Age-Related Peculiarities of the Effect of α-Adrenoreceptor Blockade on Cardiac Function in Rats

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Blockade of α_1-adrenoreceptors with prazosin produces bradycardia. The degree of this bradycardia in rats depends on age. In adult (20-week-old) rats bradycardia is pronounced, in 3-week-old rats it is insignificant, and in 1-week-old rats bradycardia does not develop. Prazosin moderates bradycardia induced by vagal stimulation in rats of different age.

Key Words: *heart; α_1-adrenoreceptors; nervous regulation; rat; vagus*

Interaction between the sympathetic and parasympathetic nervous systems underlies the mechanisms of nervous regulation of the cardiac function. The sympathetic influences on the heart are mediated via α- and β-adrenoreceptors (AR). α-AR are divided into presynaptic α_2-AR and postsynaptic α_1-AR [2,9]. It was previously considered that β-AR actively participate in the regulation of cardiac function, while α-AR regulate the vascular tone.

The major role of α_1-AR is regulation of cytoplasmic Ca^{2+} concentration and shortening of myofilaments [4].

There is evidence that α_1-AR are equally distributed in the left and right ventricles of rat heart, while the density of these receptors in atrial myocardium surpasses that in ventricles. It is established that the content of α_1-AR in the sinoatrial and atrioventricular nodes is higher than in the adjacent myocardium, which confirms the important role of α_1-AR in the regulation of not only inotropic, but also chronotropic function of the heart [8].

It was shown that cardiac α_1-AR participate in the development of positive inotropic effects [5]. It is noteworthy that α_1-adrenoblocker prazosin increases heart rate (HR) in mammals. Tachycardia produced by blockade of α_1-RA with prazosin can result from stimulation of β-AR with catecholamines. There are data that intravenous injection of prazosin either decreases HR or does not change it (despite expected reflex tachycardia due to pronounced hypotensive effect of prazosin) [7].

Thus, blockade of β-AR produces pronounced bradycardia at various stages of ontogeny [1]. At the same time functional role of α_1-AR in the regulation of cardiac function (in particular, its age-related aspects) remains unclear.

The objective of the present work was to study heart function under conditions of α_1-AR blockade with prazosin in 1-, 3-, and 20-week-old rats.

MATERIALS AND METHODS

The study was carried out on 1-, 3-, and 20-week-old random-bred albino rats (n=45). The rats were intraperitoneally anesthetized with urethane (1000 mg/kg, 25% solution). Prazosin (0.1 mg/kg, Sigma) was injected into the right femoral vein. Stimulation of the right vagus nerve was performed with an ESL-2 stimulator. The parameters of electrical pulses were: constant amplitude 5 V, duration 10-12 msec, delay 0.2-0.4 msec, and repetition rate 0.7-10.0 Hz.

Electrocardiogram (ECG) and volumetric rheogram were visually controlled using an S1-83 oscillograph. Twenty-one parameters of ECG and 7 parameters of volumetric rheogram were recorded and processed on-line on a computer. The results were analyzed statistically using Student's t and Wilcoxon tests.

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RESULTS

Injection of prazosin to adult rats produced a gradual decrease in HR. The maximum effect was observed on minute 30 postinjection, when the mean cardiointerval (X_M) increased from 166.0±8.9 to 236.0±11.1 msec ($p<0.05$, Fig. 1). The changes in parameters of variational pulsogram, which reflect vegetative homeostasis, attested to moderation of the effect of the sympathetic system on cardiac function. However, the maximum changes of these parameters were observed on minute 15 postinjection. Variational range (DX) increased from 6.4±1.9 msec to 36.6±22.4 msec, and then decreased to 18.0±7.7 msec on minute 30 postinjection. Autonomic balance index (ABI) decreased from 9545±3696 to 1743±915 arb. units, but on minute 30 postinjection it increased to 3080±1459 arb. units.

X_M increased mainly due to lengthening of *T—P* interval from 97.6±5.9 msec to 166.0±34.8 msec and due to widening of *T* wave from 72.2±4.4 msec to 98.0±11.7 msec. In adult rats stroke volume (SV) increased from 0.280±0.088 ml to 0.313±0.086 ml on postinjection minute 1, then it dropped to 0.231±0.036 ml on minute 15 and attained 0.297±0.045 ml on minute 30.

Injection of prazosin to 3-week-old rats increased X_M by 12%. Thus, bradycardia was less pronounced at this age than in adult rats (Fig. 1). During 30-min observation, the changes in parameters of variational pulsogram were diverse. On postinjection minute 5, ΔX increased from 1.80±0.37 to 2.8±0.8 msec, while ABI decreased from 45,900±10,527 to 23,100±4916 arb. units, which attests to moderation of sympathetic influences. A tendency to recovery of ΔX and ABI was observed on postinjection minute 15: ΔX decreased to 2.4±0.7 msec, while ABI increased to 30,600± 9537 arb. units. Variational pulsogram revealed that moderation of sympathetic activity was more pronounced on postinjection minute 30 than on minute 5. Virtually all ECG intervals and peaks contributed to the increase in X_M. SV decreased from 0.09±0.02 to 0.08±0.02 ml on postinjection minute 5 and increased to 0.10±0.03 ml on minute 30.

Blockade of α_1-AR in 1-week-old rats produced no marked changes in cardiac function. The maximum changes in X_M (from 176±10 to 170.0±9.2 msec) were observed on postinjection minute 5 (Fig. 1). The time course of the parameters of variational pulsogram showed that prazosin decreased sympathetic activity in the newborn rats. On minute 15 postinjection, ΔX increased from 1.80±0.37 to 3.60±0.24 msec, mode amplitude decreased from 60.0±5.2% to 47.0±4.2%, ABI dropped from 41,900±11,448 to 13,400±1613 arb. units, and strain index decreased from 127000±9592 to 40400±6414 arb. units.

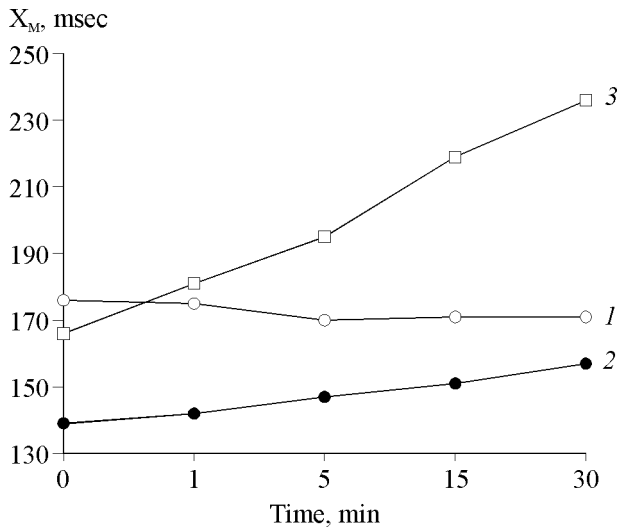

Fig. 1. Dynamics of mean cardiointerval (X_M) during prazosin administration to 1- (*1*), 3- (*2*), and 20-week-old rats (*3*).

It is noteworthy that X_M little changed, but *T* wave increased from 67.8±3.9 to 78.6±4.4 msec on minute 1 postinjection. On minute 30, SV also increased from 0.042±0.004 to 0.052±0.004 ml.

For investigation of age-related peculiarities of the effect of α_1-AR blockade on parasympathetic regulation of the heart, 3 experimental series were carried out with stimulation of the right vagus nerve before and after injection of prazosin to 1-, 3-, and 20-week-old rats. In adult rats vagal stimulation before injection of prazosin decreased HR by 75% (Fig. 2). The observed changes in the parameters of variational pulsogram attested to activation of the parasympathetic cardiotropic influences. By contrast, this stimulation performed against the background blockade of α_1-AR produced less pronounced bradycardia (Fig. 2). In addition, changes of all parameters of variational

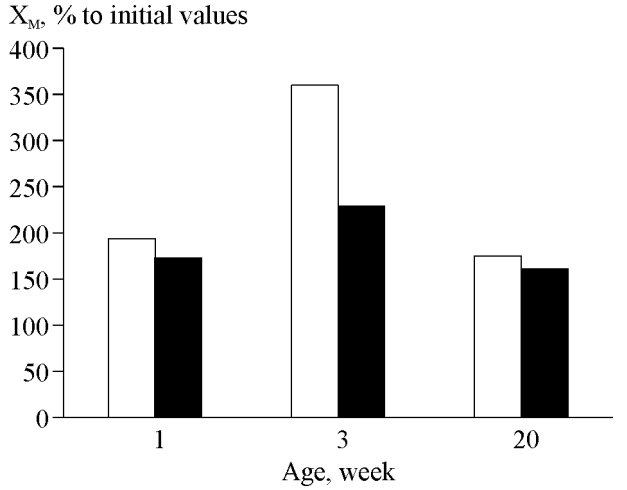

Fig. 2. Effect of vagal stimulation on X_M in control (light bars) and in prazosin-treated rats (solid bars).

pulsogram decreased. The increase in *R—R* interval developed mainly at the expense of *T—P* interval shortening both before and after prazosin injection.

Vagal stimulation in intact 3-week-old rats increased X_M by 260% (Fig. 2). The changes of variational pulsogram parameters attested to the prevalence of parasympathetic influences over the sympathetic ones. Vagus-induced bradycardia was less pronounced after prazosin injection (Fig. 2). The increase in X_M was accompanied by lengthening of *T—P* and *P—Q* intervals and *P* wave.

Injection of prazosin to 1-week-old rats attenuated the effect of vagal stimulation (Fig. 2). Before injection, *R—R* interval increased at the expense of *T—P* interval and *T* wave, while after injection it increased due to lengthening of *T—P* interval and *P* wave. Therefore, α_1-AR blockade moderated vagus-induced bradycardia in all age groups. It should be noted that this blockade had no effect on changes in SV induced by vagal stimulation in the rats of all age groups.

Injection of prazosin to adult rats produced a significant decrease in HR ($p<0.05$). By contrast, reactions of 1- and 3-week-old rats to the blocker were different: in 3-week-old rats only minor bradycardia was observed, while in 1-week-old rat pups it was absent. These age-related peculiarities in cardiac response to α_1-AR blockade can be explained by the development of the sympathetic innervation in rat heart at the age of 3 weeks.

We previously demonstrated that β-AR blocker propranolol significantly decreased HR in newborn rats, so it can be hypothesized that the age-related differences observed during α_1-AR blockade are associated with age-dependent peculiarities in the density and activity of various types of AR at different stages of postnatal ontogeny in rats.

It is widely known that blockade of various subtypes of α-AR produces opposite effects on HR [6]. It can be assumed that the relative content of α_{1A}- and α_{1B}-AR in the heart underlies the observed peculiarities in heart response to prazosin in rats of different age. Moderation of vagus-induced bradycardia with prazosin corroborates the theory of "accentuated antagonism" between sympathetic and parasympathetic influences [3]. It can be assumed that population of α-AR participate in the fine tuning of parasympathetic regulation of the heart.

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