PHYSIOLOGY

NO-Dependent Mechanism of Adrenergic Reaction of Systemic Hemodynamics

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Blockade of NO synthesis in narcotized rats potentiated pressor effects of phenylephrine by 55% and increased total peripheral resistance by 153%. Vasodilation caused by enhanced NO secretion modulated pressor shifts evoked by stimulation of α_1-adrenoceptors with phenylephrine.

Key Words: *blood pressure; phenylephrine; blockade of NO synthesis*

Endothelial secretion of NO, which is a chemical basis of endothelium-derived relaxation factor [9] is an important mechanisms of vascular tone regulation [2,8, 10]. Elevation of NO release is induced by mechanical stimuli increasing shear stress on the internal surface of the vascular wall (changes in pulse amplitude, blood pressure (BP) and blood flow velocity) and inducing vasodilation [1,2,8,11]. This agrees with the fact that blockade of NO-synthase results in vasoconstriction and arterial hypertension [2] and confirms the involvement of NO into the regulation of not only regional, but also systemic circulation. We proved participation of the NO-dependent mechanism in the development of the response of systemic hemodynamics to increased volume of circulating blood and orthostasis in rats [4].

Our aim was to elucidate the role of NO in the development of response of systemic hemodynamics (changes in BP, cardiac output, and total peripheral resistance) triggered by stimulation of postsynaptic α_1-adrenoceptors. Activation of these receptors in vascular smooth muscles agonists induces vasoconstriction [5].

The examined reactions of systemic hemodynamics could be considered as a model of functioning of the cardiovascular system under conditions adrenergic stimulation (injection of adrenomimetics, stimulation of various subdivisions of sympathetic system, *etc*.). The involvement of endothelial NO-dependent mechanism into the development of systemic vasoconstrictor reactions to physiological stimuli is little studied.

MATERIALS AND METHODS

The experiments were carried out on mature male Wistar rats (220-340 g) narcotized with urethane (1.2-1.5 g/kg) and injected with heparin (500 U/kg). The rats were ventilated with a Vita apparatus. BP was recorded in the femoral artery with a PDP-400 transducer. BP signal was digitized and analyzed on-line. During the experiments, systolic, diastolic and mean BP were calculated and printed. Cardiac output was measured with RKE-2 electromagnetic flowmeter connected to a transducer (diameter 2 mm) placed on the ascending aorta. The signal was recorded on an H-3021 ink-pen recorder. The total peripheral resistance was calculated as mean BP divided by cardiac output measured in the same time interval.

α_1-Adrenoceptor agonist phenylephrine (mezaton) was injected into the femoral vein in concentration of 10^{-8} mg/ml (0.1 ml per 100 g body weight).

NO-synthase was blocked with N^{ω}-nitro-L-arginine methyl ester (L-NAME) injected into femoral

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vein (2 mg/100 g body weight). Phenylephrine was injected 15 min after L-NAME.

The data were processed statistically using standard software and Student's *t* test.

RESULTS

The experiments were carried out on 6 rats. Initially, BP and mean cardiac output were 102.5±7.6 mm Hg and 80.6±8.8 ml/min, respectively (Table 1, Fig. 1).

Injection of phenylephrine under conditions of NO-synthase blockade significantly increased BP and the total peripheral resistance by 55% and 153%, respectively.

Phenylephrine administered before and after blockade of NO synthesis increased mean BP by 32% and 59%, respectively. The corresponding values for the total peripheral resistance were 24 and 52%. Therefore, blockade of NO synthesis and subsequent decrease in its release in response to endothelium-related events are the major phenomena underlying changes in the examined cardiovascular reactions during blockade of NO-synthase.

Potentiation of the pressor effects of phenylephrine under conditions of NO-synthase blockade is a manifestation of vasodilator mechanism caused by enhanced NO release triggered by stimulation of α_1-adrenoceptors. Therefore, changes in the baseline release of NO caused by stimulation of α_1-adrenoceptors observed in local vascular reactions [14] can be an important factor regulating systemic circulation.

Stimulation of α_1-adrenoceptors in isolated arterioles increases Ca^{2+} concentration in endotheliocytes, which increases NO synthesis and induces vasodilation. Inhibition of NO synthesis augments contractile responses of arterioles [14].

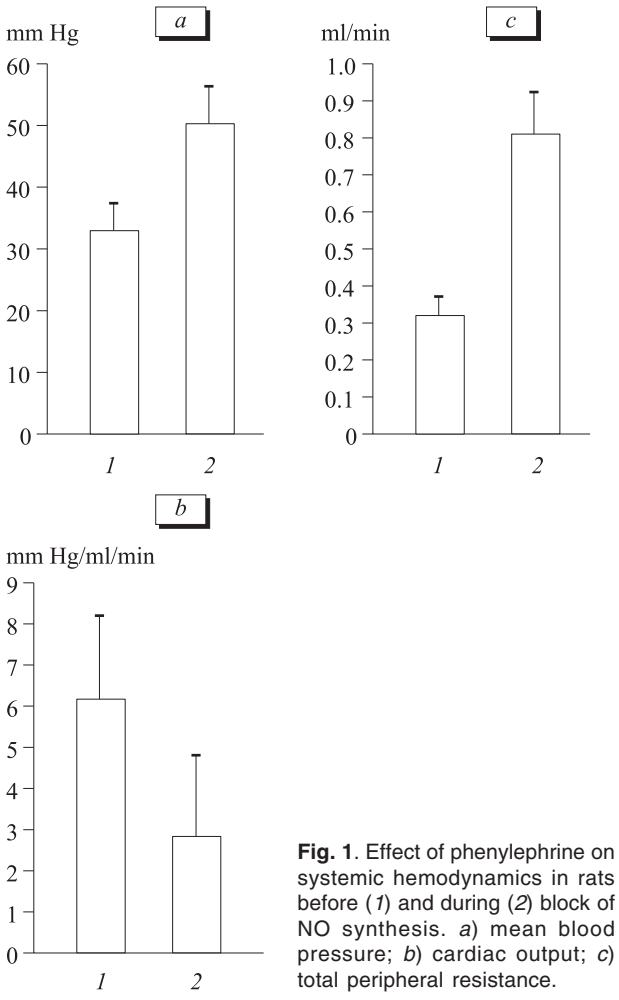

Fig. 1. Effect of phenylephrine on systemic hemodynamics in rats before (*1*) and during (*2*) block of NO synthesis. *a*) mean blood pressure; *b*) cardiac output; *c*) total peripheral resistance.

It is known that stimulation of α_1-adrenoceptors with phenylephrine up-regulates endothelial secretion of NO in isolated rat arterioles [7]. Norepinephrine

TABLE 1. Effect of NO Synthase Blockade on Responses of Systemic Hemodynamics to Phenylephrine (*M*±*m*)

Parameter	Initial value	After phenylephrine
Before block		
mean pressure, mm Hg	102.5±7.6	32.9±3.7
systolic pressure, mm Hg	123.8±8.0	35.6±3.3
diastolic pressure, mm Hg	83.3±12.3	32.7±4.1
cardiac output, ml/min	80.7±8.8	6.2±2.1
total peripheral resistance, mm Hg/ml/min	1.30±0.08	0.32±0.05
During block		
mean pressure, mm Hg	85.3±3.3	50.3±5.5*
systolic pressure, mm Hg	97.9±4.9*	44.5±9.1
diastolic pressure, mm Hg	75.2±2.8	48.8±6.0*
cardiac output, ml/min	62.7±9.6	2.8±1.9
total peripheral resistance, mm Hg/ml/min	1.56±0.19	0.81±0.13**

Note. *$p<0.05$, **$p<0.01$ compared to the value before blockade.

stimulates NO release in feline arterial endothelium, which increases elasticity of arteries; this effect can be abolished by blockade of NO synthesis [6].

Up-regulation of NO synthesis upon activation of α_1-adrenoceptors can be related not only to direct action of their agonists on the epithelium, but also can result from increased shear stress in the vascular wall during vasoconstriction caused by these agonists [3]. Both factors promote the anticonstrictor effect of NO.

Some papers describe the inhibitory effects of NO-dependent vasodilation on vasoconstriction caused by stimulation of sympathetic centers or sympathetic nerves [12,15].

Our experimental findings agree with the data [13] on the role of NO as the second (after baroreflexes) regulatory system, which damps out BP oscillations of vascular origin and contributes to stabilization of BP at the optimal level. Probably, this stabilization exemplifies the physiological role of NO-dependent endothelial vasodilation caused by up-regulation of NO synthesis by adrenergic stimulation.

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