GENERAL PATHOLOGY AND PATHOLOGICAL PHYSIOLOGY

Stimulation of Vagus Nerve Modifies Negative Chronotropic and Hypotensive Effects of Adenosine

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The effects of electrical stimulation of the vagus nerve on the negative chronotropic and hypotensive effects of adenosine were studied on adult rats. Intravenous injection of adenosine to control rats significantly reduced the heart rate and induced a transient blood pressure drop followed its increase. Preliminary electrical stimulation of the right vagus nerve reduced the magnitude and duration of adenosine-induced bradycardia and changed the dynamics of adenosine-induced arterial pressure perturbations.

Key Words: *heart; adenosine; vagus nerve; arterial pressure; rat*

Purine agents are involved in the regulation of cardiovascular activity [4]. Adenosine is a basic transmitter of the purinergic system [2]. The effect of adenosine is mediated via adenosine receptors on intra- and extracardiac neurons, cardiomyocytes, and endothelial and smooth muscle cells [9,14]. Activation of these receptors modulates function of acetylcholine- and ATP-dependent K^+-channels [6,8,11]. Adenosine regulates slow Ca^{2+} current via modulation of the adenylate cyclase—cAMP system [3,7]. These mechanisms underlie the vasodilator and negative chrono-, dromo- and inotropic effects of adenosine [1].

Adenosine can affect the cardiac functions by tuning activity of the sympathetic and parasympathetic systems at the presynaptic and postsynaptic levels [1,2]. The presynaptic effects of adenosine are realized via inhibition of norepinephrine and acetylcholine release [10,12]. The postsynaptic effects of adenosine can result from either direct activation of acetylcholine-dependent K^+-channels coupled to M_2 muscarinic and A_1 adenosine receptors via G-proteins or indirect cAMP-dependent inhibition of adenylate cyclase coupled to β-adrenergic receptors and A_1-adenosine receptors.

Our aim was to study the effect of electrical stimulation of the vagus nerve (VN) on the cardiovascular effects of adenosine.

MATERIALS AND METHODS

The study was carried out on random-bred albino rats (n=14). The rats were anesthetized with intraperitoneal urethane (1 g/kg, 25% solution). A single bolus of adenosine (0.25 mg/kg in 0.05 ml) was injected into the femoral vein. In rats adenosine was applied 5 min after vagal stimulation (group 1, n=7) or without preliminary vagal stimulation (group 2, n=7).

The right VN was isolated under a microscope and lifted on ligatures. Vagal stimulation was performed with an ESL-2 stimulator (5 V pulse amplitude, 10-12 msec pulse duration, 0.2-0.4 msec delay, and 0.7-10 Hz repetition rate). The stimulation parameters were chosen individually for each animal and remained constant throughout the experiment. Stimulation was carried out over 100 cardiac intervals.

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Blood pressure (BP) was continuously recorded via a catheter passed through the right femoral artery. ECG and BP signals were recorded and processed with a computer. Original software yielded 28 parameters of ECG and variational pulsogram as well as the value of BP.

The results were analyzed statistically using Student's *t* and Wilcoxon tests.

RESULTS

During the first minutes postinjection, adenosine provoked the most pronounced bradycardia. To second 5 postinjection, the mean cardiac interval (X_m) increased from 170.2±6.0 to 532±68 msec ($p \leq 0.01$, Fig. 1, *a*). The dynamics of variational pulsogram attested to a shift in autonomic homeostasis towards parasympathetic influences. To minute 1 and 2 postinjection, X_m decreased to 197±14 and 189±12 msec, respectively. X_m and parameters of variational pulsogram returned to normal by minute 15 postinjection (X_m=170.0±5.8 msec). The maximum hypotensive effect was observed on second 5 postinjection, when BP dropped from 87.0±0.8 to 62.0±7.3 mm Hg ($p \leq 0.05$, Fig. 1, *b*). After 40 sec BP increased to 91.0±4.2 mm Hg, and over the following 15 min increased insignificantly to 92.0±3.1 mm Hg. BP returned to the baseline 60 min after adenosine injection.

Preliminary vagal stimulation significantly moderated adenosine-induced bradycardia. On second 10 postinjection, X_m increased from 147.0±5.3 to 182±14 msec ($p \leq 0.05$, Fig. 1, *a*). To this moment, BP dropped from 76.0±2.1 to 65.6±6.7 mm Hg (Fig. 1, *b*). Then X_m rapidly decreased to 160.0±9.2 and 150.0±4.2 msec on second 20 and minute 3, respectively. BP increased to 91.0±8.1 msec to second 40 postinjection, but then dropped to 67.0±3.4 and 57.0±6.1 mm Hg to second 60 and minute 15, respectively (Fig. 1, *b*).

Therefore, exogenous adenosine significantly decreased the heart rate in rats. At the same time, hypotensive effect of adenosine was short-lasting and was followed by a BP rise, which probably is a response to initial drastic BP drop. Adenosine infused after activation of the parasympathetic system via electrical stimulation of the right VN reduced the degree and duration of bradycardia. Repeated vagal stimulation applied every 5 min to control rats did not moderate bradycardia. Preliminary vagal stimulation changed the timeline of BP variations induced by adenosine. The initial drop in BP was followed by a short-term rise and then by the second drop. In this case, BP did not return to the baseline value. These findings indicate peculiarities of cholinergic and purinergic mechanisms regulating the chronotropic parameters of the heart and BP.

The observed partial inhibition of the effects of adenosine after preliminary vagal stimulation can be explained from different viewpoints. First, this effect has common features with cardiac escape from vagal influences. However, in our experiments it was induced by long-term vagal stimulation, whose duration was constant and corresponded to 100 cardiac intervals. In control experiments, repeated stimulation of the right VN induced significant bradycardia.

Second, it is known that during long-term stimulation of the right VN the sinoatrial node partially escapes from vagal influences. Therefore, partial inhibition of adenosine-induced bradycardia after preliminary vagal stimulation can be explained by competitive action of acetylcholine and adenosine on postsynaptic structures determining parameters of pacemaker activity. It is known that stimulation of M_2 muscarinic and A_1 adenosine receptors produces similar effects on

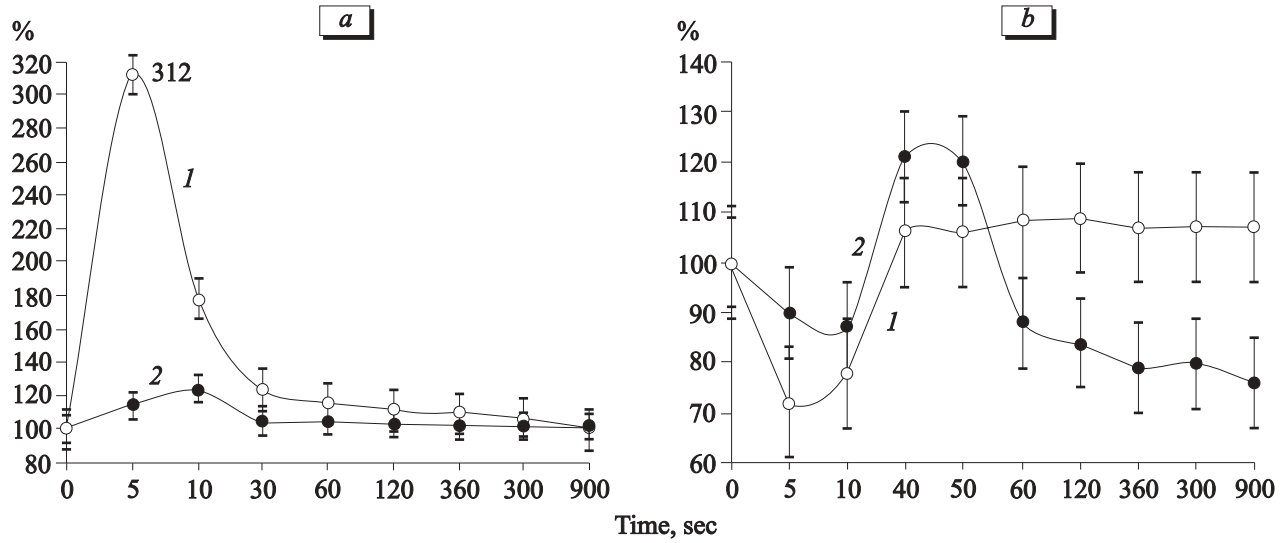

Fig. 1. Effect of adenosine on *R-R* interval (*a*) and arterial pressure (*b*) without preliminary vagal stimulation (1) and after vagal stimulation (*2*).

the second messengers system via G-proteins and guanosine triphosphatase, which finally leads to activation of acetylcholine-dependent K^+ channels thereby exerting direct and cAMP-independent action on the myocardium. An indirect argument in favor of the second hypothesis is long interval (5 min) between preliminary vagal stimulation and adenosine injection in this study.

Thus, our findings can be explained by identical biochemical reactions induced by acetylcholine and adenosine in the atria and conducting system, which finally determine the negative chrono- and dromotropic effects of these agents on the heart.

The problem of adenosine action on autonomic regulation of cardiac functions has important practical implications, since apart from adreno- and cholinotropic agents, adenosine preparations are now widely used in cardiology. Combined use of these drugs can produce unwanted side effects such as extrasystole, atrial flutter, and ventricular tachycardia [5,13].

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