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Peculiar Effects of Selective Blockade of α_2-Adrenoceptor Subtypes on Cardiac Chronotropy in Newborn Rats

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We studied the effects of selective blockade of various subtypes of α_2-adrenoceptors on cardiac chronotropy in newborn rats. This period in rats is characterized by the absence of adrenergic regulation of heart function. Blockade of $\alpha_{2A/D}$- and α_{2B}-adrenoceptors in 1-week-old rats provoked tachycardia. In contrast, blockade of α_{2C}-adrenoceptors in newborn rats had no effect on heart rate.

Key Words: *heart; chronotropy; α_2-adrenoceptors*; *ontogeny; rats*

It is a common knowledge that α_2-adrenoceptors (α_2-AR) modulate the regulatory influences in mammal heart. Being located on the presynaptic membrane, α_2-AR inhibit presynaptic release of norepinephrine. All subtypes of α_2-AR decrease activity of adenylate cyclase resulting in a drop of intracellular cAMP. At present, three subtypes of α_2-AR are postulated: α_{2A}-, α_{2B}-, and α_{2C}-AR [7]. The dominant role of α_{2A}-AR in control over the cardiovascular system was demonstrated by the studies where knockout of the gene coding these receptors elevated AP and HR [5]. Norepinephrine release from cardiac sympathetic axons is controlled by presynaptic α_{2A}- and α_{2C}-AR [9]. Some papers report on implication of α_{2A}- and α_{2C}-AR in the development of cardiac hypertrophy and heart failure [4,8]. In contrast, α_{2B}-AR are located mostly in the postsynaptic membrane [9]. In mature rats, both stimulation and inhibition of α_2-AR subtypes produce pronounced cardiovascular effects [1,12]. Despite numerous data on the role of α_2-AR, their presence and functionality in the heart of humans and animals have been the subject of many studies [6,7,10]. Further investigation of α_2-AR subtypes will shed more light on their role in the regulation of body functions and suggest an effective therapeutic strategy based on blockade or activation of the entire repertoire of α_2-AR subtypes. Recent papers are vigorously discussing the clinical importance of early involution of the sympathetic branch of cardiac ANS in cardiovascular pathology [2]. In this connection, the studies focused on cardiac functions in the animals with non-developed sympathetic regulation seem to be important [3,11].

Our aim was to examine the effects of selective blockade of α_2-AR subtypes on cardiac chronotropy in the newborn rats.

MATERIALS AND METHODS

The experiments were carried out on 1-week-old random-bred newborn rats (n=30), which were narcotized intraperitoneally with 25% urethane (800 mg/kg body weight). The blockers of α_2-AR were injected into the right femoral artery. $\alpha_{2A/D}$-, α_{2B}-, and α_{2C}-AR were blocked selectively with RX821002 (0.1 mg/kg), imiloxan hydrochloride (1 mg/kg), and JR-1302 (0.3 mg/kg, Tocris), respectively. During the entire period of experiment, 21 parameters of ECG and variational pulsogram were recorded and analyzed.

The data were processed statistically with Student's t.

RESULTS

Injection of RX821002 (a blocker of $\alpha_{2A/D}$-AR) to newborn rats provoked tachycardia: to minute 3 postinjection, the mean cardiointerval (X_m) decreased from

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127.0±2.4 to 121.0±2.1 msec (by 5.0±1.4%, $p<0.05$). During the following 60 min, X_m did not significantly change (Fig. 1).

Intravenous injection of imiloxan hydrochloride, a selective α_{2B}-AR antagonist, also induced tachycardia. To the end of postinjection minute 1, X_m decreased from 126.0±1.7 to 121.0±2.6 msec (by 4.0±0.9%, $p<0.001$). During the following 30 min, X_m gradually decreased down to 119.0±3.1 or 94.0±1.5% of initial level ($p<0.01$, Fig. 2).

In only one series of experiments with the newborn rats employing selective blockade of α_{2C}-AR with JP-1302 revealed no chronotropic effect: in this case, X_m did not change significantly (Fig. 3).

The data presented herein revealed important peculiarities in the regulation over cardiac activity by various subtypes of α_2-AR in newborn rats. According to the degree of chronotropic action, one can conclude that in the newborn rats, which have no adrenergic innervation in the heart, only $\alpha_{2A/D}$- and α_{2B}-AR are functionally important cardiac regulators. Blockade of these subtypes of AR induced chronotropic changes in the heart of newborn rats. According to available data, these receptors reside on presynaptic membrane.

It is worthy of note that the data obtained on newborn rats markedly differ from the results of our experiments on mature rats [1]. In mature rats, blockade of $\alpha_{2A/D}$-AR initially induced bradycardia followed by tachycardia (Fig. 1). In contrast, newborn rats demonstrated no bradycardia during the first 10 min postinjection. Selective blockade of α_{2B}-AR in mature rats produced far stronger tachycardia than that observed in newborn rats (Fig. 2). The most pronounced age-related peculiarities in the dynamics of cardiac chronotropic effect were observed in experiments with selective blockade of α_{2C}-AR (Fig. 3). While this blockade produced virtually no effect on X_m in newborn rats, in mature rats it provoked tachycardia accompanied with elevation of AP [1].

The observed peculiarities in cardiac chronotropic reactions in newborn rats are most probably related to the degree of adrenergic innervation of the heart. No signs of sympathetic innervation were observed in the rat heart during the first postnatal week despite the use of various methods [3,11]. The lack of developed postganglionic sympathetic fibers in newborn rats casts doubts on functional rationality of presynaptic AR. Namely for this reason, the greatest differences in cardiac chronotropic reactions between the newborn and mature rats we observed during selective blockade of $\alpha_{2A/D}$- and α_{2C}-AR. The selective blockade of these adrenoceptor subtypes revealed the changes in dynamics of cardiac chronotropic reactions in newborn rats.

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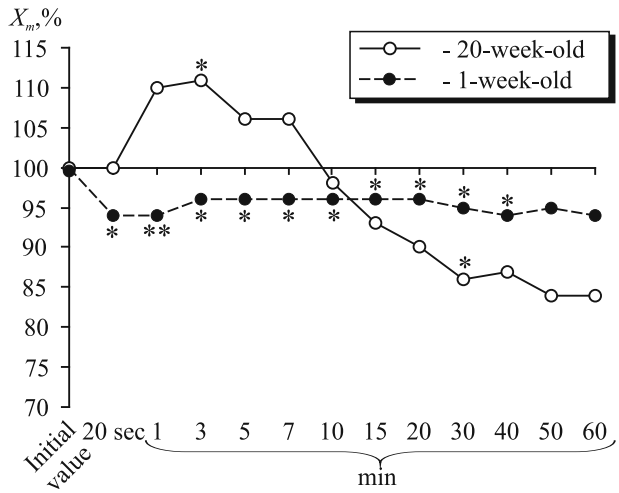

Fig. 1. Effect of blockade of $\alpha_{2A/D}$-AR on the heart rate in newborn rats and adult animals. Here and in Figs. 2, 3: ordinate, *RR* interval; abscissa, postinjection time. **p*<0.05, ***p*<0.01 in comparison with initial values.

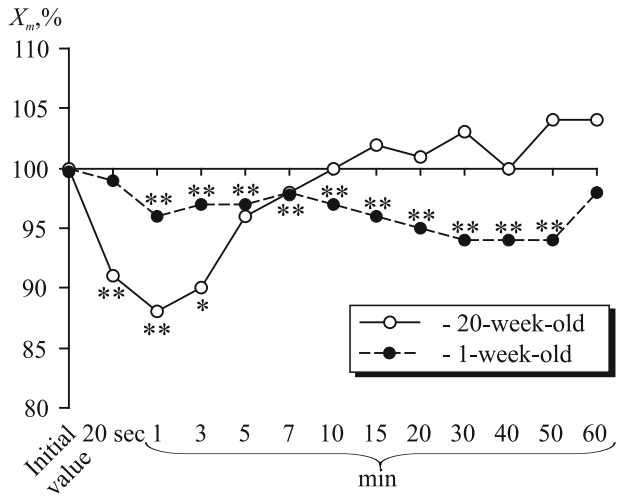

Fig. 2. Effect of blockade of α_{2B}-AR on the heart rate in newborn rats and adult animals.

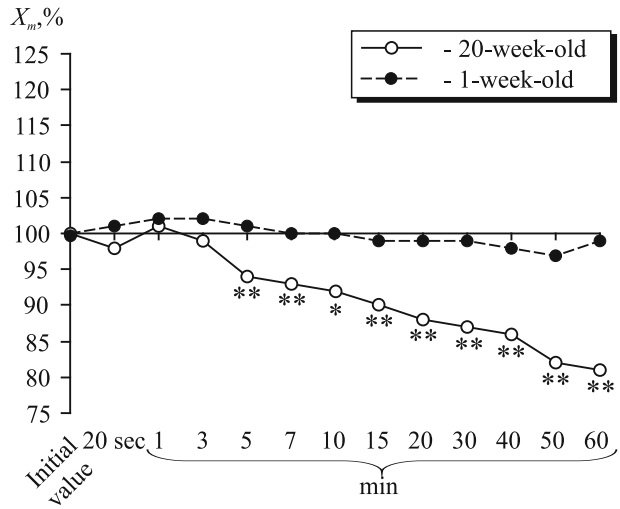

Fig. 3. Effect of α_{2C}-AR blockade on the heart rate in newborn and adult rats.

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