Comparative Analysis of the Impact of α1- and α2-Adrenoreceptor Blockade on Cardiac Function in Rats during Postnatal Ontogeny

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We compared the effects of α1-and α2-adrenoreceptor blockade on cardiac function in rats aged 1, 3, 6 and 20 weeks. Administration of α1-adrenoblocker prazosin decreased heart rate in 20- and 6-week-old rats; in 3-week-old rats, this decrease was insignificant and in 1-week-old rats was absent. Blockade of α2-adrenoreceptors with yohimbine did not change heart rate in 6- and 20-week-old rats and induced bradycardia in 1- and 3-week old rats.

Key Words: *heart; α-adrenoreceptor; sympathetic regulation; rat; ontogeny*

According to classical concepts, the sympathetic and parasympathetic nervous systems contribute significantly to heart rhythm generation and regulation. Of particular interest are mechanisms that determine the heart rate (HR) at various stages of ontogeny [3-5,12]. It is known that in rats, sympathetic innervation of the heart develops later than the parasympathetic one, and that it determines changes in cardiac activity during the postnatal ontogeny. Sympathetic influences on the heart are realized through catecholamine (CA) interaction with various adrenoreceptors (AR) on heart cells. AR are present in all tissues and organs, they are involved in the regulation of metabolism, secretion, blood pressure, muscle contraction [6-8,11,14]. α- and β-AR have been identified, their structure and function have been thoroughly studied, G-proteins and second messenger systems modulated by interactions between AR and CA have been identified [9,13]. It is noteworthy that function of β-AR in the heart has been studied more intensively [1,2]. The role of cardiac α-AR is still the subject to debate [15]. It is shown that there are two subtypes of α-AR: α1-AR and α2-AR [10]. At the same time, functional role of various subtypes of α-AR in rat heart remains unclear. Involvement of different subtypes of α-AR in the development of mechanisms regulating cardiac activity at different stages of postnatal ontogeny is poorly studied.

Here we studied the effects of α1- и α2-AR blockade in 1-, 3-, 6-, and 20-week old rats.

MATERIALS AND METHODS

The study was carried out on 1, 3, 6 and 20-week-old random-bred albino rats (n=62). The animals were narcotized with 25% urethane (1000 mg/kg intraperitonally). α1-AR blocker prazosin (0.1 mg/kg, Sigma) and α2-AR blocker yohimbine (1 mg/kg, Sigma) were injected into the right femoral vein. ECG was visually monitored throughout the experiment. Twenty-one parameters of ECG and variation pulsogram were recorded and processed.

The results were analyzed statistically and the reliability of differences was evaluated by Student's t test using Microsoft Excel software.

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RESULTS

Injection of prazosin to adult animals resulted in gradual HR deceleration. The maximum effect was observed 30 min after drug administration. Mean cardiac interval (Xm) increased from 166.0±8.9 to 236.0±11.1 msec ($p<0.05$; Fig. 1). Changes in the parameters of variation pulsogram reflecting vegetative homeostasis attested to weakening of the effects of the sympathetic nervous system on the heart. Bolus intravenous administration of α2-AR blocker yohimbine did not significantly change HR in adult rats (Fig. 2). Xm increased from 204.5±16.4 to 207.3±19.6 msec during the 1st minute after injection and then decreased to 199.5±0.8 msec by the 5th minute of observations; by the 30th minute this parameter was 210.6±16.5 msec. Parameters of variation pulsogram did not change significantly throughout the experiment.

α1-AR blockade with prazosin reduced HR in 6-week-old animals; Xm increased from 152.5±3.5 to 188.8±2.1 msec during the 1st minute of the experiment ($p<0.01$); then this parameter continued to increase and attained 196.8±7.0 msec ($p<0.01$) after 5 min and 209.5±9.7 msec ($p<0.01$, Fig. 1) by the end of the observation period. The increase in Xm was accompanied by significant changes in HR variability. In 6-week-old animals, α2-AR blockade did not change Xm (Fig. 2). No significant changes in the analyzed parameters of variation pulsogram were noted.

Administration of α1-AR blocker to 3-week-old animals increased Xm by 12% (Fig. 1), *i.e.* bradycardia in these animals was less pronounced than in adult animals (42%). In 3-week-old rats, Xm considerably increased from 122.5±0.7 to 135.0±3.1 msec ($p<0.01$) during the first minute of α2-AR blockade with yohimbine. Then bradycardia progressed and 5 min after yohimbine injection Xm was 141.0±4.9 msec ($p<0.01$, Fig. 2). The severity of bradycardia then decreased and after 15 min Xm was 136.5±3.5 msec, which significantly surpassed the initial value ($p<0.01$). After 30 min, Xm decreased to 131±2 msec, but still significantly surpassed the initial value ($p<0.05$). Administration of yohimbine to 3-week-old rats significantly modulated the analyzed parameters of HR variability. It should be noted that these changes were most pronounced on minutes 1 and 5 after drug administration, which suggests that the blocker produced a short-term effect.

The effects of prazosin administration to newborn animals differed from those in other age groups. The blockade of α1-AR in 1-week-old rats caused no marked changes in cardiac activity. On the 5th minute after administration of the drug, changes in Xm were maximum: it decreased from 176±10 to 170.0±9.2 msec (Fig. 1), *i.e.* mild tachycardia was observed. Blockade of α2-AR with yohimbine produced bradycardia in 1-week-old rats, but in contrast to yohimbine-induced HR deceleration in 3-week-old rats bradycardia in newborn rats developed gradually and reached maximum by the 30th min of observation. During the first minute after injection of yohimbine, Xm slightly increased from 160.8±3.2 to 164.8±4.1 msec; after 5 min, Xm was 173.4±7.9 msec, but this increase was insignificant; 15 and 30 min after drug injection Xm increased to 179.2±7.6 msec ($p<0.05$) and 183.2±8.3 msec ($p<0.05$), respectively (Fig. 2).

Thus, administration of prazosin to adult and 6-week-old rats significantly decelerated HR ($p<0.05$). The reaction to administration of the blocker differed

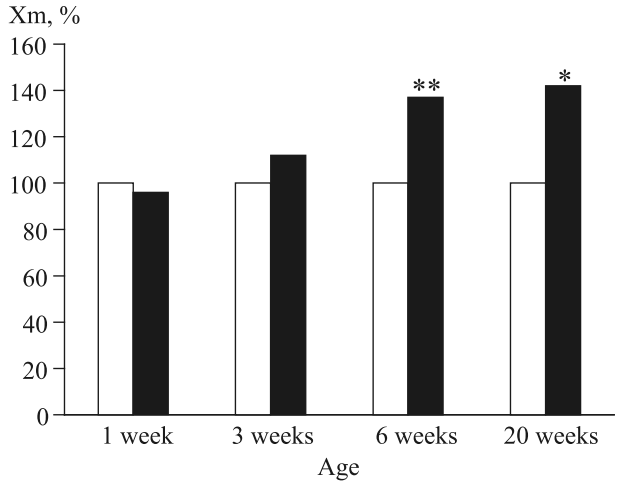

Fig. 1. Effect of α1-AC blockade with prazosin on cardiac activity in rats at various stages of postnatal ontogeny. Light bars: initial values; dark bars: prazosin. *$p<0.05$, **$p<0.01$ in comparison with baseline values.

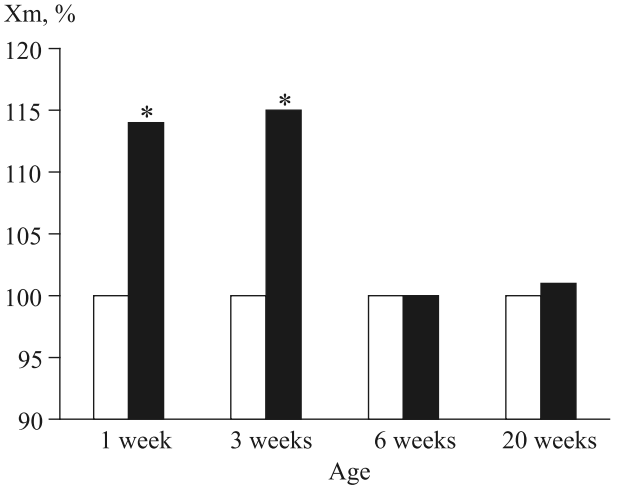

Fig. 2. Effect of α2-AC blockade with yohimbine on cardiac activity in rats at various stages of postnatal ontogeny. Light bars: initial values; dark bars: yohimbine. *$p<0.05$ in comparison with baseline values.

significantly in 1- and 3-week-old rats: HR slightly decreased in 3-week-old rats and remained unchanged in 1-week-old rats.

It should be noted that at various stages of early postnatal ontogeny, there are age-related differences in the effects of α2-AR blockade on chronotropic function of the heart. The severity of bradycardia after administration of yohimbine decreased with age. Significant HR deceleration was recorded only in 1- and 3-week-old rats, *i.e.* in animals with incompletely formed sympathetic innervation of the heart. Moreover, in 1-week-old rats bradycardia developed slowly and gradually reached a maximum by the 30th minute of observation, while in 3-week-old rats bradycardia was most pronounced immediately after administration of yohimbine.

Based on these results we can conclude that α1-AR and α2-AR are involved in adrenergic regulation of HR in rats. At the same time, there are marked age-related peculiarities in the effects of blockade of these receptors. The severity of bradycardia after α1-AR blockade increased with age against the background of developing cardiac sympathetic innervation. On the contrary, the degree of HR deceleration after α2-AR blockade decreases with age. It was previously thought that α1-AR and α2-AR are located primarily post- and presynaptically. Further studies demonstrated different localization of these receptors. It can be assumed that the expression of different subtypes of α-AR in the heart varies and, consequently, their synaptic localization changes with age. Another possible explanation of our results is the difference in the second messenger systems activated upon the interaction of the ligand with different α-AR. The interaction of CA with α1-AR activates second messengers, including inositol triphosphate and diacylglycerol, whereas α2-AR activation modulates activity of the adenylate cyclase/cAMP cascade. The development of cardiac sympathetic innervation in postnatal ontogeny undoubtedly affects activity of AR.

Our findings are related to the existence of some age-related differences in the expression, density, location, and characteristics of ion channels in the heart. These changes in activity of ion currents are the ultimate effect of autonomic regulation of cardiac activity.

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