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## THE EFFECT OF BLOCKADE OF $\alpha_{2A/D}$ -ADRENORECEPTORS ON MYOCARDIAL CONTRACTILITY IN DEVELOPING RATS

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### Abstract:

Previously, it was believed that  $\alpha_2$ -AR in the mammal heart modulate regulatory influence, by ranging presynaptically and regulating the release of norepinephrine. Currently, it is known that  $\alpha_2$ -AR are present in the smooth vascular muscles, on the presynaptic adrenergic fiber membranes, and on the postsynaptic membranes of myocardiocytes. Further investigation of the functional characteristics of  $\alpha_2$ -adrenergic receptor subtypes will help to clarify their role in the regulation of the cardiovascular system of the developing organism. We studied *in vitro* the contractile activity of the myocardium strips. The atria and ventricle strips of rats at different stages of early postnatal ontogenesis were placed in the reservoir with process solution. To solve the set problem, the process solution was added with selective blocker  $\alpha_{2A/D}$ -AR (RX 821002), at a concentration of  $10^{-5}$ ,  $10^{-6}$ ,  $10^{-7}$ ,  $10^{-8}$ ,  $10^{-9}$  mol. Contractile force (F) was stated in grams (g). The study of dose-dependent response of myocardial contractile function of the atria and ventricles in rats of different ages to the introduction of  $\alpha_{2A/D}$ -adrenergic receptor blocker in the concentration range of  $10^{-9}$ - $10^{-5}$  has shown that the blockade of the  $\alpha_{2A/D}$ -AR subtypes causes multidirectional inotropic effect in animals of different age groups. A multidirectional effect and age characteristics of the blockade  $\alpha_2$ -adrenergic receptor subtypes may be associated with changes in the synthesis, localization and activity of various receptor structures of the heart.

**Keywords:** Heart, Chronotropic effect,  $\alpha_2$ -Adrenergic receptors, a rat.

### 1. Introduction

Currently, there are nine subtypes of adrenergic receptors (AR), designated as:  $\alpha_{1A}$ -,  $\alpha_{1B}$ -,  $\alpha_{1D}$ -,  $\alpha_{2A}$ -,  $\alpha_{2B}$ -,  $\alpha_{2C}$ -,  $\beta_1$ -,  $\beta_2$ - and  $\beta_3$ -AR [1]. Various methods show the role of  $\alpha_2$ -adrenergic receptors in various physiological functions, particularly in the regulation of the cardiovascular system, and in the activity of the central nervous system. Originally, the fourth subtype was also described –  $\alpha_{2D}$ -AR. It has been also found in various animal species [2, 3].

date, it is believed that the subtypes of  $\alpha_{2A}$ - and  $\alpha_{2D}$ -AR are identical but found in different species of animals.

Humans, pigs, dogs and rabbits have  $\alpha_{2A}$ -adrenergic receptors, while rats, mice and cattle have  $\alpha_{2D}$ -AR. Therefore, these subtypes are designated in different studies as  $\alpha_{2A}$ -AR,  $\alpha_{2D}$ -AR or  $\alpha_{2A/D}$ -AR [4].

All three subtypes of  $\alpha_2$ -adrenergic receptors have been found by immunoblotting in the cardiac tissue of rats, namely in the right atrium and the left ventricle. The mRNA level of the three  $\alpha_2$ -AR subtypes found in the left and right atria and the left ventricle do not differ significantly [5]. We have detected a  $\alpha_{2A/D}$ -AR protein expression in the individual cardiomyocytes [6]. There is a maximum expression of  $\alpha_2$ -adrenergic receptors in fetal cardiac tissue of rats, though it decreases with an increasing gestational age. An indirect immunofluorescence microscopy with subtype-specific antibodies and Western blot analysis has shown the presence of  $\alpha_{2A/D}$  and  $\alpha_{2C}$  adrenergic receptors, with the exclusion of  $\alpha_{2B}$ -AR, in a population of fetal cardiomyocytes [7]. The PCR analysis has revealed in a human heart the presence of mRNA of all three subtypes of  $\alpha_2$ -adrenergic receptors [8].

Previously, it was believed that  $\alpha_2$ -AR in the mammal heart modulate regulatory influence, by ranging presynaptically and inhibiting the release of norepinephrine. Currently, it is known that  $\alpha_2$ -AR are present in the smooth vascular muscles, on the presynaptic adrenergic fiber membranes, and on the postsynaptic membranes of myocardiocytes [6, 9, 10]. Inhibiting the sympathetic regulatory effects,  $\alpha_2$ -adrenergic receptors may cause a reduction in systemic blood pressure [10]. Age-specific features of chronotropic responses to the  $\alpha_2$ -AR blockade are also shown [11, 12, 13]. We have revealed pronounced cardiovascular effects on the stimulation and blockade of  $\alpha_2$ -AR subtypes in adult rats [14, 15]. Currently, the presence and functional significance of  $\alpha_2$ -AR in human and animal heart is a subject of intensive research [1, 10, 13]. Further investigation of the role of  $\alpha_2$ -adrenergic receptor subtypes will help to clarify their value in the regulation of the cardiac functions. Objective of this research was to study the impact of the blockade of  $\alpha_{2A/D}$ -adrenergic receptors on myocardial contractility of atria and ventricles in 20-, 6-, 3- and 1-week-old rats.

## **2. Methods**

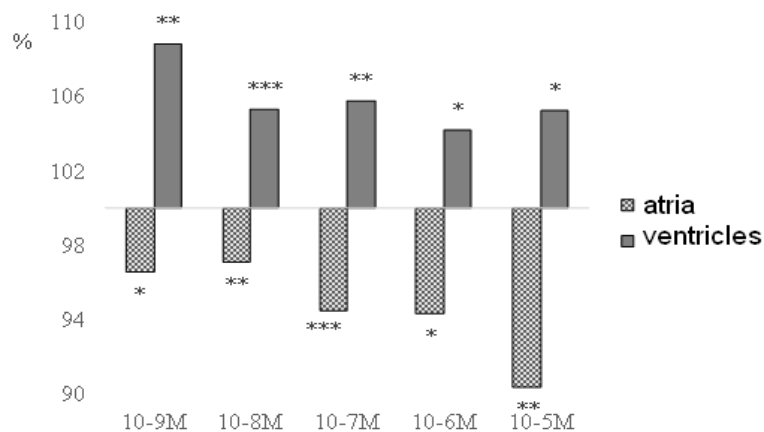
The experiments were conducted on 1-, 3-, 6-, and 20-week-old outbred rats (n=32). 1-week-old infant rats have no adrenergic regulation of the heart, which only starts developing in 3-week-old rats. Age of 6 weeks is prepubertal; at this age, the formation of the adrenergic innervation of the rat heart is completed, and 20-week-old animals are considered mature. The animals were anesthetized with 25% urethane solution (800 mg per kg intraperitoneally). We studied the contractile activity of the myocardium strips on the Power Lab (AD Instruments, Australia), using

Statgraphics software package. The rat atria and ventricle strips cut out according to anatomical structure of the heart

were placed in the reservoir with process solution. To record the contractile force of myocardium strips, the process solution was added with the selective blockers  $\alpha_{2A/D}$ -AR (RX 821002), (Tocris), at a concentration of  $10^{-5}$ ,  $10^{-6}$ ,  $10^{-7}$ ,  $10^{-8}$ ,  $10^{-9}$  mol. Contractile force (F) was stated in grams (g). Statistical analysis and identification of the reliability of differences in the results of research by Student and Wilcoxon T-test were performed in Microsoft Excel editor.

### 3. Results

In *in vitro* experiments, the  $\alpha_{2A/D}$ -AR blockade in rats aged 20 weeks caused a negative inotropic effect in the atria. A selective antagonist  $\alpha_{2A/D}$ -AR RX 821002 at a concentration of  $10^{-9}$  mol reduced the contractile force (F(g)) of the isolated atrial myocardium strips by  $3 \pm 1.36$  % ( $p < 0.05$ ) from  $0.3701 \pm 0.0706$  g to  $0.3630 \pm 0.0706$  g. The  $\alpha_{2A/D}$ -AR blocker at a concentration of  $10^{-8}$  mol reduced F(g) by  $3 \pm 0.76$ % ( $p < 0.01$ ) from  $0.4045 \pm 0.0561$  g to  $0.3953 \pm 0.0553$  g. Antagonist at a concentration of  $10^{-7}$  mol reduced F(g) by  $6 \pm 0.93$ % ( $p < 0.001$ ) from  $0.4093 \pm 0.0606$  g to  $0.3888 \pm 0.0582$  g, at a concentration of  $10^{-6}$  mol reduced F(g) by  $6 \pm 1.71$ % ( $p < 0.05$ ) from  $0.3867 \pm 0.0591$  g to  $0.3709 \pm 0.0594$  g, at a concentration of  $10^{-5}$  mol reduced F(g) by  $10 \pm 2.27$ % ( $p < 0.01$ ) from  $0.3681 \pm 0.0569$  g to  $0.3334 \pm 0.0543$  g. Blockade of the  $\alpha_{2A/D}$ -AR in the ventricular myocardium of 20-week-old rats caused positive inotropic effect. A selective antagonist  $\alpha_{2A/D}$ -AR RX 821002 at a concentration of  $10^{-9}$  mol increased the contractile force (F(g)) of the isolated ventricle myocardium strips by  $9 \pm 1.68$  % ( $p < 0.01$ ) from  $0.2661 \pm 0.0370$  g to  $0.2935 \pm 0.0452$  g. The  $\alpha_{2A/D}$ -AR blocker at a concentration of  $10^{-8}$  mol increased F(g) by  $5 \pm 0.84$ % ( $p < 0.001$ ) from  $0.2950 \pm 0.0538$  g to  $0.3099 \pm 0.0561$  g. Antagonist at a concentration of  $10^{-7}$  mol increased F(g) by  $6 \pm 1.62$ % ( $p < 0.01$ ) from  $0.2879 \pm 0.0582$  g to  $0.2999 \pm 0.0567$  g, at a concentration of  $10^{-6}$  mol - by  $4 \pm 1.44$ % ( $p < 0.05$ ) from  $0.2070 \pm 0.0192$  g to  $0.2143 \pm 0.0180$  g, at a concentration of  $10^{-5}$  mol - by  $5 \pm 1.55$ % ( $p < 0.05$ ) from  $0.2642 \pm 0.0487$  g to  $0.2750 \pm 0.0486$  g (Fig. 1).

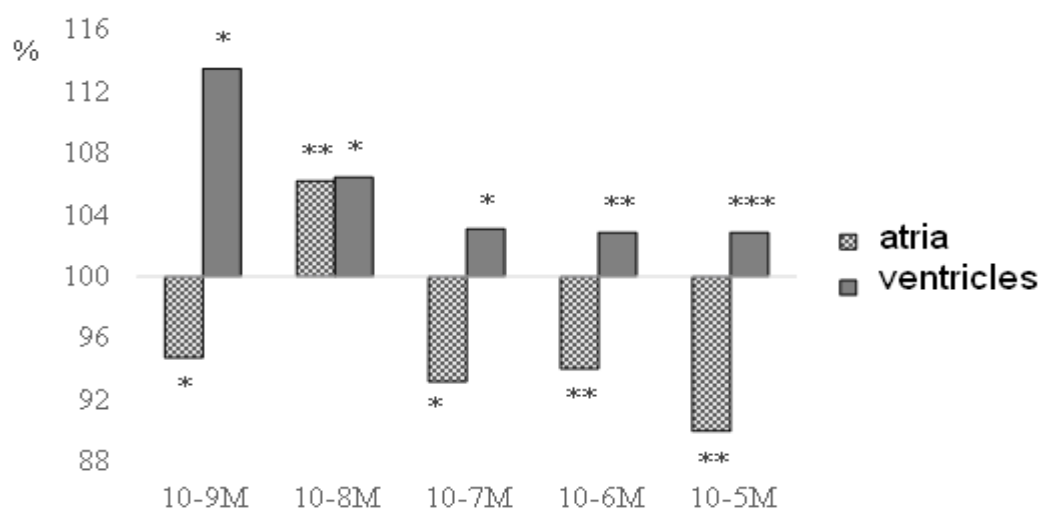


**Fig. (1).** The effect of the  $\alpha_{2A/D}$ -AR blockade on the contractile force of myocardium strips in 20-week-old rats. Y-axis – myocardium strips contractile force (F, %), X-axis – antagonist concentration (c, mol).

Note: \* - data reliability as compared with initial values:  $p < 0.05$ , \*\* - data reliability as compared with initial values:

$p < 0.01$ , \*\*\* - data reliability as compared with initial values:  $p < 0.001$

The  $\alpha_{2A/D}$ -AR blockade in 6-week-old rats caused a multidirectional effect on contractility of the strips of the atrial myocardium. A selective antagonist  $\alpha_{2A/D}$ -AR RX 821002 at a concentration of  $10^{-9}$  mol reduced the contractile force (F(g)) of the isolated atrial myocardium strips by  $5 \pm 1.72\%$  ( $p < 0.05$ ) from  $0.3165 \pm 0.0291$  g to  $0.3006 \pm 0.0277$  g. The  $\alpha_{2A/D}$ -AR blocker at a concentration of  $10^{-8}$  mol increased F(g) by  $6 \pm 1.45\%$  ( $p < 0.01$ ) from  $0.2949 \pm 0.0124$  g to  $0.3130 \pm 0.0129$  g. Antagonist at a concentration of  $10^{-7}$  mol reduced F(g) by  $7 \pm 2.40\%$  ( $p < 0.05$ ) from  $0.2478 \pm 0.0410$  g to  $0.2368 \pm 0.0412$  g, at a concentration of  $10^{-6}$  mol - by  $6 \pm 1.46\%$  ( $p < 0.01$ ) from  $0.2446 \pm 0.0443$  g to  $0.2324 \pm 0.0430$  g, at a concentration of  $10^{-5}$  mol - by  $10 \pm 2.39\%$  ( $p < 0.01$ ) from  $0.2123 \pm 0.0478$  g to  $0.1885 \pm 0.0423$  g. The  $\alpha_{2A/D}$ -AR blockade caused a positive inotropic effect upon studying the contractility of the strips of the ventricle myocardium in 6-week-old rats. A selective antagonist  $\alpha_{2A/D}$ -AR RX 821002 at a concentration of  $10^{-9}$  mol increased the contractile force (F(g)) of the isolated ventricle myocardium strips by  $13 \pm 5.12\%$  ( $p < 0.05$ ) from  $0.1965 \pm 0.0281$  g to  $0.2156 \pm 0.0272$  g. The  $\alpha_{2A/D}$ -AR blocker at a concentration of  $10^{-8}$  mol increased F(g) by  $6 \pm 1.90\%$  ( $p < 0.05$ ) from  $0.2075 \pm 0.0258$  g to  $0.2177 \pm 0.0240$  g. Antagonist at a concentration of  $10^{-7}$  mol increased F(g) by  $3 \pm 1.24\%$  ( $p < 0.05$ ) from  $0.2124 \pm 0.0213$  g to  $0.2188 \pm 0.0223$  g, at a concentration of  $10^{-6}$  mol - by  $3 \pm 0.64\%$  ( $p < 0.01$ ) from  $0.2133 \pm 0.0276$  g to  $0.2195 \pm 0.0288$  g, at a concentration of  $10^{-5}$  mol - by  $3 \pm 0.37\%$  ( $p < 0.001$ ) from  $0.2156 \pm 0.0270$  g to  $0.2222 \pm 0.0286$  g (Fig. 2).



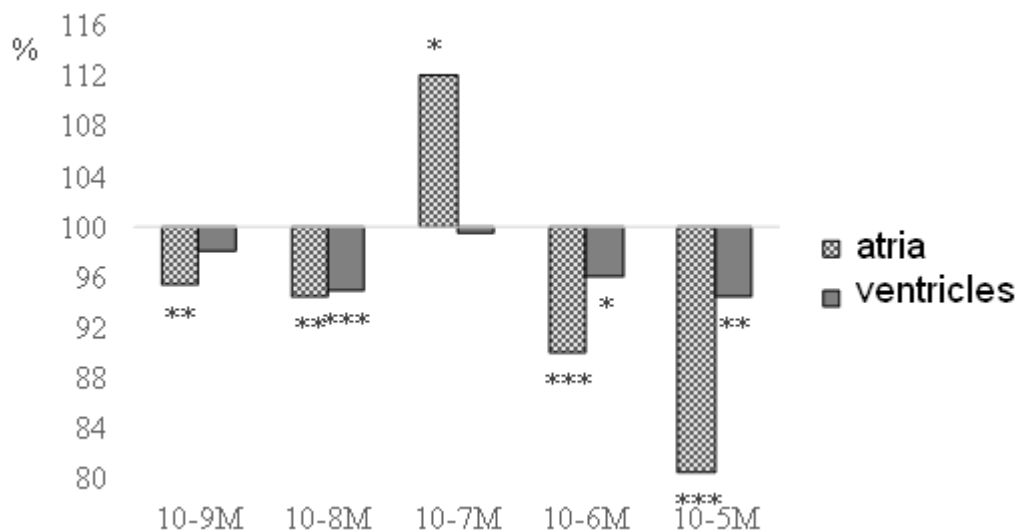
**Fig. (2).** The effect of the  $\alpha_{2A/D}$ -AR blockade on the contractile force of myocardium strips in 6-week-old rats.

**Y-axis** – myocardium strips contractile force (F, %), **X-axis** – antagonist concentration (c, mol).

Note: \* - data reliability as compared with initial values:  $p < 0.05$ , \*\* - data reliability as compared with initial values:

$p < 0.01$ , \*\*\* - data reliability as compared with initial values:  $p < 0.001$

The  $\alpha_{2A/D}$ -AR blockade in 3-week-old rats caused a multidirectional effect on contractility of the atrial myocardium. A selective antagonist  $\alpha_{2A/D}$ -AR RX 821002 at a concentration of  $10^{-9}$  mol reduced the contractile force (F(g)) of the isolated atrial myocardium strips by  $5 \pm 1.16$  % ( $p < 0.01$ ) from  $0.1293 \pm 0.0167$  g to  $0.1232 \pm 0.0162$  g. The  $\alpha_{2A/D}$ -AR blocker at a concentration of  $10^{-8}$  mol reduced F(g) by  $5 \pm 1.07$ % ( $p < 0.01$ ) from  $0.1191 \pm 0.0168$  g to  $0.1133 \pm 0.0169$  g. Antagonist at a concentration of  $10^{-7}$  mol increased F(g) by  $12 \pm 3.87$ % ( $p < 0.05$ ) from  $0.0982 \pm 0.0060$  g to  $0.1091 \pm 0.0045$  g, at a concentration of  $10^{-6}$  mol - by  $10 \pm 1.12$ % ( $p < 0.001$ ) from  $0.1029 \pm 0.0072$  g to  $0.0924 \pm 0.0061$  g, at a concentration of  $10^{-5}$  mol - by  $20 \pm 3.58$ % ( $p < 0.001$ ) from  $0.0925 \pm 0.0067$  g to  $0.0745 \pm 0.0064$  g. The  $\alpha_{2A/D}$ -AR blockade caused a negative inotropic effect on the contractility of the strips of the ventricle myocardium in 3-week-old rats. A selective antagonist  $\alpha_{2A/D}$ -AR RX 821002 at a concentration of  $10^{-9}$  and  $10^{-7}$  mol had no effect on the contractile force (F(g)) of the isolated ventricle myocardium strips (Fig. 3). The  $\alpha_{2A/D}$ -AR blocker at a concentration of  $10^{-8}$  mol reduced F(g) by  $5 \pm 0.57$ % ( $p < 0.001$ ) from  $0.2502 \pm 0.0176$  g to  $0.2378 \pm 0.0175$  g. Antagonist at a concentration of  $10^{-6}$  mol reduced F(g) by  $4 \pm 1.11$ % ( $p < 0.05$ ) from  $0.2590 \pm 0.0155$  g to  $0.2483 \pm 0.0140$  g, at a concentration of  $10^{-5}$  mol - by  $5 \pm 1.11$ % ( $p < 0.01$ ) from  $0.2846 \pm 0.0360$  g to  $0.2688 \pm 0.0334$  g (Fig. 3).



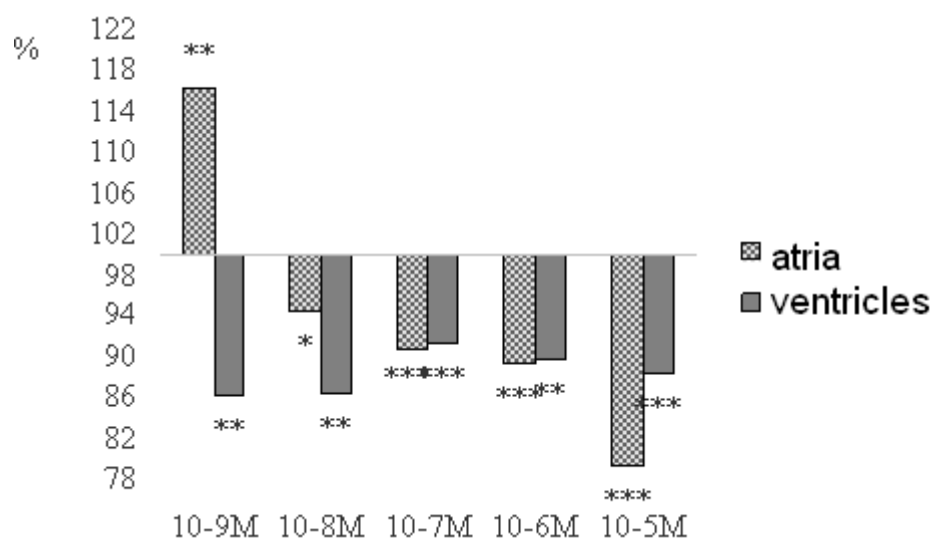
**Fig. (3).** The effect of the  $\alpha_{2A/D}$ -AR blockade on the contractile force of myocardium strips in 3-week-old rats.

**Y-axis – myocardium strips contractile force (F, %), X-axis – antagonist concentration (c, mol).**

Note: \* - data reliability as compared with initial values:  $p < 0.05$ , \*\* - data reliability as compared with initial values:  $p < 0.01$ , \*\*\* - data reliability as compared with initial values:  $p < 0.001$

The  $\alpha_{2A/D}$ -AR blockade in the atria of 1-week-old rats caused a multidirectional effect. A selective antagonist  $\alpha_{2A/D}$ -AR RX 821002 at a concentration of  $10^{-9}$  mol increased the contractile force (F(g)) of the isolated atrial myocardium strips by  $16 \pm 4.03$  % ( $p < 0.01$ ) from  $0.0481 \pm 0.0084$  g to  $0.0547 \pm 0.0087$  g. The  $\alpha_{2A/D}$ -AR blocker at a concentration of  $10^{-8}$  mol reduced F(g) by  $6 \pm 2.39$ % ( $p < 0.05$ ) from  $0.0565 \pm 0.0079$  g to  $0.0528 \pm 0.0071$  g. Antagonist at a concentration

of  $10^{-7}$  mol reduced F(g) by  $10 \pm 1.21\%$  ( $p < 0.001$ ) from  $0.0724 \pm 0.0074$  g to  $0.0656 \pm 0.0067$  g, at a concentration of  $10^{-6}$  mol - by  $11 \pm 0.13\%$  ( $p < 0.001$ ) from  $0.0717 \pm 0.0052$  g to  $0.0639 \pm 0.0047$  g, at a concentration of  $10^{-5}$  mol - by  $21 \pm 2.71\%$  ( $p < 0.001$ ) from  $0.0647 \pm 0.0064$  g to  $0.0513 \pm 0.0053$  g (Fig. 4). The  $\alpha_{2A/D}$ -AR blockade caused a negative inotropic effect in the experiments on the strips of the ventricle myocardium in 1-week-old rats. A selective antagonist  $\alpha_{2A/D}$ -AR RX 821002 at a concentration of  $10^{-9}$  mol reduced the contractile force (F(g)) of the isolated ventricle myocardium strips by  $14 \pm 3.07\%$  ( $p < 0.01$ ) from  $0.0812 \pm 0.0113$  g to  $0.0707 \pm 0.0107$  g. The  $\alpha_{2A/D}$ -AR blocker at a concentration of  $10^{-8}$  mol reduced F(g) by  $14 \pm 3.03\%$  ( $p < 0.05$ ). Antagonist at a concentration of  $10^{-7}$  mol reduced F(g) by  $9 \pm 1.07\%$  ( $p < 0.001$ ) from  $0.0648 \pm 0.0145$  g to  $0.0596 \pm 0.0138$  g, at a concentration of  $10^{-6}$  mol - by  $10 \pm 2.72\%$  ( $p < 0.01$ ) from  $0.0788 \pm 0.0162$  g to  $0.0724 \pm 0.0163$  g, at a concentration of  $10^{-5}$  mol - by  $12 \pm 1.40\%$  ( $p < 0.001$ ) from  $0.0762 \pm 0.0163$  g to  $0.0673 \pm 0.0144$  g (Fig. 4).



**Fig. (4).** The effect of the  $\alpha_{2A/D}$ -AR blockade on the contractile force of myocardium strips in 1-week-old rats.

**Y-axis** – myocardium strips contractile force (F, %), **X-axis** – antagonist concentration (c, mol).

Note: \* - data reliability as compared with initial values:  $p < 0.05$ , \*\* - data reliability as compared with initial values:  $p < 0.01$ , \*\*\* - data reliability as compared with initial values:  $p < 0.001$

#### 4. Conclusion

Thus, we have shown that the blockade of  $\alpha_{2A/D}$ -AR subtypes causes multidirectional inotropic effect on contractility of the atrial and ventricular myocardium in 20-, 6-, 3- and 1-week-old rats.

#### 5. Conclusion

The conducted studies have revealed that the selective blockade of  $\alpha_{2A/D}$ -AR affects the strength of myocardial strips contraction in all age groups of rats. The selective blockade of  $\alpha_{2A/D}$ -AR subtypes can have both positive and negative

inotropic effect. The tendency of the contractile effects upon blocking this  $\alpha_2$ -AR subtype has a distinct age-specific dependence. Age differences were observed mostly upon blocking the  $\alpha_{2A/D}$ -AR in strips of ventricular myocardium. Administration of  $\alpha_{2A/D}$ -AR blocker in 1- and 3-week-old rats caused a negative inotropic effect, more pronounced in newborn animals. Blockade of  $\alpha_{2A/D}$ -AR in strips of ventricular myocardium of 6- and 20-week-old rats caused a positive inotropic effect. Blockade of  $\alpha_{2A/D}$ -AR in atria of 1-, 3- and 6-week old rats caused multidirectional effects at different concentrations of the blocking agent. Only mature animals showed a clear dose-dependent response to the  $\alpha_{2A/D}$ -AR blockade. A multidirectional effect and age characteristics of the blockade  $\alpha_2$ -adrenergic receptor subtypes may be associated with changes in the synthesis, localization and activity of these receptor structures of the heart. It is known that  $\alpha_2$ -ARs bind to inhibitory Gi and Go proteins and reduce the adenylate cyclase activity. However, there is evidence that the  $\alpha_2$ -adrenergic receptors can bind to Gs proteins too, increasing thereby the adenylate cyclase activity. Furthermore, it is also known that activation of  $\alpha_2$ -adrenergic receptors with low concentration of agonists leads to a decrease in intracellular cAMP levels, while higher agonist concentrations increase the amount of cAMP [9].

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