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PHYSIOLOGY

Effect of Selective Blockade of α_{2C}-Adrenoceptors on Cardiac Activity in Growing Rats

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Selective blockade of α_{2C}-adrenoceptors had different effects on the cardiovascular system in rats of various age groups. Blockade of α_{2C}-adrenoceptors in adult rats and 3-week-old animals produced the positive and negative chronotropic effects, respectively. HR in 1-week-old and 6-week-old rats did not change during α_{2C}-adrenoceptor blockade. Selective blockade of α_{2C}-adrenoceptors in adult rats and 3-week-old animals was followed by the increase in BP. BP in 6-week-old rats was shown to decrease under these conditions.

Key Words: *cardiovascular system; chronotropism; α-adrenoceptors; rat*

α_2-Adrenergic receptors (α_2-AR) are involved in the regulation of various physiological systems [7]. Molecular and genetic studies revealed the following three subtypes of α_2-AR: α_{2A}-AR (α_{2D}-AR in the rat), α_{2B}-AR, and α_{2C}-AR [5,6,9]. It was previously hypothesized that presynaptic α_2-AR in the mammalian heart inhibiting the release of norepinephrine only modulate the regulatory influences. Recent studies showed that α_2-AR are present in vascular smooth muscles, on presynaptic membranes of adrenergic fibers, and on postsynaptic membranes of cardiomyocytes [8,11,13]. Age-related differences in the chronotropic response to α_2-AR blockade were revealed [1,2]. The dominating role of α_{2A}-AR in the regulation of the cardiovascular system was demonstrated in experiments with α_{2A}-AR gene knockout followed by HR increase [4]. The release of norepinephrine from the sympathetic nerve endings of the heart is regulated by presynaptic α_{2A}-AR and α_{2C}-AR [12], while knockout of these AR subtypes is followed by cardiac hypertrophy and heart failure due to chronic stimulation of norepinephrine release in the heart and increase in epinephrine secretion from the adrenal glands [3,10]. As differentiated from α_{2A}-AR and α_{2C}-AR, most α_{2B}-AR are located postsynaptically [12]. α_{2B}-AR are probably involved in the pathogenesis of acute coronary diseases [4]. Stimulation and blockade of α_2-AR were shown to produce a potent cardiovascular effect in adult rats [2,15].

This work was designed to study the age-dependent effect of selective α_{2C}-AR blockade on chronotropism and BP in rats during early postnatal ontogeny.

MATERIALS AND METHODS

Experiments were performed on 30 outbred rats aging 1, 3, 6, and 20 weeks. Adrenergic regulation of the heart is absent in 1-week-old rats, and only develops in 3-week-old animals. The development of sympathetic regulation of the heart is completed by the age of 6 weeks; 20-week-old rats are considered adult.

The rats were intraperitoneally narcotized with 25% urethane in a dose of 800 mg/kg. A selective α_{2C}-AR antagonist JP-1302 (Tocris) in a dose of 0.3 mg/kg was injected into the right femoral vein. ECG was continuously monitored and analyzed with a computer

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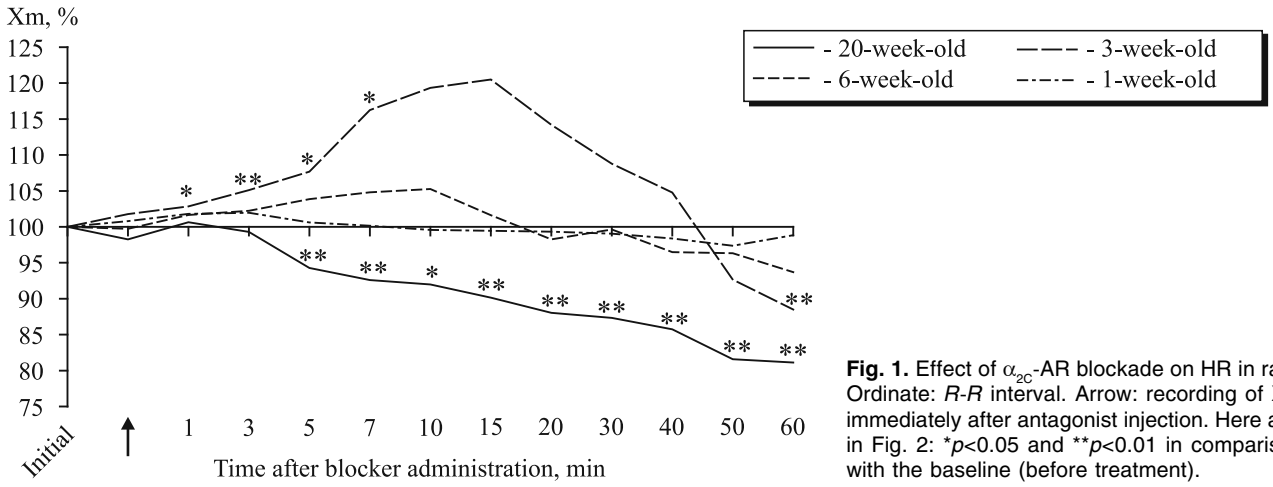

Fig. 1. Effect of α_{2C}-AR blockade on HR in rats. Ordinate: *R-R* interval. Arrow: recording of Xm immediately after antagonist injection. Here and in Fig. 2: **p*<0.05 and ***p*<0.01 in comparison with the baseline (before treatment).

system. BP was measured using a SDK-1 device for noninvasive systolic pressure measurement. The data were transmitted to a computer and analyzed by L-Graf software.

The results were analyzed statistically. The significance of differences was evaluated by Student's test and Wilcoxon's tests (Microsoft Excel software).

RESULTS

The mean *R-R* interval (Xm) decreased by 6.0±1.4% (from 190.0±12.4 to 179.0±1.2 msec; $p<0.01$) on the 5th minute after *in vivo* administration of an α_{2C}-AR antagonist JP-1302. By the 20th minute, Xm was shown to decrease by 12.0±2.1% ($p<0.01$). Xm decreased progressively in the follow-up period and was minimum by the 60th minute after antagonist injection (Fig. 1). Xm in 6-week-old rats increased insignificantly by the 10th minute of the study (by 5.0±5.2%; from 143.0±8.3 to 149.0±7.4). Xm was reduced 20 min after antagonist injection. However, the decrease in HR under these conditions was also statistically insignificant. Xm in 3-week-old rats increased by 8.0±2.8% ($p<0.05$) 5 min after antagonist injection. Xm progressively increased over 15 min after treatment, but decreased on the 60th minute of the study ($p<0.01$; Fig. 1). α_{2C}-AR blockade had no effect on Xm in 1-week-old rats (Fig. 1). Systolic BP in adult rats was shown to increase by 4.0±1.5% (from 101.0±9.8 to 106.0±9.9 mm Hg; $p<0.05$) 5 min after α_{2C}-AR blockade. The increase in BP was most significant 15 min after treatment ($p<0.05$; Fig. 2). BP in 6-week-old rats decreased by 8.0±2.1% after 5 min ($p<0.05$). BP in these animals was reduced by 87.0±3.1% on the 50th minute after treatment ($p<0.01$). Systolic BP in 3-week-old rat pups was elevated immediately after antagonist injection ($p<0.05$). BP increased most significantly by the 20th minute after treatment ($p<0.01$) and remained unchanged in the follow-up period (Fig. 2).

Our study revealed the age-dependent effect of selective α_{2C}-AR blockade on the cardiovascular system. Selective blockade of α_{2C}-AR in adult animals was

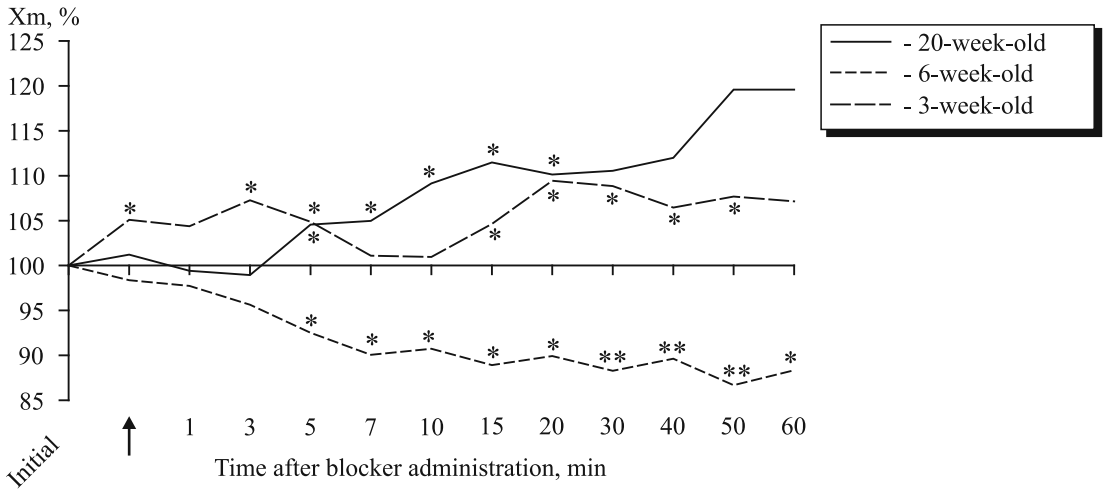

Fig. 2. Effect of α_{2C}-AR blockade on systolic BP in rats.

followed by the increase in HR and BP. Three-week-old rats were characterized by the decrease in HR and increase in BP. It should be emphasized that selective blockade of α_{2C}-AR had no chronotropic effect in newborn and 6-week-old animals. BP was shown to decrease in 6-week-old rats. α_2-AR are coupled to inhibitory Gi and Go proteins and decrease the activity of adenylate cyclase. At the same time, α_2-AR can bind to Gs proteins and increase adenylate cyclase activity [8]. Selective blockade of various subtypes of α_2-AR produces various effects, which is probably related to different localization of these receptors. We showed that α_{2C}-AR blockade has the opposite effect on chronotropic activity of the heart and systolic BP in rats, which depends on the maturity of cardiac sympathetic regulation.

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