Opposite Changes in Cardiac Chronotropy Induced by Selective Blockade of α_{1A}-Adrenoceptors in Rats of Different Age

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 152, No. 7, pp. 22-24, July, 2011
Original article submitted February 28, 2011

Selective blocker of α_{1A}-adrenoceptors WB4101 induced changes in heart rate in rats: it caused bradycardia in 3-, 6-, or 20-week-old rats (severity of bradycardia increased with increasing animal age) and increased heart rate in newborn rat pups.

Key Words: *heart; α_{1A}-adrenoceptors*; *nervous regulation; rats; ontogeny*

It is a common view that catecholamines exert a positive chronotropic and inotropic effect on the heart in close cooperation with (predominantly) β-adrenoreceptors (β-AR). We previously examined the effect of non-selective blockade of β-AR in rats with propranolol [2]. This agent produced a pronounced negative inotropic effect in all age groups, but the severity of bradycardia was different in rats of various age groups [1]. The effect of α-AR on the cardiovascular system can be explained mostly by the vasoconstrictor action of these receptors. At present, the existence of various types of α-AR in mammalian heart is firmly established [4,11]. Species-specific peculiarities of the proportions of various cardiac AR were demonstrated. These studies showed that the numbers of α_1-AR and β-AR are virtually identical in the hearts of rat and guinea pig [3]. Thus, the heart of rat, the most popular laboratory animal, contains comparable numbers of α_1- and β-AR. Ventricular cardiomyocytes of rats carry α_{1A}-AR, α_{1B}-AR, and α_{1D}-AR [6,7,9]. In rat heart, α_{1A}-AR are most abundant [12]. This fact prompted a hypothesis that in addition to other functions, α-ARs are involved in the regulation of cardiac chronotropy. This hypothesis is corroborated by studies of the density of α_1-AR in the sinoatrial node of the heart conduction system, which showed that these node contain a greater number of α_1-AR than the neighboring working myocardium [8,10]. Further studies of AR demonstrated that the subtypes of α_1-AR could modulate duration of the diastolic depolarization in the sinoatrial node cells [5].

This work examines the peculiarities of the effect of α_1-AR blockade on cardiac chronotropy in rats at different stages of the postnatal ontogeny.

MATERIALS AND METHODS

The experiments were carried out on random-bred albino rats aging 1, 3, 6, or 20 weeks (n=45). The rats were anesthetized intraperitoneally with 25% urethane (1000 mg/kg body weight). WB4101, a selective blocker of α_{1A}-AR, was injected into the right femoral artery in the dose of 1 mg/kg. During the entire period of the experiment, 21 parameters of ECG and variational pulsogram were recorded and analyzed.

The data were processed statistically using Microsoft Excel software and Student's t test at $p<0.05$.

RESULTS

Intravenous bolus injection of WB4101, a selective blocker of α_{1A}-AR, significantly increased the mean cardiointerval (X_m) in adult animals. During the first

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0007-4888/11/1521-0019

postinjection minute, X_m increased from 190.6±20.9 to 301.4+33.5 msec (p<0.05). In the following, X_m increased still more, and on postinjection minutes 5, 15, and 30 attained the values of 325.4±19.2 msec (p<0.01), 333.4±24.0 msec (p<0.01), and 363.6+38.4 msec (p<0.01), respectively (Fig. 1).

This period was characterized with pronounced changes in the heart rate variability indices attesting to moderation of the regulatory sympathetic influences and predominant activity of the parasympathetic branch of ANS. This observation agreed with the changes in variation range (ΔX), mode amplitude (*MA*), and strain index (*SI*).

Selective blockade of α_{1A}-AR in 6-week-old rats with WB4101 also produced a negative chronotropic effect. One and 5 min postinjection, X_m increased from 144.0+10.7 to 179.0±6.8 msec (p<0.05) and 189.0±8.4 msec (p<0.05), respectively. On minute 15, X_m somewhat decreased to 185.8+9.5 msec, but still significantly surpassed the initial value (p<0.05, Fig. 1). On minute 30, X_m attained the level of 193.2+16.3 msec (p<0.05). It is noteworthy that WB4101-induced negative chronotropy was less pronounced in 6-week-old rats than in adult animals.

The changes of the heart rate variability indices in 6-week-old rats were also less pronounced than in the adult animals. However, the increase in ΔX and decrease in *MA* in 6-week-old rats attest to down-regulation of the cardiotropic regulatory sympathetic influences. At the same time, the drop of *SI* in 6-week-old rats did not significantly differ from that in adult rats. The data support the hypothesis that the development

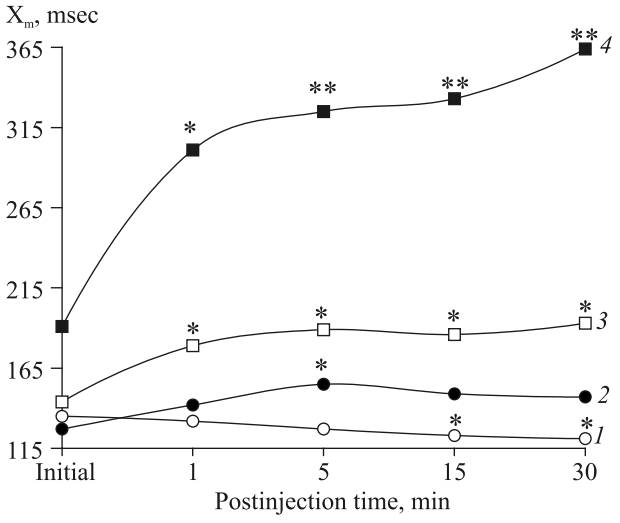

Fig. 1. Effect of WB4101, a selective blocker of α_{1A}-AR, on the mean cardiointerval (X_m) in rats of different age. *1*) 1-week-old rats; *2*) 3-week-old rats; *3*) 6-week-old rats; *4*) mature 20-week-old rats. *p<0.05, **p<0.01 in comparison with the initial values of X_m recorded in narcotized rats after stabilization of the heart rate before injection of α_{1A}-AR blocker.

of bradycardia in response to blockade of α_{1A}-AR is clearly age-dependent. This observation corroborates the view that sympathetic innervation of the heart improves with age.

Intravenous injection of WB4101 to 3-week-old rat pups insignificantly increased X_m during the first five postinjection minutes. On postinjection minute 1, this index increased from 126.6±7.5 to 142.3+11.8 msec. On postinjection minute 5, the increase of X_m in comparison with initial value became significant attaining the level of 154.5+11.3 msec (p<0.05). In the following, X_m decreased during 25 min (Fig. 1). On postinjection minutes 15 and 30, the values of X_m were 149.3±9.7 and 147.0+12.3 msec, respectively, albeit the increment of this parameter in comparison with the initial values was insignificant. Still greater changes were observed in dynamics of variational pulsogram indices. Mathematical processing revealed no significant changes in the basic parameters that describe the sympathovagal balance. The values of *MA* and SI changed insignificantly. Comparison of data on 3-week-old rat pups with those of 6-week-old and mature animals completely corroborated the view on age dependence of the degree of bradycardia after the selective blockade of α_{1A}-AR. However, there were no significant changes in parameters of variational pulsogram during the entire period of the experiment in this age group.

Opposite results were obtained in the study of the effect of selective blockade of α_{1A}-AR on the heart performance in the newborn (1-week-old) rat pups. In this case, intravenous injection of WB4101 decreased X_m. On postinjection minute 1, X_m changed from 135.0±2.7 to 131.7+3.14 msec; then, this value continued to decrease: on postinjection minutes 5 and 15 it was 126.5+2.9 and 122.8±3.8 msec, respectively, and decreased to 121.0+4.2 msec by the end of the experiment (p<0.05, Fig. 1).

It seems especially important that injection of WB4101 significantly decreased *MA*, which is the most informative index of sympathetic activity. However, this decrease was not accompanied by bradycardia. On the contrary, the mean RR interval decreased.

Thus, these findings corroborated the view on significant peculiarities in the cardiotropic adrenergic control in the newborn rat pups. Only in this age group, selective blockade of α_{1A}-AR did not moderate heart rate (common effect in all other age groups), but accelerated heart work. In other age groups, the severity of bradycardia after selective α_{1A}-AR blockade with WB4101 increased with age. These data refute the hypothesis that adrenergic regulation of rat heart is effected only via β-AR. There are several ways to explain the opposite effects of

α_{1A}-AR blockade on the heart work in rats of different age. First, the membrane receptors could couple to several different G-proteins with age-dependent expression. In this case, the selective interaction of a receptor with one or another G-protein can exert opposite effects on the second messengers and/or ionic channels. Second, there are age-relating peculiarities in the synthesis of various intracellular enzymes. It is known that the delayed consequence of α_1-AR stimulation is activation of protein kinase C, whose various isoforms are present in the heart. In addition, activation of protein kinase C is induced by diacylglycerol, which is one of the second messengers in the adrenergic system. All these factors can modulate activity of various effectors, thus determining cardiac sympathovagal modulation. The triggering mechanism leading to the age-dependent differences in the heart work under the selective blockade of α_{1A}-AR seems to be a dramatic enhancement of norepinephrine release (and, probably, neuropeptide Y) in relation to the development of sympathetic cardiac innervation during the examined stages of the postnatal ontogenesis.

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