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EXPERIMENTAL PAPERS

Stimulation of Alpha-2 Adrenoreceptors against the Background of Hyperpolarization-Activated Current Blockade at Different Formation Stages of Cardiac Adrenergic Innervation

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Abstract—In different periods of postnatal development, the components of the autonomic nervous system, including specific receptors and neurotransmitters involved in the control of cardiovascular functions, are characterized by significant dynamics and variability. Although in humans and animals, α_2-adrenoceptors (α_2-ARs) and the hyperpolarization-activated current (I_f) are widespread and involved in the regulation of multiple functions, their modulatory role at different stages of the formation and development of cardiac adrenergic regulation has been insufficiently studied. The present study was carried out on isolated hearts of 1-week-old, 3-week-old, and adult white rats. Heart rate (HR) and coronary flow (CF) in the Langendorff rat heart were recorded upon α_2-AR activation with clonidine hydrochloride (10^{-6} M) against the background of I_f blocker ZD7288 application at 10^{-9} M and 10^{-5} M. In 1-week-old rat pups, α_2-ARs activation evoked bidirectional changes in CF depending on I_f blocker concentration, causing its significant increase at 10^{-9} M and bidirectional dynamics at 10^{-5} M. In 3-week-old rat pups, α_2-AR stimulation reduced CF, while against the background of preliminary I_f blockade, the CF dynamics changed to positive. In adult rats, α_2-AR activation against the background of I_f blockade caused a decrease in CF. The α_2-AR agonist evoked bidirectional changes in HR in 1-week-old and adult rats, causing only a significant reduction in HR in 3-week-old rat pups. Stimulation of α_2-ARs against the background of I_f blockade did not alter the HR dynamics in 3-week-old rats and abolished bidirectional HR changes in adult and 1-week-old animals, causing only a decrease in HR in adults and an increase in HR in newborns. The obtained results demonstrate that α_2-adrenergic cardiac regulation is modulated by I_f, with the degree and direction of the effects depending on the maturity level of cardiac sympathetic innervation.

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Keywords: alpha-2 adrenergic receptor, hyperpolarization-activated current, isolated heart, ontogenesis, rat

INTRODUCTION

Heart development is a multistage process controlled by neural and humoral regulatory mechanisms. During different periods of postnatal development, the components of the autonomic nervous system, including specific receptors and neurotransmitters involved in the control of cardiovascular functions, are characterized by significant dynamics and variability [1–2]. A review of modern literature presents a wide range of results on the early formation and further development of sympathetic and parasympathetic nerve fibers in the heart [3–4]. Fluorescence microscopy does not detect sympathetic fibers in the heart tissues of rat pups during the first 21 postnatal days. The ability to uptake norepinephrine defines the functional maturity of sympathetic nerves, which is first observed on day 21 after birth, reaching the levels of mature animals by day 30 [5]. Experiments with radioactively labeled norepinephrine revealed the formation of the sympathetic nervous system on day 31 of life [5–6].

Adrenergic regulation of cardiac activity is implemented through multiple subtypes of adrenoceptors [7]. In humans and animals, α_2-adrenoceptors (α_2-ARs) are widely distributed in the central and peripheral nervous systems, autonomic ganglia, on the presynaptic membrane of adrenergic fibers and the postsynaptic membrane of cardiomyocytes, in vascular smooth muscles, as well as in the intestinal and renal epithelia [8–9]. α_2-ARs localized on presynaptic membranes are involved in modulating norepinephrine release [10], inhibiting acetylcholine release from cholinergic synapses, stimulating platelet aggregation, and vasoconstriction [11]. Activation of postsynaptic α_2-ARs in the central nervous system causes a sedative effect, inhibits sympathetic activity, and reduces blood pressure [12].

Previous studies have revealed the involvement of α_2-ARs in the regulation of cardiac performance parameters at different levels of organization of the organism. In in vivo studies, α_2-AR activation causes bradycardia and reduces systolic pressure in rats; in series of in vitro experiments, the contractility of rat ventricular myocardial strips changes bidirectionally relative to the atria [13]. In the ex vivo Langendorff (i.e. isolated perfused) heart model, α_2-AR activation reduces left ventricular (LV) pressure and causes bidirectional changes in heart rate (HR) and coronary flow (CF) [14].

Alpha-2 adrenoreceptors play a special role in the development and clinical course of cardiovascular diseases. Rats with a model of spontaneous arterial hypertension, demonstrate an increase in the expression of α_2-AR subtypes and a dysfunction thereof, as well as a reduced efficacy of associated signaling cascades [15]. The use of an α_2-AR agonist (dexmedetomidine) in hypoxia/oxygenation-induced LV dysfunction exerts a cardioprotective effect, as manifested in sympatholysis, stabilization of hemodynamics, and activation of endothelial nitric oxide synthase (eNOS) [16].

Cyclic nucleotide-dependent, hyperpolarization-activated (HCN) channels, nonselectively conducting Na^+ and K^+ ions, are blocked by millimolar concentrations of extracellular Cs^+, and are modulated by cyclic nucleotides, mainly cAMP [17]. The operation of HCN channels is based on the hyperpolarization-activated inward current, which is called the "funny current" (I_f) in the cells of the sinoatrial node of the heart and I_h in the nervous system and nerve cells [17].

Since I_f discovery and description in the 1980s by DiFrancesco et al. [17], a large number of studies have been conducted to identify the involvement of these currents in the regulation of the cardiovascular system functions in the developing organism under normal and pathological conditions [18–20]. At the early stages of embryonic development, HCN channels are abundantly expressed in all parts of the heart, while by the time of birth, their expression in working cardiomyocytes decreases and remains at a low level in adults, which is essential for preventing pathological remodeling [21]. An increased expression of HCN channels has been revealed in heart failure and after myocardial infarction [22–23]. It has been established that I_f blockade causes bradycardia and reduces CF in laboratory rats of different ages [24–26]. Inhibition of I_f affects the contractile activity of the atrial and ventricular myocardium in rats at various ontogenetic periods [27].

It has been found that I_f activity is controlled by cAMP levels and is regulated by sympathetic and parasympathetic influences of the autonomic nervous system [28]. The formation of nerve fibers plays a key role in regulating ion currents of myocardial cells and the development of cardiovascular reflexes

[29]. I_f and α_2-ARs are present in cardiomyocytes at all stages of the formation and further development of the cardiovascular system, while I_f may be an important effector of adrenergic regulation in the developing heart.

The aim of this study was to investigate the effect of α_2-AR stimulation against the background of hyperpolarization-activated current (I_f) blockade on the parameters of an isolated rat heart at different developmental stages of cardiac sympathetic innervation.

MATERIALS AND METHODS

Drugs, solutions, chemical agents. The experiments were carried out on isolated heart preparations from white outbred rats of two age groups, 1-week-old ($n = 22$) and 3-week-old ($n = 24$). In 1-week-old rat pups, cardiac sympathetic innervation is yet absent, while at the age of 3 weeks, its formation gets started [30]. Adult animals (20-week-old, $n = 24$) with a fully formed cardiovascular regulatory system were chosen as controls.

In a study on the Langendorff isolated perfused rat heart, a Krebs-Henseleit solution for warm-blooded animals of the following composition (mmol/L) was used: NaCl 118.0, KCl 4.7, $NaHCO_3$ 25.0, $MgSO_4$ 1.2, $CaCl_2$ 2.5, KH_2PO_4 1.2, glucose 5.5. The solution was saturated with carbogen (95% O_2, 5% CO_2); the pH of the solution was maintained at 7.3–7.4 at a temperature of 37°C.

To stimulate α_2-ARs, its agonist clonidine hydrochloride (Sigma-Aldrich, USA) was used at a concentration of 10^{-6} M; for I_f blockade, its blocker ZD7288 (Tocris, UK) was applied at concentrations of 10^{-9} M and 10^{-5} M. After stabilization of the isolated heart parameters, we recorded control 1, after which added ZD7288 to the perfusate, followed (after 5 min) by clonidine hydrochloride, and recorded control 2 (ZD7288). Perfusion of the isolated heart was recorded for 20 min. Different animals were used in each series of experiments. In the graphs, the values of the isolated heart parameters, recorded at the 5th min after ZD7288 addition to the perfusate, were taken as 100% (Table 1, control 2).

Preparing the Langendorff isolated perfused rat heart. Rats of both sexes were anesthetized with a 25% urethane solution (800 mg/kg body weight), and the chest was opened. The heart was isolated and flushed with an ice-cold (~2°C) working Krebs–Henseleit solution. The isolated heart was fixed by the aorta to a cannula, and oxygenated working solution was supplied in the Langendorff apparatus (ADInstruments, Australia) at a temperature of 37°C. Gravitational retrograde perfusion was performed through the aorta under a constant hydrostatic pressure of 70–75 mm Hg. To monitor HR throughout the experiment, ECG was recorded using atraumatic electrodes placed directly on the heart. Changes in CF in response to pharmacological exposures were also recorded. Signals were recorded using a PowerLab 8/35 data acquisition device (ADInstruments, Australia) and LabChart-Pro software.

Statistics. Statistical data processing was performed in MS Excel (Microsoft Corp.) and using one-way ANOVA with the *t*-test for independent variables and the *t*-test for dependent samples in Statistica 13.0 (StatSoft, Inc.). Data are presented as $M \pm SEM$. Differences were considered statistically significant at $p < 0.05$.

RESULTS

In 1-week-old rat pups ($n = 8$), the α_2-AR agonist clonidine (10^{-6} M) exerted a bidirectional effect on the HR of the isolated heart, decreasing it in some rats by 11% ($n = 4$, $p < 0.05$), while increasing it in the others by 30% ($n = 4$, $p < 0.05$, Fig. 1a). In 3-week-old rat pups, clonidine (10^{-6} M) decreased HR by 31% vs. baseline values ($n = 10$, $p < 0.01$). In control (adult) rats, α_2-AR stimulation with clonidine (10^{-6} M) caused bidirectional changes in HR: a 10% increase ($n = 4$, $p < 0.05$) and a 25% decrease ($n = 4$, $p < 0.05$) (Fig. 1a).

The α_2-AR agonist clonidine (10^{-6} M) added against the background of preliminary I_f blockade with ZD7288 (10^{-9} M) caused the following events. In 1-week-old rat pups, it increased HR from 192.4 ± 19.3 to 220.8 ± 22.8 bpm by the 5th min of the experiment. By the 15th min, HR increased to 225.8 ± 21.4 bpm ($p < 0.05$), and by the 20th min, it reached 232.9 ± 29.9 bpm ($n = 7$, $p < 0.05$) (Figs. 1b, 2b; Table 1). The overall increase in HR amounted to 20% vs. baseline values. In 3-week-old rat pups, HR decreased from 176.7 ± 17.6 to 152.9 ± 17.0 bpm ($p < 0.05$) by the 5th min of the experiment. By the 15th min, HR decreased to 145.0 ±

Table 1. Effect of α_2-adrenoreceptor stimulation against the background of I_f blockade on heart rate and coronary flow in the Langendorff heart in rats of different ages

HEART RATE

	ZD7288 (10^{-9} M) + clonidine (10^{-6})			ZD7288 (10^{-5} M) + clonidine (10^{-6})	
Age	1 week ($n = 7$)	3 weeks ($n = 7$)	adult ($n = 7$)	1 week ($n = 7$)	3 weeks ($n = 6$)
Control 1	216.4 ± 19.2	222.2 ± 24.2	181.2 ± 22.0	199.1 ± 9.5	246.6 ± 10.2
1 min	204.5 ± 15.2	199.7 ± 17.3	164.9 ± 18.7	201.4 ± 13.7	246.3 ± 10.2
5 min, control 2	192.4 ± 19.3	176.7 ± 17.6	148.0 ± 18.4	204.3 ± 14.4	218.1 ± 8.7
5 min	220.8 ± 22.8	152.9 ± 17.0*	124.3 ±2 1.2	182.2 ± 10.5	189.2 ± 10.3*
15 min	225.8 ± 21.4*	145.0 ± 18.3**	71.2 ± 16.0*	170.9 ± 11.8*	187.7 ± 13.2*
20 min	232.9 ± 29.9	142.6 ± 20.9**	70.9 ± 15.9*	170.3 ± 12.2*	184.2 ± 7.1**

CORONARY FLOW

	ZD7288 (10^{-9} M) + clonidine (10^{-6})			ZD7288 (10^{-5} M) + clonidine (10^{-6})		
Age	1 week ($n = 7$)	3 weeks ($n = 7$)	adult ($n = 7$)	1 week ($n = 7$)		3 weeks ($n = 6$)
				($n = 4$)	($n = 3$)	
Control 1	0.6 ± 0.1	1.6 ± 0.1	11.6 ± 2.2	0.9 ± 0.1	1.8 ± 0.1	1.8 ± 0.1
1 min	0.6 ± 0.1	1.5 ± 0.1	11.2 ± 2.2	0.9 ± 0.1	1.7 ± 0.1	1.7 ± 0.1
5 min, control 2	0.6 ± 0.1	1.3 ± 0.1	9.3 ± 2.1	0.8 ± 0.1	1.5 ± 0.1	1.5 ± 0.1
5 min	0.6 ± 0.1	1.3 ± 0.1	7.5 ± 1.8*	0.8 ± 0.1	1.4 ± 0.1	1.5 ± 0.1
15 min	0.7 ± 0.1	1.4 ± 0.1*	6.1 ± 1.8*	1.0 ± 0.1	1.4 ± 0.1	1.9 ± 0.1
20 min	0.8 ± 0.1*	1.5 ± 0.1**	5.8 ± 1.8**	1.0 ± 0.1*	1.3 ± 0.1*	2.1 ± 0.1***

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$—vs. baseline values (control 2); $M \pm SEM$. Control 1—control heart rate (HR) and coronary flow (CF) values before ZD7288 application. Control 2– control HR) and CF values before clonidine administration against the background of ZD7288 application.

18.3 bpm ($p < 0.01$), and by the 20th mine, it was 142.6 ± 20.9 bpm ($n = 7$, $p < 0.01$). The overall decrease in HR amounted to 19% (Figs. 1b, 2a). In adult rats, HR decreased by 52% ($n = 8$, $p < 0.01$).

The α_2-AR agonist clonidine (10^{-6} M) added against the background of preliminary I_f blockade with ZD7288 at a higher concentration (10^{-5} M) exerted the following effects. In 1-week-old rat pups, HR decreased by the 5th min of the experiment from 204.3 ± 14.4 to 182.2 ± 10.5 bpm. By the 15th min, HR decreased to 170.9 ± 11.8 bpm ($p < 0.05$). By the final (20th) minute of observation, HR was 170.3 ± 12.2 bpm ($n = 7$, $p < 0.05$ (Fig. 1c), i.e., there was an overall 15% decrease vs. baseline values. In 3-week-old rat pups, HR decreased by the 5th min of the experiment from 218.1 ± 8.7 to 189.2 ± 10.3 bpm ($p < 0.05$). At the 15th min of observation, HR decreased to 187.7 ± 13.2 bpm ($p < 0.05$). By the 20th min, HR decreased to 184.2 ± 7.1 bpm ($n = 6$, $p < 0.01$), the decrease amounted to 16% vs. baseline values. In adult rats, HR decreased by 25% ($n = 8$, $p < 0.01$) (Fig. 1c).

Coronary flow (CF) in 1-week-old rat pups ($n = 8$) changed bidirectionally upon α_2-AR activation. In some rats ($n = 5$), a slight (5%) decrease in CF was observed, while in another subset of rats ($n = 3$), CF increased by 4% vs. baseline values (Fig. 3a). In 3-week-old rat pups, CF decreased by 11% ($n = 10$, $p < 0.05$) vs. baseline values. In control (adult) rats, CF decreased by 45% ($n = 8$, $p < 0.001$) (Fig. 3a).

Activation of α_2-ARs against the background of preliminary I_f blockade with ZD7288 (10^{-9} M) altered CF

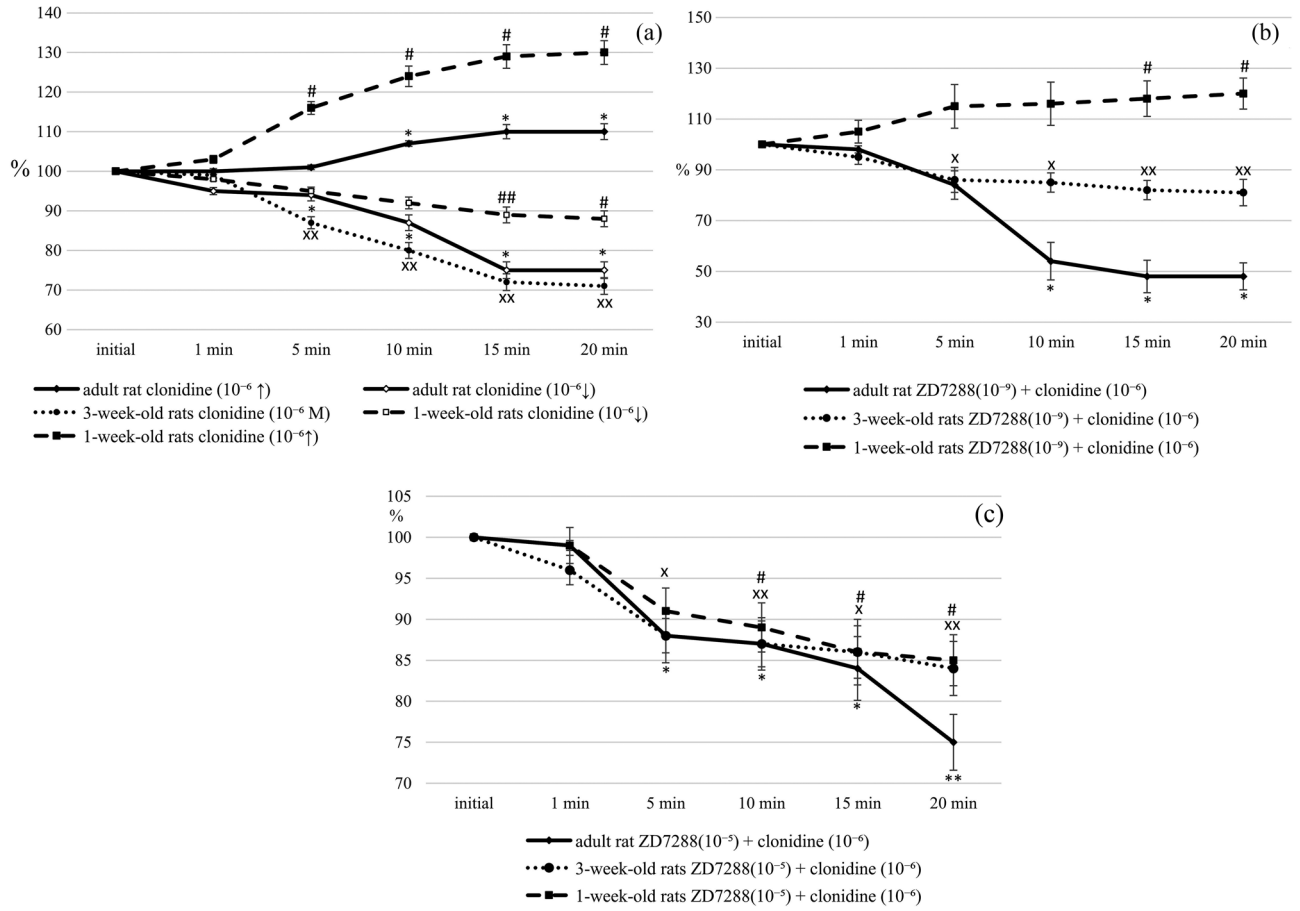

Fig. 1. Effect of α_2-adrenoreceptor stimulation with clonidine hydrochloride (10^{-6} M) alone (a) and against the background of I_f blockade with ZD7288 at concentrations of 10^{-9} M (b) and 10^{-5} M (c) on heart rate (HR) of the Langendorff heart in rats of different ages. *Ordinate*: HR (%), *abscissa*: experiment time (min). Significant differences vs. baseline values: $^{*x\#}$—$p < 0.05$; ^{**xx}—$p < 0.01$. *—Adult rats; ^{x}—3-week-old rat pups; $^{\#}$—1-week-old rat pups.

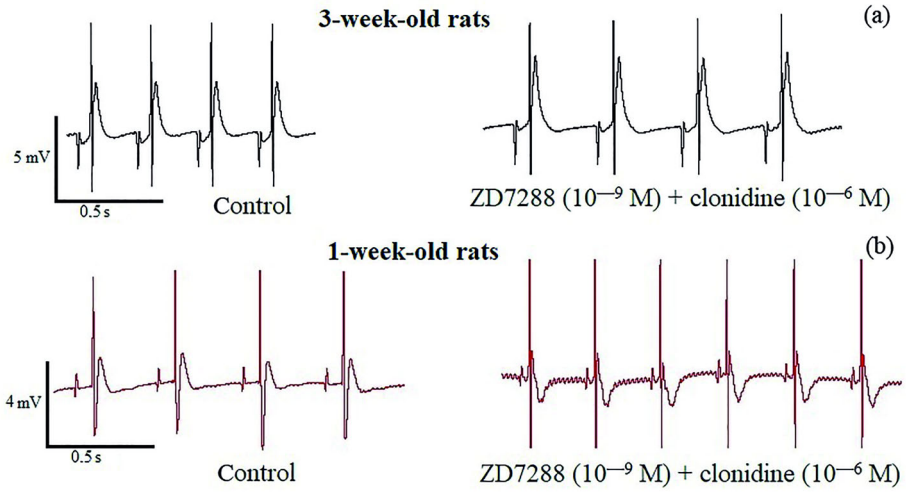

Fig. 2. Representative recordings of the Langendorff heart ECG in 3-week-old (a) and 1-week-old (b) rats in control and upon stimulation of α_2-adrenergic receptors with clonidine hydrochloride (10^{-6} M) against the background of I_f blockade with ZD7288 (10^{-9} M).

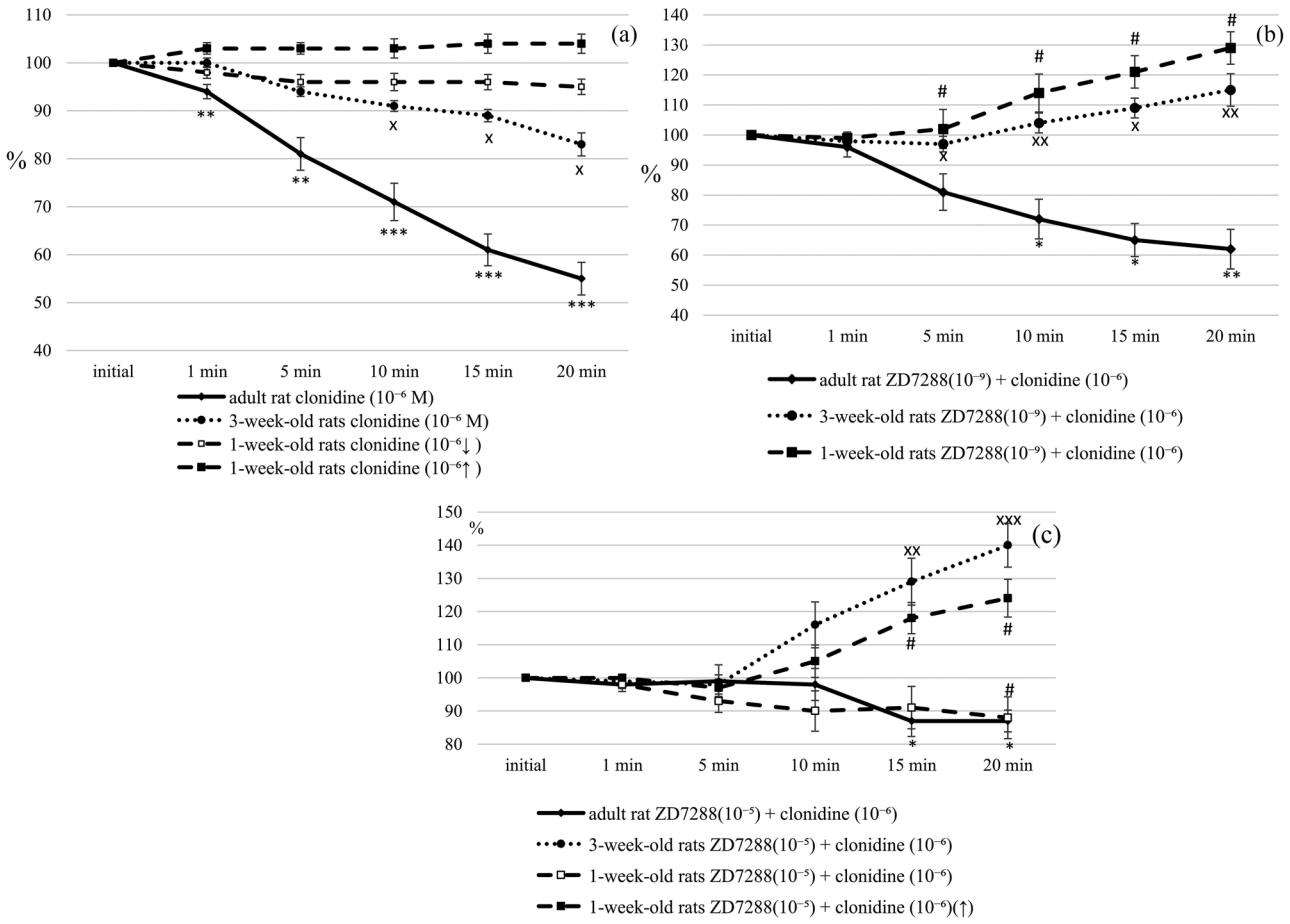

Fig. 3. Effect of α_2-adrenoreceptor stimulation with clonidine hydrochloride (10^{-6} M) alone (a) and against the background of I_f blockade with ZD7288 at concentrations of 10^{-9} M (b) and 10^{-5} M (c) on the coronary flow (CF) in the Langendorff heart in rats of different ages. *Ordinate*: CF (%), *abscissa*: experiment time (min). Significant differences vs. baseline values: $*^{X\#}$—$p < 0.05$; $**^{XX}$—$p < 0.01$. *—Adult rats; ^{X}—3-week-old rat pups; $^{\#}$—1-week-old rat pups.

in 1-week-old rat pups from 0.5 ± 0.1 to 0.6 ± 0.1 mL/min by the 5th min of observation. By the 20th min, CF increased to 0.8 ± 0.1 mL/min ($n = 7$, $p < 0.01$) (Fig. 3b). In 3-week-old rat pups, CF increased from 1.3 ± 0.1 to 1.4 ± 0.1 mL/min by the 10th min. By the 20th min of the experiment, CF increased to 1.5 ± 0.1 mL/min ($n = 7$, $p < 0.05$) (Fig. 3b). The overall change in CF amounted to 15%. In adult animals, CF decreased by 38% ($n = 8$, $p < 0.05$).

Activation of α_2-ARs against the background of preliminary I_f blockade with ZD7288 at a higher concentration (10^{-5} M) exerted a bidirectional effect on CF in 1-day-old rat pups ($n = 7$). In some of them, the baseline CF value was 0.8 ± 0.1 mL/min, while by the 10th min of observation, it increased to 0.9 ± 0.1 mL/min. Then, by the 20th min, it further increased by 24% vs. baseline values and reached 1.1 ± 0.1 mL/min ($n = 3$, $p < 0.05$). In another subset of rats, the baseline CF value was 1.5 ± 0.1 mL/min, while by the 5th minute of the experiment, it decreased to 1.4 ± 0.1 mL/min. Subsequently, CF was 1.4 ± 0.1 mL/min by the 15th min, and changed to 1.3 ± 0.1 mL/min by the 20th min ($n = 4$, $p < 0.05$) (Fig. 3c). The decrease amounted to 12% vs. baseline values. In 3-week-old rats, CF increased from 1.5 ± 0.1 to 1.9 ± 0.1 mL/min ($p < 0.01$) by the 15th min of observation. Then, by the 20th min, it increased to 2.1 ± 0.1 mL/min ($n = 6$, $p < 0.01$) (Fig. 3c). Overall, CF increased by 40% vs. baseline values. In adult animals, CF decreased by 17% ($n = 8$, $p < 0.05$).

DISCUSSION

Our study on the modeling influence of α_2-AR stimulation against the background of I_f blockade revealed changes in HR and CF dynamics during the

stages of adrenergic innervation formation in the isolated rat heart. In 3-week-old rat pups, the vasoconstriction of coronary vessels, observed during α_2-AR stimulation, changed to vasodilation upon α_2-AR stimulation with clonidine hydrochloride against the background of I_f blockade by ZD7288 (10^{-9} M, 10^{-5} M), with the most pronounced effect being observed using the blocker at a higher concentration. Apparently, the formation of adrenergic fibers and receptors during this age period is associated with active regulation of the coronary bed and the involvement of α_2-ARs located in both vascular smooth muscle and endothelial cells [31]. In 1-week-old rat pups, α_2-AR activation caused non-significant bidirectional changes in CF. Stimulation of α_2-ARs against the background of I_f blockade (ZD7288, 10^{-9} M) led to a significant increase in CF, while against the background of I_f blockade at a higher blocker concentration (ZD7288, 10^{-5} M), a bidirectional dynamic of CF changes was observed. However, the vasodilatory effect was more pronounced than the vasoconstrictor effect. Thus, α_2-adrenergic regulation of CF in the isolated rat heart depends on the maturity level of cardiac sympathetic innervation. The maximum influence of α_2-AR activation on CF was observed in adult animals, the smallest—in newborn (1-week-old) rat pups. Meanwhile, once I_f is blocked, the effect of α_2-AR stimulation in newborn and 3-week-old rat pups alters the dynamics and severity of CF changes. Probably, the regulation of the coronary vascular lumen in animals of this age requires the involvement of not only α_2-ARs but also hyperpolarization-activated currents, although their presence in coronary arteries is questionable, as currently there are data on the presence of HCN channels only in smooth muscle cells of lymphatic vessels and the portal vein [32].

The α_2-AR agonist causes bidirectional changes in HR in 1-week-old and adult rats, and only in 3-week-old rat pups, a decrease in contraction rate was observed. Stimulation of α_2-ARs against the background of I_f blockade (ZD7288, 10^{-9} M) does not change the HR dynamics in 3-week-old rats and abolishes the bidirectional HR changes in adult animals, causing a reduction in HR, while in newborn rat pups, it causes an increase in HR. Since the 3-week age is characterized by a maximum HR throughout postnatal development [24], the modeling influence of α_2-ARs through I_f is also aimed only at reducing HR and may be associated with the preliminary I_f blockade that caused bradycardia. The absence of sympatho-parasympathetic interactions in newborn animals requires the involvement of various levels of α_2-AR modulation to ensure the cardiac adaptation to changing conditions.

By the literature data, several mechanisms of interaction between α_2-ARs and HCN channels can be assumed. Clonidine hydrochloride directly inhibits I_f [32], although our experiments demonstrate significant changes in HR and CF even against the background of HCN channel blockade. On the other hand, it has been shown that α_2-AR activation via G proteins leads to the inhibition of hyperpolarization-activated currents. It is also possible that α_2-ARs may be co-associated not only with the cAMP pathway but also, in some cells, with the inositol phosphate pathway. Accordingly, Ca^{2+} release upon α_2-AR activation may also be associated with the activation of protein kinase C. Furthermore, the inhibitory effect of clonidine on hyperpolarization-activated currents is associated not with the cAMP level but with the activation of protein kinase C [33–34]. Against this background, the fact of the positive chronotropic effect of clonidine, which in newborn rat pups is not abolished even after HCN channel blockade, remains not entirely clear. Thus, the pathway of activation of a particular receptor apparently depends on cardiac metabolic requirements and the concentration of biologically active substances.

AUTHORS' CONTRIBUTION

Conceptualization and experimental design (A.M.K., N.I.Z., T.L.Z.), data collection (A.M.K., N.G.I.), data processing (A.M.K., N.G.I.), text writing and editing (A.M.K., N.I.Z., A.L.Z., T.L.Z.).

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ETHICS APPROVAL

Animal experiments were carried out in compliance with the NIH Guidelines for the care and use of

laboratory animals (http://oacu.od.nih.gov/regs/index.htm), as well as the requirements of the Basel Declaration and legal acts of the Russian Federation. Experimental protocols were approved by the Ethics Committee of Sechenov Institute of Evolutionary Physiology and Biochemistry of Kazan (Volga Region) Federal University (Minutes no. 39 of December 22, 2022).

CONFLICT OF INTEREST

The authors of this work declare that they have no conflicts of interest.

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