Effect of β-Adrenoceptor Blockade on Cardiac Activity in Rats during Postnatal Ontogeny

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 136, No. 9, pp. 265-268, September, 2003
Original article submitted March 26, 2003

Electrical stimulation of the right stellate ganglion produces a positive chronotropic effect in 21-, 56-, and 100-day-old rats. The response of the heart rate to suprathreshold stimulation increased from the 21st to 100th day. By contrast, during β-adrenoceptor blockade the heart rate response decreased. The data suggest that the role of β-adrenoceptor in the regulation of cardiac chronotropic function increased with age.

Key Words: *heart; β-adrenoceptors; sympathetic control; rat*

Sympathetic influences on the chronotropic function of the heart are mediated via α- and β-adrenoceptors (AR). Myocardial AR are dynamic structures: the number of AR and the proportions of their types and subtypes can vary with age during tissue differentiation, in response to changes in hormone levels and to some physiological factors. The development of sympathetic innervation of the heart is accompanied by a decrease in the sensitivity and density of both types of cardiac AR [7]. The population of β-AR predominates. The number of these receptors decreases after suckling period due to the development of sympathetic innervation and this process is accompanied by an increase in norepinephrine content in the heart [7]. The age-related changes in the heart rate (HR) during ontogeny are probably associated with changes in the relationships between different β-AR subtypes [6]. There are views that sympathetic influences develop from week 3 to week 6 of postnatal ontogeny [8,9]. It also known that the formation of adrenergic influences on cardiac chronotropic function in rats occurs from week 3-4 to month 1.5-2. The studies of the age dynamics of cardiac AP with the use of specific blockers can reveal the terms of maturation of these receptors determining the cardiac chronotropic function.

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MATERIALS AND METHODS

The study was carried out on three groups of animals: 21-day-old suckling rats, 56-day-old prepubertal rats, and 100-day-old mature rats. The rats were narcotized with 25% urethane (1.3 g/kg body weight intraperitoneally). After fixation of the animal on the operation table the right stellate ganglion was prepared under a MBS-2 binocular microscope. Electrical stimulation of the stellate ganglion was performed with an ESL-2 laboratory stimulator (0.7 and 5.0 V pulse amplitude, 1 msec duration, 10 Hz repetition rate). Cardiac activity was assessed by ECG. Data recording and ECG analysis were performed on a complex electrophysiological setup and a Conan software. ECG was processed as described elsewhere [2]. Propranolol solution was injected into femoral vein (0.8 mg/kg body weight).

RESULTS

For evaluation of the involvement of α_1- and β-AR in the regulation of cardiac chronotropic function, stimulation of the right stellate ganglion was carried out after administration of nonspecific β-AR blocker propranolol. This agent blocks β_1- and β_2-AR, thus reducing both HR and contraction force [1,3,4].

Intravenous injection of propranolol decreased HR in all groups, but to a different degree (Table 1).

0007-4888/03/1363-0231$25.00

On min 15 postinjection, HR response was 25% in 21-day-old rats and 13% in 56- and 100-day-old rats ($p<0.05$ compared to initial values), which agrees with published data [1,4]. Experiments with pharmacological and surgical sympathectomy revealed tonic sympathetic influences in canine heart [5]. These cardiac chronotropic influences gradually decrease during ontogeny, which is also true for rats. Analysis of cardiac variation pulsogram showed that blockade of β-AR modifies all parameters of cardiac rhythm variability in all age group. A specific feature was the decrease in mode amplitude (MA) reflecting activity of sympathetic regulation in 21- ($p<0.05$) and 100-day-old rats immediately after injection, which did not recovered 15 min postinjection. Variation range (ΔX) increased in 56- and 100-day-old animals ($p<0.05$), which was probably a compensatory reaction reflecting activity of the parasympathetic regulation of the heart at this age (Table 1).

Electrical stimulation of the right stellate ganglion with electric pulses (0.7 V amplitude, 10 Hz repetition rate) had no effects on parameters of cardiac activity under control conditions and during blockade of β-AR with propranolol.

Control stimulation of the sympathetic ganglion with high-amplitude pulses (5 V) at 10 Hz induced a positive chronotropic effect in all groups. The most pronounced HR response was observed in 100-day-old animals (26%), while in 21- and 56-day-old rats it was 19% and 16%, respectively. Stimulation of the right stellate ganglion with the same pulses under conditions of propranolol blockade and with intact cardiac α-AR induced a positive chronotropic reaction: 24% ($p<0.001$) in 21-, 12% ($p<0.05$) in 56-, and 10% ($p<0.05$) in 100-day-old rats (Fig. 1).

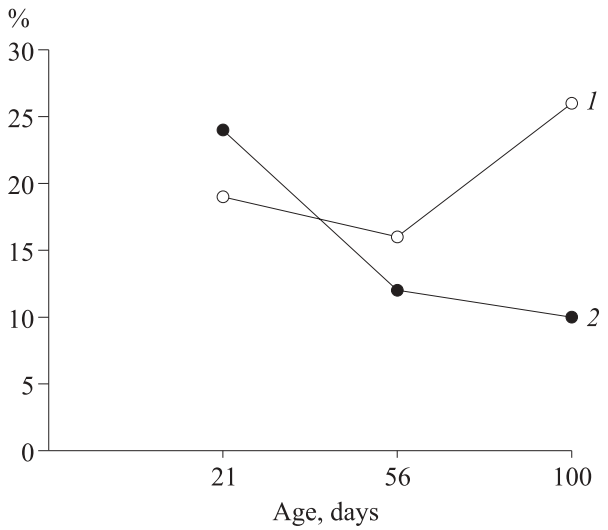

Fig. 1. Effect of suprathreshold stimulation of right stellate ganglion on heart rate in control (*1*) and propranolol-treated (*2*) rats.

Comparative analysis of HR data showed that in comparison with control rats, stimulation of the right

TABLE 1. Effect of Propranolol on Cardiac Activity in Rats during Postnatal Ontogeny ($M \pm m$)

Age (days) and index		Initial value	Immediately postinjection	On postinjection minute 15
21	HR, bpm	338.0±10.6	330.0±9.2	255.0±7.7*
	ΔX, msec	11±2	15.0±2.5	9.0±1.1
	MA, %	41.74±0.32	28.11±3.08**	37.71±3.04
56	HR, bpm	328.0±12.4	320.0±13.9	285±14**
	ΔX, msec	14.0±2.9	20.0±5.6**	9.0±1.6
	MA, %	32.74±4.29	25.84±3.54	43.84±3.54**
100	HR, bpm	269.0±15.1	258.0±11.3	235.0±8.7**
	ΔX, msec	9.0±1.3	13.0±2.1**	12.0±2.4**
	MA, %	41.21±4.67	30.48±4.78	34.81±3.94
21	HR, bpm	338.0±10.6	330.0±9.2	255.0±7.7*
	ΔX, msec	11±2	15.0±2.5	9.0±1.1
	MA, %	41.74±0.32	28.11±3.08**	37.71±3.04
56	HR, bpm	328.0±12.4	320.0±13.9	285±14**
	ΔX, msec	14.0±2.9	20.0±5.6**	9.0±1.6
	MA, %	32.74±4.29	25.84±3.54	43.84±3.54**
100	HR, bpm	269.0±15.1	258.0±11.3	235.0±8.7**
	ΔX, msec	9.0±1.3	13.0±2.1**	12.0±2.4**
	MA, %	41.21±4.67	30.48±4.78	34.81±3.94

Note. *$p<0.001$, **$p<0.05$ compared to initial values.

TABLE 2. Effect of Suprathreshold Stimulation of Right Stellate Ganglion on Cardiac Activity in Control and Propranolol-Treated Rats of Different Ages (*M*±*m*)

Age and stage of experiment	Control			Propranolol		
	HR, bpm	ΔX, msec	MA, %	HR, bpm	ΔX, msec	MA, %
21-day-old rats						
initial value	315.0±9.3	8.0±0.8	43.74±2.56	249.0±8.5	9.0±1.4	41.34±4.50
immediately after stimulation	376.0±10.6*	7.0±0.6	46.17±3.90	309.0±14.8*	9.0±0.9	36.36±4.20
1 min after stimulation	364.0±10.6	7.0±0.7	45.95±3.46	296.0±13.4**	8±1	42.48±2.85
2 min after stimulation	353.0±10.8	7.0±0.9	47.98±2.70	284.0±11.6**	9±1	38.11±2.37
5 min after stimulation	340.0±11.2	8.0±1.1	42.55±3.19	265±10	9.0±1.4	36.6±3.3
10 min after stimulation	329.0±11.8	9.0±1.4	40.45±3.25	258.0±11.1	10.0±1.5	37.64±2.79
56-day-old rats						
initial value	327.0±13.9	15.0±3.4	28.81±4.40	278±194	11.0±2.1	40.84±5.91
immediately after stimulation	380±14***	11.0±1.9	35.15±2.80	312.0±15.2**	17.0±4.7	29.83±2.79
1 min after stimulation	362.0±14.7***	11±2	37.24±3.50	298.0±14.7***	11.0±1.4	35.48±4.31
2 min after stimulation	352.0±14.5	11.0±1.9	33.45±3.50	289.0±14.7	9.0±1.1	33.71±3.62
5 min after stimulation	338.0±17.1	14.0±2.9	32.08±3.30	283.0±14.7	10.0±1.6	36.80±4.76
10 min after stimulation	340.0±16.8	11.0±1.6	33.21±4.20	280.0±14.7	12.0±1.7	37.68±5.56
100-day-old rats						
initial value	266.0±9.9	8±1	39.23±3.44	235.0±9.9	13.0±1.6	33.41±6.30
immediately after stimulation	334.0±11.4*	12.0±1.7***	43.27±4.36	258.0±13.7***	15.0±2.3	25.72±2.26
1 min after stimulation	310.0±9.3**	8±1	42.11±5.64	246.0±11.8***	12.0±2.4	33.87±6.13
2 min after stimulation	296±10***	9.0±2.4	45.68±5.50	241.0±10.4	16.0±5.4	29.07±3.67
5 min after stimulation	286.0±12.2	8.0±1.2	38.27±4.16	238.0±9.8	14.0±3.9	32.28±7.71
10 min after stimulation	278.0±13.1	8.0±1.8	41.43±5.53	233.0±9.2	14±3	28.56±7.71

Note. *p<0.001, **p<0.01, ***p<0.05 compared to initial values.

stellate ganglion in rats with blocked β-AR produced an insignificant (5%) increase in 21-day-old rats, while in 56- and 100-day old rats it decreased HR by 4 and 16%, respectively (Fig. 1). Therefore, in control rats HR response to suprathreshold stimulation of the right stellate ganglion increased from 21- to 100-day age, while in the experimental rats with blocked β-AR it decreased with age.

The increase in ΔX after control stimulation was observed only in 100-day-old rats ($p<0.05$), which indicates maturity of the parasympathetic regulation at this age. MA increased in all age groups (Table 2). In propranolol-treated rats, electric stimulation increased ΔX and decreased MA in all groups. The most pronounced decrease in MA was observed in 56- (27%) and 100-day-old rats (23%), respectively.

The pronounced HR response to stimulation of the right stellate ganglion in 21-day-old rats with blocked β-AR attests to the dominant role of α_1-AR in mediating the sympathetic influences on HR at this age, which is in line with their earlier maturation in the myocardium [7]. The observed HR response in 100-day-old rats indicates growing role of β-AR in the regulation of chronotropic cardiac function during ontogeny [3].

This work was supported by the Russian Foundation for Basic Research (grant No. 01-04-49456).

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