,10].

MATERIALS AND METHODS

The experiments were carried out on mature random-bred laboratory male and female rats. A rubber cuff with steel electrodes for ECG recording was placed on the thorax. The electrode wires were collected in a common cable on the back. The rat was placed in a screened chamber (70×50 cm) where it could move freely. ECG was recorded under original software with a P4Ch-02 polygraph and fed to PC via a 12-bit ADC at a sampling rate of 1 kHz. To select the length of records, we compared the data obtained from 30-sec and 2-min records. No significant differences in the wave power ratio in these variants were found. Then we used 2-min records. The respiration rate was measured from spectrum analysis of *QRS* amplitude values (variation of *R*-peak amplitude): these variations corresponded to respiratory excursions [3]. In pharmacological analysis we used muscarinic receptor blocker atropine (0.5-2.0 mg/kg) and β-AB propranolol (obsidian, 0.5-1.0 mg/kg) and atenolol (1 mg/kg). In some experiments, atropine and propranolol were

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applied simultaneously (all drugs were injected intramuscularly). The experiments were started with recording of initial data, which were collected during quiet behavior periods at least 3 times with 10-min intervals. After injection of the test drug, ECG was recorded at least 5 times at the same 10-min interval.

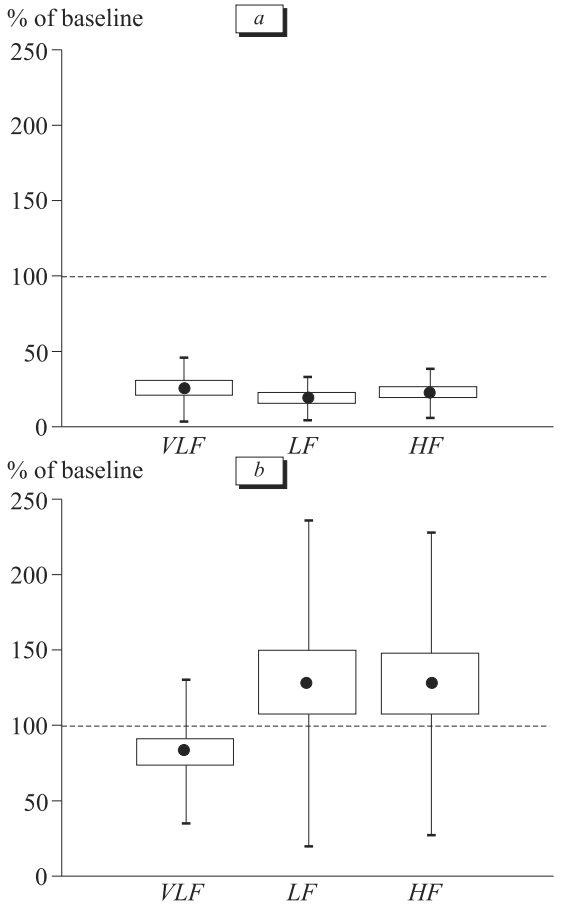
The data were processed using Statistica software. The spectrum analysis was performed with fast Fourier transform smoothed using 5-point Hemming window with preliminary subtraction of the mean level and elimination of the trend. The power spectrum was analyzed in the very low frequency (VLF), LF, and high frequency (HF) bands. According to published data [5,6,10,11] and our findings, the corresponding frequency ranges (bands) were <0.25 Hz, 0.25-0.70 Hz, and 0.7-1.8 Hz. In each experiment, the mean values of spectrum power were calculated for VLF, LF, and HF for all control and experimental ECG records. The effects of the drugs were assessed by changes in these powers induced by the test drugs. The data were analyzed statistically using Student's *t* test and Student's *t* test for paired samples.

RESULTS

In all experiments (n=14), atropine markedly decreased the spectrum power of all waves of the oscillating heart rate. The powers of VLF, LF, and HF waves decreased by on average 83, 77, and 78%, respectively (Table 1). Propranolol (23 experiments on 16 rats, 7 rats were injected twice with an interval of several days) decreased VLF spec-

TABLE 1. Percent of Experiments with Established Effect of Drugs on Power Spectrum in VLF, LF, and HF Bands

Drug and effect		VLF	LF	HF
Atropine	decrement	100	100	100
	increment	—	—	—
	insignificant	—	—	—
Propranolol	decrement	47.8	47.8	34.8
	increment	26.1	39.1	39.1
	insignificant	26.1	13.0	26.1
Atenolol	decrement	66.7	33.3	44.4
	increment	33.3	33.3	55.6
	insignificant	—	33.3	—



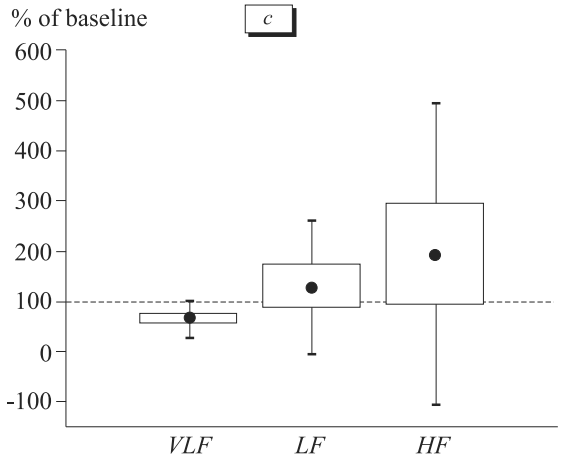


Fig. 1. Effect of atropine (*a*), propranolol (*b*), and atenolol (*c*) on spectrum power of VLF, LF, and HF waves.

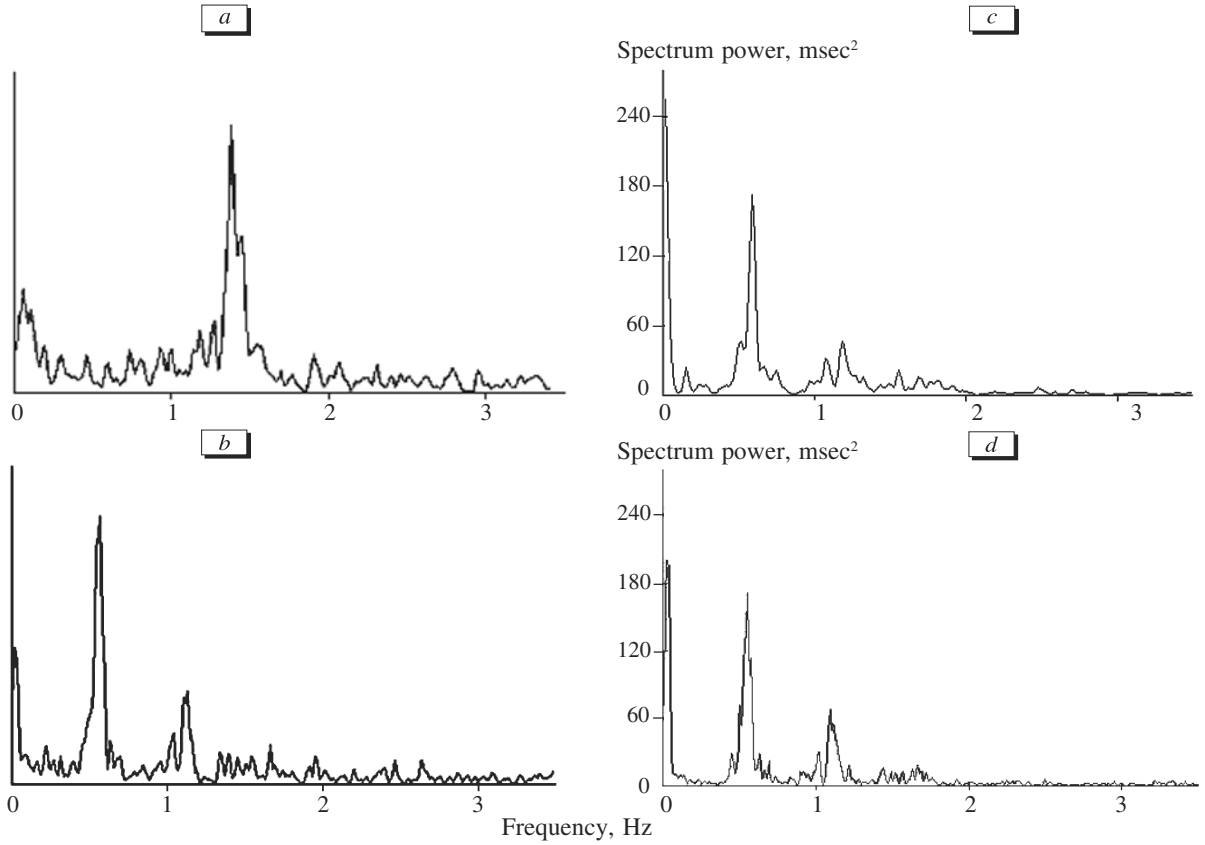


Fig. 2. Spontaneous deceleration of respiration in rats. *a*, *b*: spectrum power density of *QRS* amplitude variations; *c*, *d*: *RR*-spectrograms. The data were obtained in the same experiment at 10-min interval.

trum power by 19% and increased LF and HF powers by on average 28 and 27%, respectively. These values show only average trend for LF and HF in all experiments, while some rats responded oppositely (Fig. 1): LF increased in 9 of 23 cases (39%) and decreased in 11 cases (48%); HF increased in 9 of 23 cases (39%) and decreased in 8 cases (35%). Even in the cases, when propranolol was injected twice to the same rat, its effect could be opposite: 2 of 7 animals demonstrated opposite changes in LF power and one rat responded with opposite changes in HF power. The mean trend of propranolol-induced increase in LF and HF powers reflects the fact, that their increments were greater than their decrements. In general, the effect of atenolol (9 tests) was similar to that of propranolol. However, in atenolol-treated rats we observed more dramatic changes of HF than the corresponding changes induced by propranolol: HF could either increase 9-fold or decrease by 70% (Fig. 1, *c*).

Visual evaluation of the respiration rate (23 tests in 10 rats) in 12 tests (n=8) revealed variable respiration with periodic acceleration and deceleration. In two rats this respiration pattern predominated. To study in details the incidence of nonuniform respiration and the possibility of its effect on the wave structure of the heart rhythm, which is an objective albeit indirect method to assess respiration, we analyzed the spectrum power density of *QRS* amplitude variations [3]. To this end, we selected 158 records from 19 rats with pronounced periodic oscillations of the *R*-peak amplitude. In 70 records, the spectral analysis of these oscillations revealed a power peak corresponding to LF heart rate variations (Fig. 2): this peak reflected periods of slow respiration. In these cases, *RR*-spectrograms demonstrated a tendency towards relative increase in LF power, which was also corroborated by the shift in LF/(LF+HF) histogram to higher values in cases with episodes of decelerated respiration (Fig. 3). Our experiments revealed no pronounced rise in the incidence of slow respiration under the action of β-AB: in these cases, slow component of respiration was observed in 47% of 47 records, while the control incidence was 36% of 69 records. It should be emphasized that stochastic variations of the respiration rate can affect LF-power of the heart rate variations in an unpredictable way. We cannot

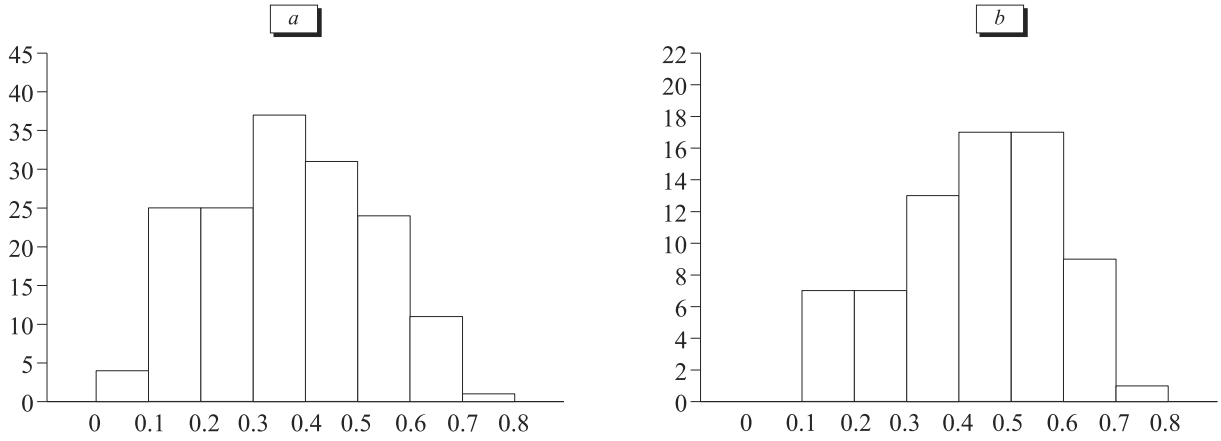


Fig. 3. Histograms of LF/(LF+HF) distribution. *a*) all records; *b*) records with episodes of decelerated respiratory rate (according to analysis of *QRS* amplitude variations).

to exclude the effect of slow respiration on LF-power during the experiment or off-line statistical processing of the data. First, "true" and "respiratory" LF-peaks overlap in the power spectrum plot. In this case, it is unknown to what degree changes in LF-power are caused by respiration (Fig. 2). Second, deceleration of respiration was observed in more than 50% records. Therefore, the non-uniform respiration is one of the normal patterns of breathing and exclusion of the corresponding records can distort the results.

Thus, blockade of muscarinic receptors dramatically decreased the power of all waves in the heart rhythm, which agrees with published data [1,3,10] and attests to the leading role of parasympathetic nervous system in the formation of wave structure of the heart rhythm.

Inconsistency of changes of LF-waves under the action of β-AB was reported by many researchers [2]. For example, it can be caused by unstable sympathetic tone in rats.

This and other [8] studies showed that propranolol and atenolol elevate the amplitude of HF waves in humans [2] and cats [1]. Some authors explain this phenomenon by central choline-stimulating effect of β-AB [3]. However, atenolol affects the central adrenergic receptors in rats only during its intravenous administration in a dose surpassing 30 mg/kg [4]. By this reason, in our experiment we exclude the direct central mechanism of augmentation of the respiratory waves during the action of atenolol. At the same time, the increment of HF power cannot be a reflex response to other effects of β-AB, *e.g.* to their inotropic action.

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