EXPERIMENTAL BIOLOGY

Age-Specific Vagus Regulation of the Chronotropic Function of the Heart in Desympathized and Intact Rats

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Comparison of the effects of stimulation of vagus nerves in intact and desympathized rats showed differences in the variation pulsogram parameters in different age groups. A similar time course of variation pulsogram parameters in response to vagus nerve stimulation was observed in normal and experimental rats.

Key Words: *rat; vagus nerve; desympathization; heart; stimulation*

The effect of vagus nerve (VN) stimulation on the chronotropic function of the heart has been studied for more than a century and a half, but the mechanisms regulating heart rhythm are still disputed. This is largely due to a variety of VN effects on heart rate [8,9].

There are several hypotheses on the mechanisms of vagus acceleration of heart rate, which are associated with the heterogeneity of nerve fibers in the VN. The number of sensitive afferent nerves is much higher than that of efferent nerves [11]. On the other hand, numerous sympathetic nerve conductors were revealed in VN of some animals [3], and therefore, stimulation of VN may stimulate the sensitive parasympathetic preganglionar and sympathetic postganglionar nerve fibers.

Age-related decline of heart rate is believed to be due to a decrease in the sympathetic and increase in the parasympathetic effects on the chronotropic function of the heart [1]. It was reported that surgical and drug desympathization directly affects the efficacy of VN stimulation [10]. Others believe that the sympathetic nervous system at rest does not influence the heart rate [8].

Our purpose was to investigate the parameters of variation pulsogram of the heart of intact and drug-desympathized rats of different age during stimulation of the left and right VN.

MATERIALS AND METHODS

Experiments were carried out on 290 outbred albino rats of both sexes aged 4, 6, 8, and 20 weeks. The animals were narcotized with 25% urethane intraperitoneally in a dose of 800 mg/kg.

For drug desympathization, guanethidine sulfate solution was injected daily in a dose of 25 mg/kg for 28 days. Such a method completely removes the sympathetic effects [4-7].

After preparation of both VN at the neck they were electrically stimulated by an ESL-2 stimulator, frequency 0.7-5 Hz, delay 8-16 msec, duration 0.8-1.6 msec, 5 V.

Intact animals of different ages were used as controls. An electrophysiological device with a microcomputer permitted a continuous recording of the electrocardiogram and monitoring 14 parameters of

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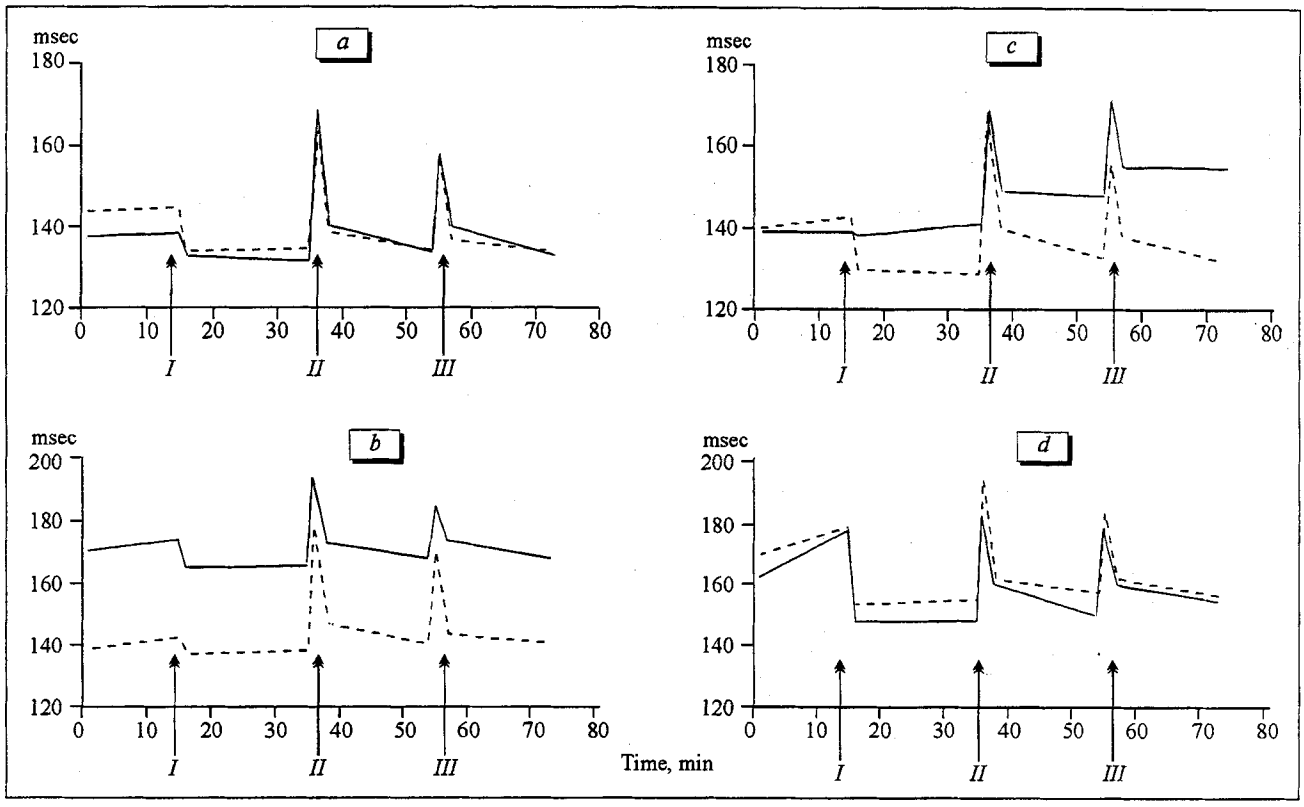

Fig. 1. The mean cardiointervals of rats aged 4 (*a*), 6 (*b*), 8 (*c*), and 20 (*d*) weeks. *I*) preparation of vagus nerves; stimulation of the right (*II*) and left (*III*) vagus nerves. Continuous line: intact; intermittent line: desympathized animals.

variation pulsogram. The data were processed by the method of R. M. Baevskii [2]. Somatic parameters reflecting the activity of different regulator mechanisms were processed using Microsoft Excel software.

RESULTS

Desympathization with guanethidine sulfate changed the mean cardiointerval (X_m) of desympathized animals in comparison with the controls. The greatest difference in the initial values of heart rate was observed in 6-week-old rats, in which the X_m in desympathized animals was 32 msec lower than in age-matched intact animals (Fig. 1, *b*). In other age groups, the initial heart rate was lower in comparison with the control, but the difference varied in degree. In 4-week-old desympathized animals the initial X_m surpassed the mean values of intact animals by 6 msec, in 20-week-old rats by 8 msec, and in 8-week-old rats there was virtually no difference in the initial X_m values of desympathized and intact animals (Fig. 1, *c*, *d*). As for other parameters of variation pulsogram, the initial values of the mode varied; this parameter reflects the activity of humoral regulation of cardiac activity [2].

Preparation of VN stems accelerated heart rate in all age groups both in intact and desympathized animals, but the degree of changes in cardiointervals was different. The highest heart rate was observed in adult intact animals. In desympathized animals of the same age an increase in heart rate was significant ($p<0.001$) but smaller (15%). In desympathized animals aged 4 and 8 weeks X_m decreased to a greater extent than in the controls. In 8-week-old desympathized animals, preparation of VN led to a significant ($p<0.01$) increase in X_m, which resulted in heart rate rise in comparison with intact animals (Fig. 1, *c*). Analysis of the time course of variation pulsogram parameters: mode amplitude, variation amplitude, and stress index during mechanical stimulation of VN stems during preparation showed an apparent increase in sympathetic effects, which was greater in intact animals.

Stimulation of the right and, 15 min later, of the left VN significantly reduced heart rate in all groups, although to a different extent. The least difference in the time course of X_m values in the experimental and control animals was observed in rats aged 4 weeks (23 and 29%, respectively, Fig. 1, *a*). In 6-week-old desympathized rats, stimulation of the right VN increased the X_m by 30% ($p<0.001$), in intact by 17% ($p<0.05$). In 8-week-old desympathized rats, stimulation of the right VN significantly (by 32%, $p<0.001$) increased the X_m *vs.* 20% in intact rats

($p<0.05$). In adult desympathized animals stimulation of the right VN increased X_m by 25% ($p<0.001$), in intact ones by 23% ($p<0.01$).

Thus, in all age groups, except 4-week-old animals, electric stimulation of the right VN markedly reduced heart rate in desympathized animals.

Subsequent stimulation of the left VN in desympathized rats of different age also resulted in changes other than in the control. In 4-week-old desympathized rats heart rate decreased by 17% ($p<0.001$), which differed little from that in age-matched intact animals (18%, $p<0.01$). In 6- and 8-week-old animals repeated stimulation of the left VN resulted in a marked reduction of heart rate in desympathized rats. The differences were the greatest in 6-week-old rats: 22% decrease in desympathized and 10% decrease in intact animals (Fig. 1, *b*). In adult desympathized rats stimulation of the left VN increased X_m by 17% ($p<0.01$). In intact animals heart rate decreased by 19%, but the significance was lower ($p<0.05$).

Study of the time course of parameters of the cardiac variation pulsograms of desympathized and intact rats of different ages during stimulation of VN revealed considerable differences, although the common trends of changes in the experimental and control groups were similar. The changes were the greatest in 6-week-old rats. This age group was the only one where the initial heart rate of intact animals was lower than in desympathized animals (Fig. 1, *b*). In other age groups the initial values of this parameter in desympathized animals were lower or approximately the same. Desympathized animals lagged behind the age-matched intact controls in their development. For example, the mean weight of a 6-week-old rats is 76% of the mean weight of an intact animal. Therefore, it is probable that sexual maturation and hormonal restructuring of the organism associated with it occur later in the rats treated with guanethidine sulfate. In other words, hormonal restructuring associated with sexual maturation starts earlier in 6-week-old intact animals than in desympathized ones.

This hypothesis is indirectly confirmed by changes in the mode parameter during stimulation of VN in this age group.

Injection of guanethidine sulfate according to our protocol did not lead to complete destruction of all sympathetic neurons [4-6]. However, a similar trend of changes in the variation pulsogram parameters during VN stimulation permits us to hypothesize that parasympathetic preganglionar fibers in the vagus play the main role in initiating heart rate deceleration observed in desympathized and intact animals.

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