PHYSIOLOGY

Inotropic Effect of Dopamine on Rat Heart during Postnatal Ontogeny

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We studied the effect of dopamine in concentrations of 10^{-9}, 10^{-8}, 10^{-7}, 10^{-6}, and 10^{-5} M on contraction strength of isolated myocardial strips from the right atrium and right ventricle of rats aging 21, 42, 56, and 100 days. Dopamine in a concentration of 10^{-9} M had a positive inotropic effect in rats of various ages. Increasing the concentration of dopamine to 10^{-7}-10^{-5} M was accompanied by a negative inotropic effect on the heart.

Key Words: *dopamine; dopamine receptors; myocardium; rat; contractility*

Dopamine is known as the major neurotransmitter in CNS and a hormone secreted by the adrenal medulla. It also acts as a chemical intrinsic reinforcement factor. This substance is involved in the regulation of motor activity, endocrine functions, emotions, and thinking in humans [14]. Moreover, dopamine plays a role in the pathogenesis of various diseases, including Parkinson's disease, schizophrenia, pathological aggressiveness, and hyperactive affective disorder in children [1].

Dopamine serves as the inhibitory transmitter in the carotid sinus and sympathetic ganglia. The results of some studies suggest the existence of a particular peripheral dopaminergic system. Dopamine was found in the sympathetic ganglia, nerves, and heart. It should be emphasized that the intensity of dopamine secretion is 10-20 times higher than that of epinephrine and norepinephrine [11].

Five subtypes of dopamine receptors identified by now (D1, D2, D3, D4, and D5) are divided into the following two families: D1-like receptors (D1 and D5 receptors) [2] and D2-like receptors (D2, D3, and D4 receptors) [5].

D1-like dopamine receptors are coupled with adenylate cyclase and stimulate phospholipase C in a cAMP-independent manner [5]. D2-like receptors are not coupled with adenylate cyclase and inhibit Ca^{2+} channels [7,12].

D1 receptors are located in the cytolemma of arterial smooth muscle cells in various organs, including the coronary arteries. D1 receptors in the heart of rats and humans were detected by biomolecular methods [13]. D2 receptors in the arterial wall are located in sympathetic postganglionic endings and inhibit the release of catecholamines [2,8]. In mammalian and human heart, D2-like receptors (subtype D4 receptors) are mainly localized in endings of sympathetic and parasympathetic postganglionic neurons and primarily in the atria [3,5,7]. The concentration of D2-like receptors in the rat atrium is higher than in the human atrium [4,13].

The effect of dopamine on the heart in low concentration is mediated via dopamine receptors [5] and in high concentration via α- and β-adrenoceptors [6]. Dopamine in low concentrations causes a positive chronotropic and inotropic effect realized via D1-like

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receptors [10]. A negative effect of dopamine can be mediated by D2-like receptors [9]. Dopamine in intermediate concentrations stimulates β1-adrenoceptors, which is accompanied by an increase in the cardiac output. Dopamine in high concentrations stimulates α-adrenoceptors and causes BP increase [9].

Despite ample data on the presence of dopamine receptors in the heart, their physiological role in various age periods remains unknown.

Here we studied the effect of dopamine in various concentrations on myocardial contractility of the right atrium and right ventricle in rats during postnatal ontogeny.

MATERIALS AND METHODS

In vitro experiments were performed on albino rats aging 21, 42, 56, and 100 days. The study was conducted in accordance with bioethical regulations. Each age group consisted of 5-8 rats. Isometric contraction of myocardial strips from the right atrium and right ventricle was recorded on a Power Lab device (ADInstruments) equipped with a MLT 050/D force transducer (ADInstruments). The hearts were rapidly removed from urethane-narcotized rats (1200 mg/kg) and placed in Petri dishes with oxygenated working solution. An ESL-2 stimulator was turned on. Myocardial strips (length 2-3 mm, diameter 0.8-1.0 mm) were prepared from the right atrium and right ventricle. The upper end of strips was attached to a force sensor with a thread and the lower end of strips was fixed to a unit. Each preparation was immersed into an individual reservoir (10 ml); working solution and carbogen (95% O_2 and 5% CO_2) were delivered through each reservoir at 28°C. The working solution contained 8 g/liter NaCl, 0.3 g/liter KCl, 3 ml/liter $CaCl_2$, 5 ml/liter $MgSO_4$, 0.04 g/liter NaH_2PO_4, and 2 g/liter glucose; pH was maintained at 7.4 with basic and acid Trizma HCl buffers (2.4-3.9 g/liter; all reagents were from Sigma). Myocardial strips were stimulated via platinum electrodes with 5-msec pulses at a frequency of 6 stimuli (for rats aging 42, 56, and 100 days) or 10 stimuli (for rats aging 21 days).

The curve was recorded on a personal computer using Chart 5.0 software. After a 30-40-min stabilization period, baseline contraction parameters were recorded over 10 min; then, dopamine (10^{-9}-10^{-5} M; Sigma) was added to the working solution and contractions were recorded over 20 min. After stimulation with dopamine, the samples were washed with working solution (3×5 min). The baseline parameters were then recorded for each subsequent dose. The strength of contraction was expressed in grams. The reaction to dopamine was calculated in percents of the baseline (taken as 100%).

TABLE 1. Effect of Dopamine in Various Concentrations on Contraction Strength (g) in the Atria and Ventricles in Rats during Postnatal Ontogeny

Age of animals, days		Concentration of exogenous dopamine, M									
		10^{-5}		10^{-6}		10^{-7}		10^{-8}		10^{-9}	
		baseline	after treatment	baseline	after treatment	baseline	after treatment	baseline	after treatment	baseline	after treatment
21	atrium	0.218±0.085	0.187±0.052*	0.179±0.010	0.166±0.010*	0.503±0.269	0.474±0.235	0.175±0.014	0.159±0.012*	0.454±0.074	0.512±0.084*
	ventricle	0.300±0.046	0.267±0.041*	0.368±0.033	0.351±0.033*	0.488±0.083	0.451±0.102	0.458±0.126	0.478±0.120	0.701±0.494	0.740±0.495*
42	atrium	0.391±0.075	0.363±0.072*	0.550±0.063	0.509±0.069*	0.596±0.097	0.558±0.097*	0.598±0.139	0.570±0.136*	0.692±0.156	0.745±0.167*
	ventricle	0.795±0.351	0.759±0.350*	0.705±0.180	0.641±0.164*	0.777±0.334	0.737±0.337*	0.499±0.137	0.525±0.129*	1.081±0.180	1.199±0.182*
56	atrium	0.292±0.076	0.277±0.075*	0.450±0.082	0.399±0.078*	0.572±0.159	0.520±0.145*	0.636±0.100	0.604±0.098*	0.660±0.157	0.732±0.173*
	ventricle	0.476±0.114	0.453±0.115*	0.424±0.120	0.391±0.112*	0.503±0.141	0.456±0.138*	0.948±0.159	0.855±0.150*	0.800±0.251	0.863±0.266*
100	atrium	1.023±0.369	0.966±0.343*	0.318±0.073	0.301±0.070*	0.301±0.138	0.291±0.135	0.303±0.079	0.298±0.079*	0.827±0.218	0.896±0.243*
	ventricle	0.642±0.230	0.601±0.214*	0.176±0.031	0.158±0.030*	0.195±0.022	0.187±0.023*	0.230±0.064	0.235±0.065*	1.136±0.249	1.266±0.272*

Note. *$p<0.05$ in comparison with the baseline.

The results were analyzed with the calculation of M, m, and σ. The significance of differences was evaluated by Student's t test ($p<0.05$).

RESULTS

In 21-day-old rats, dopamine in a concentration of 10^{-9} M had a positive inotropic effect on atrial and ventricular myocardium. The strength of contractions was shown to increase by 13.14 ($p<0.05$) and 7.43% ($p<0.05$) for the atria and ventricles, respectively (Fig. 1, *a*; Table 1). Dopamine in a concentration of 10^{-8} M caused the opposite changes in myocardial contractility of the atria and ventricles. The strength of myocardial contractions decreased in the atria (by 9.18%, $p<0.05$), but increased in the ventricles (by 6.93%). Further increase in dopamine concentration to 10^{-7}, 10^{-6}, and 10^{-5} M produced only a negative inotropic effect on the myocardium: the contraction strength decreased in the atria by 5.63, 8.63, and 10.72%, respectively, and in ventricles by 10.68, 5.53, and 13.02%, respectively ($p<0.05$; Fig. 1, *a*).

In 42-day-old rats, dopamine in a concentration of 10^{-9} M had a positive inotropic effect on the atria (8.55%) and ventricles (10.27%) ($p<0.05$; Fig. 1, *b*). After addition of 10^{-8} M dopamine, the positive reaction remained in ventricles, while contractility of the atria decreased by 5.10% ($p<0.05$). Dopamine in concentrations of 10^{-7}, 10^{-6}, and 10^{-5} M significantly decreased the strength of contractions in the atria (by 7.40, 8.23, and 6.93%, respectively) and ventricles (by 7.15, 9.44, and 7.95%, respectively; Fig. 1, *b*).

In 56-day-old rats, dopamine in a concentration of 10^{-9} M increased the strength of contractions in the atria and ventricles from (by 9.41 and 8.00%, respectively). Dopamine in other concentrations produced the same effect, which manifested in a decrease in the strength of myocardial contractions in the atria and

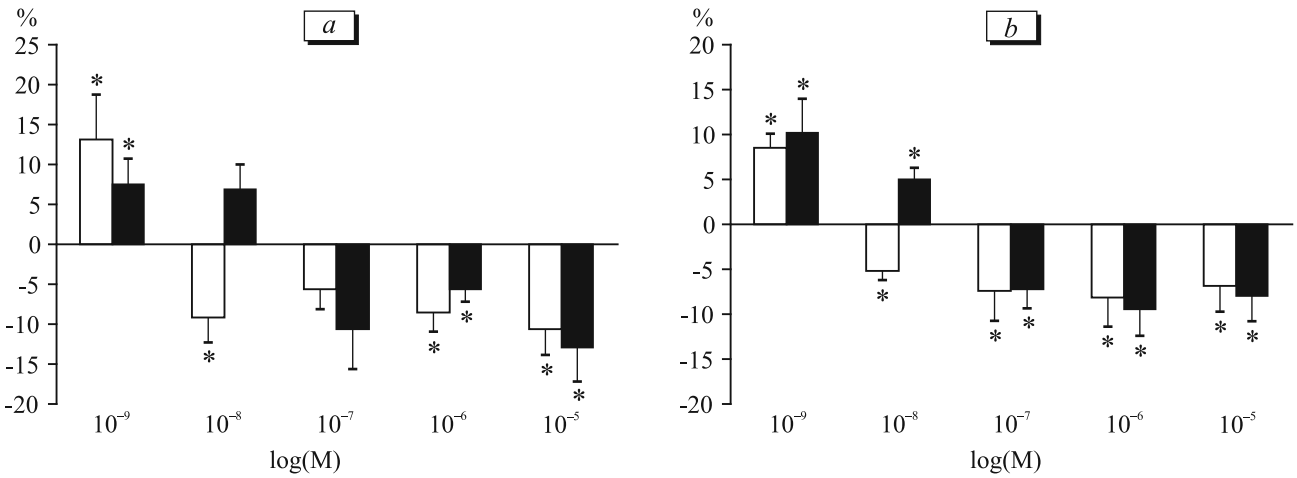

Fig. 1. Effect of dopamine in various doses on myocardial contraction strength in the atria (light bars) and ventricles (dark bars) of rats aging 21 (*a*) and 42 days (*b*). Here and in Fig. 2: *$p<0.05$ in comparison with the baseline.

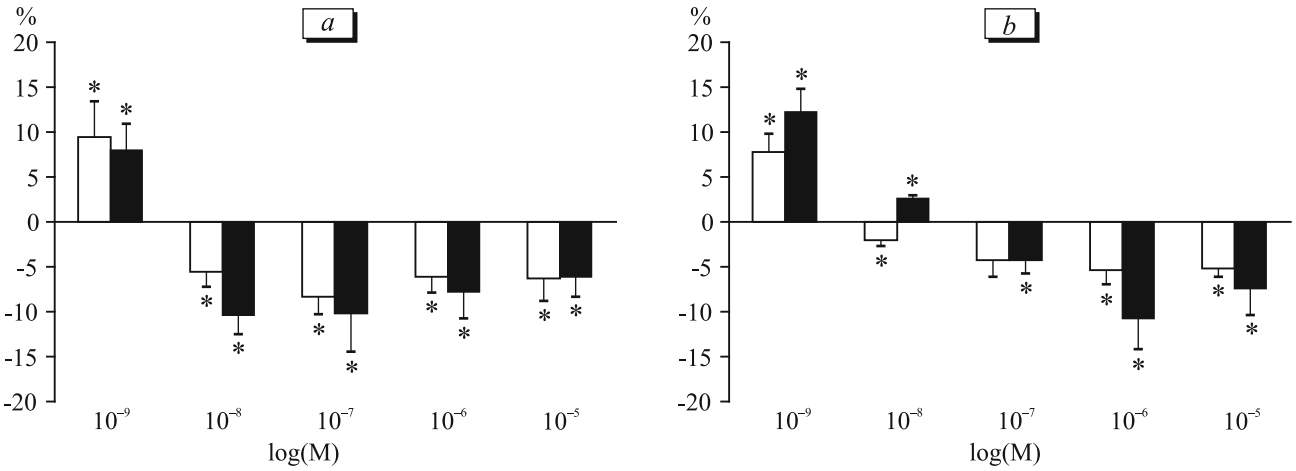

Fig. 2. Myocardial contraction strength in the atria (light bars) and ventricles (dark bars) of rats aging 56 (*a*) and 100 days (*b*) in response to treatment with dopamine in various doses.

ventricles (Fig. 2, *a*). The most significant negative reaction was observed in ventricles after treatment with dopamine in concentrations of 10^{-8}, 10^{-7}, 10^{-6}, and 10^{-5} M.

In 100-day-old rats, the maximum on effect on myocardial contractility was observed at dopamine concentration of 10^{-9} M: the contraction strength increased by 7.83 and 12.23% for atrial and ventricular strips, respectively ($p<0.05$, Fig. 2, *b*). Increasing dopamine concentration resulted in suppression myocardial contractility. For example, dopamine in a concentration of 10^{-8} M produced opposite effects: decreased contraction strength of atrial myocardial strips by 2.03% and increased contractility of ventricular strips by 2.63%, ($p<0.05$). Dopamine in concentrations of 10^{-7}, 10^{-6}, and 10^{-5} M decreased the strength of myocardial contractions by 4-10% (Fig. 2, *b*; Table 1).

Our results indicate that exogenous dopamine has a dose-dependent inotropic effect on the rat heart. The positive inotropic effect of dopamine in a concentration of 10^{-9} M in animals of all age groups is probably realized via dopamine receptors [5]. It should be emphasized that the atrial myocardial response to dopamine in rats aging 21 and 56 days is more pronounced than in animals aging 42 and 100 days. Dopamine in higher concentrations (10^{-7}, 10^{-6}, and 10^{-5} M) has a strong negative inotropic effect. The negative response was most pronounced in the ventricles (Figs. 1 and 2). We conclude that the involvement of dopamine receptors and adrenoceptors in the regulation of cardiac activity depends on the dose of a substance and age of animals.

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