PHYSIOLOGY

Regulation of Cardiac Function in Prepubertal Rats

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Prepubertal period in rats is characterized by some peculiarities of the cardiac regulatory mechanisms. In 6-week-old rats atropine produced bradycardia instead of tachycardia. Similar reaction was not observed in chemically sympathectomized age-matched rats.

Key Words: *rat; heart; nervous regulation; sexual maturation*

According to current age classification, week 6 after birth in rats corresponds to the prepubertal period [2]. At this age the rats demonstrate pronounced changes in heart rate (HR) dynamics [3]. The age-related bradycardia disappears and gives way to a pronounced acceleration of HR by the age of 7-8 weeks. This period of postnatal ontogeny is of particular interest, because the development of cardiac sympathetic innervation is accomplished at this age and it assumes the features characteristic of mature organism. The changes in cardiac regulatory mechanisms in the prepuberty can be related to rearrangement of endocrine system and the onset of sex hormone production [7]. In addition, these changes may be caused by activation of cardiotropic sympathetic regulation and the development of mature sympathetic-parasympathetic interactions of the accentuated antagonistic type [8].

Our aim was to study the role of sympathetic and parasympathetic influences in the regulation of cardiac activity in prepubertal rats.

MATERIALS AND METHODS

The study was carried out on 6-week-old random-bred rats (n=73). Chemical sympathectomy was performed in 36 neonatal rats by daily injections of guanethidine sulfate (10 ml/kg body weight) during 28 days. The rats were anesthetized with intraperitoneal urethane (800 mg/kg, 25% solution). Atropine sulfate (0.6 mg/kg) and propranolol (0.8 mg/kg) were injected into the right femoral vein.

The right and 60 min later the left vagus nerves (VN) were cut to study their tonic effects.

Vagal stimulation was performed with an ESL-2 stimulator. Stimulation parameters were chosen individually for each rat. Right and left VN were stimulated before and after injection of substances at a 15-min interval. Electrocardiogram (ECG) was visually controlled with an S1-83 oscillograph and processed with a computer [1]. The original software calculated 13 parameters of variational pulsogram from the arrays of the cardiointervals [4]. Eight parameters reflecting the major regulatory mechanisms were analyzed statistically: mean cardiointerval (X_M), mode, mode amplitude, variational range (ΔX), standard deviation, strain index, HR, and autonomic balance index (ABI).

The results were analyzed statistically using Student's t test.

RESULTS

In intact 6-week-old rats HR was 411±6 bpm, which is significantly lower than in 4- and 7-week-old rats. Most other parameters also significantly differed from the corresponding values in other age groups. The dynamics of ΔX, mode amplitude, strain index, and ABI attests to predominant activity of the parasympathetic system.

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TABLE 1. Effect of Successive Vagotomy on X_M in Intact Rats ($M \pm m$)

Experimental series, rat age	X_M, msec		
	initial	1 min postvagotomy	60 min postvagotomy
Right-sided vagotomy			
6 weeks	168.0±8.5	164.0±7.9	184.0±9.5*
20 weeks	155.00±3.97	143.0±4.8	162.0±5.7
Left-sided vagotomy			
6 weeks	202.0±9.9	197.0±9.5	213.0±7.2
20 weeks	178.0±3.8	157.0±3.7	176±4

Note. *$p<0.01$ compared to initial cardiointerval.

The experiments with vagal electrical stimulation revealed a moderation of the vagal inhibitory effect. Stimulation of the right VN increased X_M from 165±11 to 194±6 msec ($p<0.05$). It is noteworthy that in other age groups vagal stimulation produced a more pronounces deceleration of HR. Electrical stimulation of the left VN only insignificantly decreased HR, which was characteristic only of this age.

Right-sided vagotomy induced insignificant and transient tachycardia, which was most pronounced 1 min postoperation (Table 1). After 60 min HR decreased from 422±16 to 370±9 bpm ($p<0.05$). Subsequent left-sided vagotomy augmented bradycardia: 60 min after second operation HR was 347±16 bpm ($p<0.01$). Comparison of these data with that obtained in experiments with successive vagotomy on mature rats revealed no significant increase in HR after vagotomy in 6-week-old rats (Table 1). Therefore, experiments with vagal stimulation and vagotomy showed that in prepubertal rats the parasympathetic cardiotropic inhibitory effect is less pronounced than that in mature rats.

It was shown that vagal parasympathetic regulatory cardiotropic influences are species-specific [5]. This explains contradictory results obtained in the experiments with vagal stimulation, vagotomy, and atropine administration reported by other authors. Therefore, of particular importance is to study the effects of muscarinic cholinergic receptor blockade in prepubertal rats. Intravenous injection of atropine to 6-week-old rats produced bradycardia instead of tachycardia (Table 2). One minute postinjection, X_M increased from 168±8 to 187±2 msec ($p<0.05$). In addition, atropine significantly increased standard deviation, ΔX, mode ($p<0.05$), and mode amplitude ($p<0.001$). Codirected atropine-induced shifts of variational pulsogram parameters characterizing activity of the sympathetic and parasympathetic systems are characteristic only of cardiac reaction in 6-week-old rats.

To study the possible modulating effect of the sympathetic system on the vagal chronotropic regulation of the heart in the studied period of postnatal ontogeny, we analyzed the effect of muscarinic receptor blockade on cardiac rhythm variability in sympathectomized rats. In contrast to intact rats, no changes in HR were produced in 6-week-old sympathectomized rats by intravenous atropine. Other parameters of variational pulsograms also remained unchanged. The data obtained in experiments with atropine injection to intact and sympathectomized 6-week-old rats suggest that the peculiarities of vagal control of cardiac activity are determined by maturation of the sympathetic system at this period of rat ontogeny [9]. It should be stressed that significant differences between intact and sympathectomized rats in initial HR (174±9 and 143±3 bpm, respectively; $p<0.05$) were observed only during the prepuberty.

To evaluate the involvement of cardiac β-adrenoreceptors in the modulation of parasympathetic con-

TABLE 2. Effect of Atropine on X_M in Intact (Control) and Sympathectomized (Experimental) Rats ($M \pm m$)

Age, weeks	X_M, msec			
	initial		after atropine	
	control	experiment	control	experiment
6	168.0±8.5	141±4	187.0±1.5	141±9
20	155±4	157.0±3.8	154.0±1.3	155.0±4.9

TABLE 3. Effect of Atropine on X_M against the Background of Propranolol in 6-Week-Old Rats ($M \pm m$)

Group	X_M, msec	
	initial	after atropine
Intact	228±19	198.0±5.1
Sympathectomized	195±7	171.0±8.7

trol of cardiac function in 6-week-old rats, stimulation of VN and vagotomy were performed against the background of nonselective β-adrenoblocker propranolol. This agent produced significant ($p<0.001$) drop in HR in both intact and sympathectomized rats and did not prevent bradycardia induced by vagal electrical stimulation. Atropine injected intravenously after propranolol increased HR in the experimental and control groups (Table 3). Therefore, premedication with propranolol modified cardiac response to muscarinic receptor blockade in 6-week-old rats.

Thus, peculiarities in the regulation of cardiac rhythm were revealed in prepubertal rats. The most interesting phenomenon is atropine-induced bradycardia. The absence of this reaction in age-matched sympathectomized rats suggests that the age-related peculiarities of the cardiac control are determined by the formation and activation of mature sympathetic innervation of the heart. The revealed peculiarities can also result from changes in the density and activity of subpopulations of α-adrenoreceptors [6]. Age-related changes in α-adrenosensitivity of rat heart are mediated by neuropeptide Y [10]. The synthesis of neuropeptide Y is activated during prepuberty and triggers cascade modifications of the mechanisms of cardiac control.

REFERENCES

1. R. M. Baevskii, O. I. Kirillov, and S. Z. Kletskin, *Mathematical Analysis of Cardiac Rhythm Variations Under Stress* [in Russian], Moscow (1984).
2. I. P. Zapadnyuk, I. V. Zapadnyuk, and B. V. Zapadnyuk, *Laboratory Animals: Development, Maintenance, and Use in Experiments* [in Russian], Kiev (1983).
3. T. L. Zefirov, in: *Physiology of Autonomic Nervous System* [in Russian], Kuibyshev (1988), p. 57.
4. T. L. Zefirov and V. I. Timofeev, in: Ed. F. G. Sitdikov, *Organism Growth Under Muscle Activity* [in Russian], Kazan (1990), p. 64.
5. V. M. Smirnov, *Kardiologiya*, **29**, No. 7, 85-88 (1989).
6. U. Del Balzo, M. R. Rosen, G. Malfatto, *et al.*, *Circ. Res.*, **67**, 1535-1551 (1990).
7. X. J. Du, R. A. Riemersma, and A. M. Dart, *J. Cardiovasc. Pharmacol.*, **21**, No. 6, 977-982 (1993).
8. M. N. Levy, *Circ. Res.*, **29**, 437-445 (1971).
9. R. Robinson, *Cardiovasc. Res.*, **31**, 68-86 (1996).
10. L. S. Sun, P. C. Ursell, and R. B. Robinson, *Am. J. Physiol.*, **261**, 969-973 (1991).