Role of NO in the Systemic Hemodynamic Response to β_2-Adrenoceptor Stimulation

L. I. Osadchii, T. V. Balueva, and I. V. Sergeev

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 142, No. 8, pp. 128-131, August, 2006
Original article submitted February 2, 2006

Blockade of NO synthesis in most narcotized rats was followed by an increase in depressor effects (by 45%) and decrease in total peripheral resistance (by 63%) upon treatment with isopropyl norepinephrine (isoproterenol). Our results indicate that NO secretion in the endothelium modulates the systemic hemodynamic response to β_2-adrenoceptor stimulation.

Key Words: *blood pressure; total peripheral resistance; isopropyl norepinephrine (isoproterenol); NO synthesis blockade*

Our previous studies demonstrated the role of the NO-dependent mechanism in systemic hemodynamic response to increase in circulating blood volume [2] and orthostatic stress in rats [3]. Elimination of NO-dependent vasodilation increases the degree of changes in blood pressure (BP) and total peripheral resistance (TPR) after stimulation of α_1-adrenoceptors in rats [4].

Here we studied the role of NO in systemic hemodynamic response (change in BP, TPR, and cardiac output) to stimulation of β_2-adrenoceptors in vascular smooth muscles of rats. Published data show that activation of these receptors with agonists (isoproterenol) causes vasodilation [5]. This reaction reflects the cardiovascular response to adrenergic influences. It is mediated by not only α_1- and α_2-adrenoceptors, but also β_2-adrenoceptors in vascular smooth muscles. Little is known about the NO-dependent endothelial mechanism of systemic vasodilation. The role of NO in the vascular response to β_2-adrenoceptor stimulation was studied only on isolated vessels [6-12].

MATERIALS AND METHODS

Experiments were performed on 21 adult male Wistar rats (220-340 g) anesthetized with 1.2-1.5 g/kg urethane and receiving 500 U/kg heparin. Artificial ventilation was performed on a Vita device. BP was recorded in the femoral artery using a PDP-400 detector. The value of BP was digitized with a computer system for data collection. We estimated systolic, diastolic, and mean BP. Cardiac output was estimated from blood flow velocity in the ascending aorta measured with a RKE-2 electromagnetic flowmeter. We used a detector (diameter 2 mm) and H-3021 pen recorder. TPR was calculated as the ratio of mean BP to cardiac output in the same interval of time.

β-Adrenoceptors were stimulated with isoproterenol. Isoproterenol in a concentration of 10^{-9} mg/ml was infused into the femoral vein (0.1 ml per 100 g body weight).

NO synthase was inhibited by injection of N^{ω}-nitro-L-arginine methyl ester (L-NAME) into the femoral vein (1 mg per 100 body weight). Mesatone (phenylephrine) was injected 10 min after L-NAME administration.

The results were analyzed by Student's *t* test. Data processing involved standard software.

RESULTS

Basal mean BP was 105.5±5.8 mm Hg. Mean cardiac output was 82.8±6.1 ml/min (Table 1, Fig. 1). The mean response of TPR and mean BP to isopro-

Laboratory for Physiology of Blood Circulation, I. P. Pavlov Institute of Physiology, Russian Academy of Sciences, St. Petersburg

0007-4888/06/1422-0165

terenol was -0.43±0.07 mm Hg/ml/min and -30.8± 3.3 mm Hg, respectively.

Blockade of NO synthesis in 15 rats potentiated the decrease in TPR, mean systolic BP, and mean diastolic BP. Cardiac output remained practically unchanged under these conditions (Fig. 1). Administration of isoproterenol before and after blockade decreased TPR by 31.3 and 39.3% from the basal level, respectively; BP decreased by 29.5 and 35.4%, respectively.

During NO synthesis blockade, TPR and hypotensive response underwent more significant changes compared to the pre-blockade conditions (by 63 and 45.2%, respectively).

Paired Student's *t* test revealed significant differences between the effects of isoproterenol before and during blockade of NO synthesis. This test allowed us to compare the reactions of each animal (Table 2). Figure 2 shows the dynamics of isoproterenol-induced changes in TPR before and during NO synthesis blockade. TPR and BP decreased most significantly 20 sec after isoproterenol administration.

Changes in TPR in 6 animals did not differ before and during blockade of NO synthesis. Mean BP decreased by 24.2 and 6.6% of the basal level before and during blockade of NO synthesis, respectively.

Taking into account insignificant and opposite changes in cardiac output and the fact that HR increase was observed only in 11 rats, our findings suggest that the negative shift in systemic hemodynamics of 15 animals after isoproterenol administration is associated with vascular response to β_2-adrenoceptor stimulation.

Isoproterenol is not a selective β_2-adrenoceptor agonist. However, our findings suggest that after administration of this agent in the specified doses the cardiac response was not observed, while the development of hypotension was associated with vasodilation due to stimulation of vascular β_2-adrenoceptors. Hence, changes in the reaction to β_2-adrenoceptor stimulation are determined by blockade of NO synthesis.

There is no general agreement about the role of NO in vasodilation induced by β_2-adrenoceptor stimulation. Some experiments showed that NO blockade completely [6,8,11,12] or partially prevented [10] relaxation of isolated vessels or vascular seg-

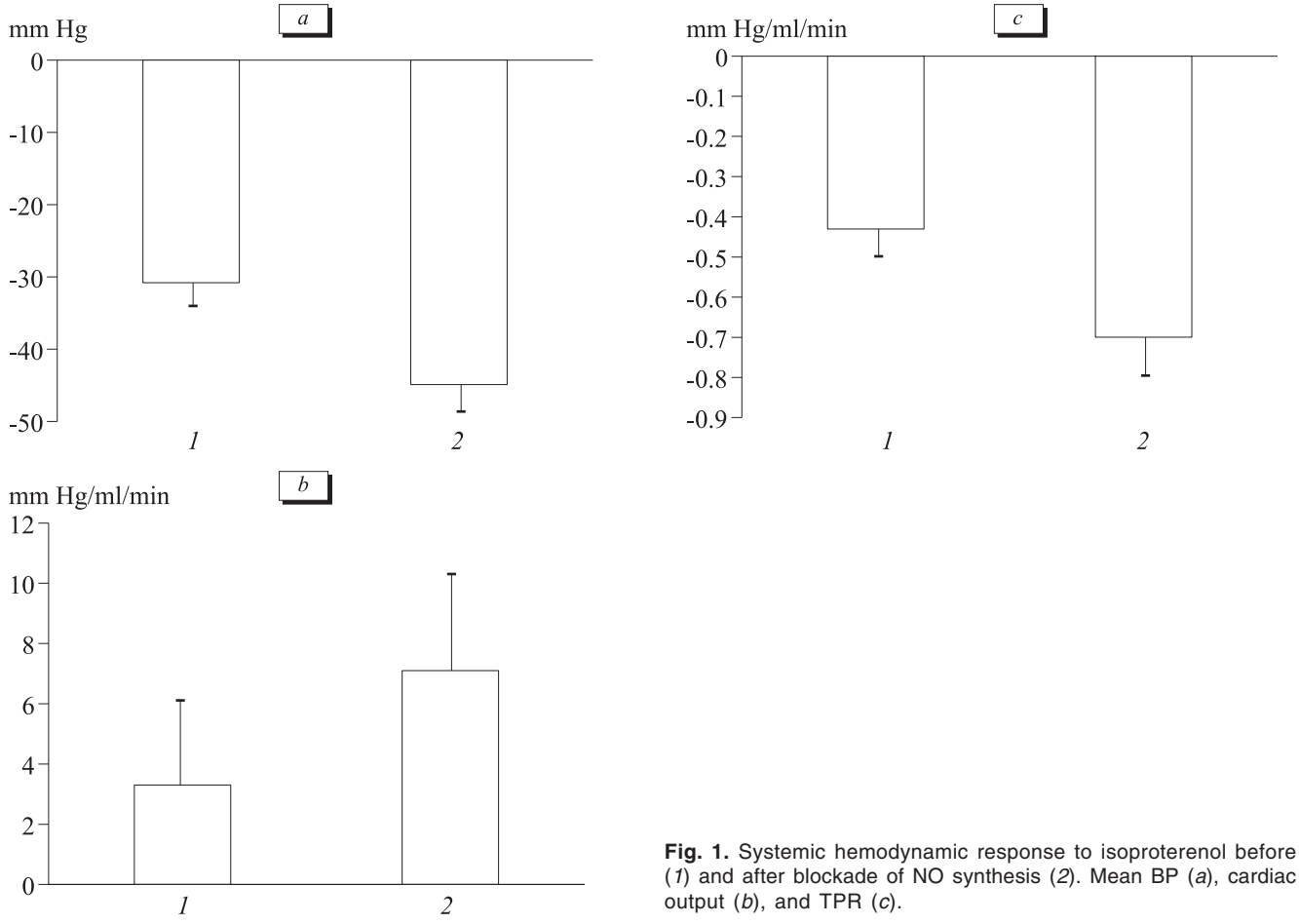

Fig. 1. Systemic hemodynamic response to isoproterenol before (*1*) and after blockade of NO synthesis (*2*). Mean BP (*a*), cardiac output (*b*), and TPR (*c*).

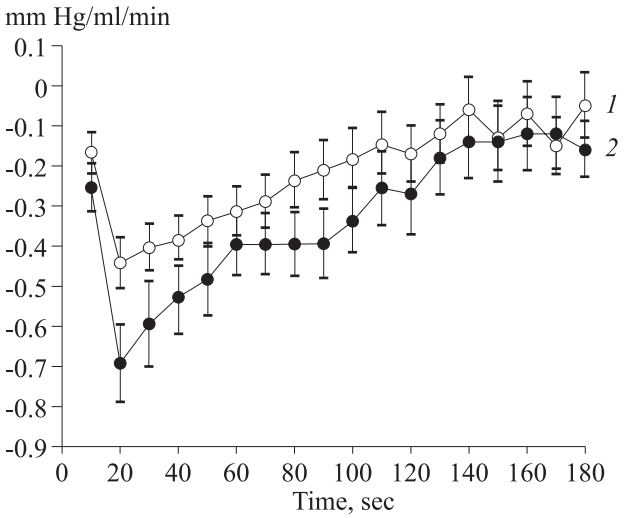

Fig. 2. Isoproterenol-induced changes in TPR before (*1*) and after blockade of NO synthesis (*2*).

ments in response to β_2-adrenoceptor stimulation. It was hypothesized that these changes were associated with the increase in NO synthesis in the endothelium after β_2-adrenoceptor stimulation, which contributed to relaxation of vascular smooth muscles. Blockade of NO synthesis decreased vasodilation [8]. Other authors [7-9] reported that blockade of NO synthesis had no effect on the degree of β_2-adrenergic vasodilation.

Our study was performed on the entire cardiovascular system. Therefore, it is important to take into account the influence of factors associated with changes in systemic hemodynamics (TPR and intravascular pressure) on the vascular endothelium. Under these conditions systemic blood flow remains practically unchanged, while vasodilation results in a decrease in shear strain of the endothelium. The observed changes are followed by a decrease in NO secretion and vasoconstriction [1].

Elimination of this mechanism after NO synthesis blockade potentiated vasodilation and caused arterial hypotension.

A similar mechanism was revealed during the orthostatic response. The reduction of shear stress under these conditions resulted from the decrease in BP and systemic blood flow [3].

The NO-dependent mechanism of vasodilation plays a role in the β-adrenergic hemodynamic response. The decrease in blood epinephrine concentration is accompanied by vasodilation, which is

TABLE 1. Effect of NO Synthase Blockade on the Systemic Hemodynamic Response to Isoproterenol (*M*±*m*, *n*=15)

Parameter		Basal level	Response to isoproterenol
Before blockade	mean BP, mm Hg	105.5±5.8	-30.8±3.3
	systolic BP, mm Hg	136.1±5.4	-31.7±4.7
	diastolic BP, mm Hg	86.5±6.3	-29.4±3.4
	cardiac output, ml/min	82.8±6.1	3.3±2.8
	TPR, mm Hg/ml/min	1.38±0.13	-0.43±0.07
During blockade	mean BP, mm Hg	123.5±5.4*	-44.9±3.9**
	systolic BP, mm Hg	150.2±5.3	-39.4±4.1
	diastolic BP, mm Hg	105.9±5.6*	-45.3±4.1**
	cardiac output, ml/min	74.9±5.8	7.1±3.2
	TPR, mm Hg/ml/min	1.78±0.15	-0.7±0.1*

Note. *p<0.05 and **p<0.001 compared to the pre-blockade parameter.

TABLE 2. Differences between Basal Levels and Isoproterenol-Induced Responses before and during NO Synthesis Blockade (*M*±*m*, *n*=15)

Parameter		Differences between basal levels	Differences between isoproterenol-induced responses
BP, mm Hg	mean	17.9±5.7**	-14.1±2.3***
	systolic	14.1±5.4*	-7.7±4.2
	diastolic	19.4±5.9**	-15.9±2.6***
Cardiac output, ml/min		7.9±2.8*	3.7±3.4
TPR, mm Hg/ml/min		0.4±0.1**	-0.27±0.09**

Note. *p<0.05, **p<0.01, and ***p<0.001 compared to the pre-blockade parameter.

realized via β_2-adrenoceptors. By contrast, the increase in epinephrine concentration causes vasoconstriction due to binding of this compound to α_1-adrenoceptors [5].

We conclude that NO prevents vasodilation during the β_2-adrenergic response of systemic hemodynamics. This mechanism mediates the decrease in the range of BP variations upon adrenergic influences on the circulatory system via vascular β_2-adrenoceptors.

REFERENCES

1. A. M. Mel'kumyants, S. A. Balashov, and S. P. Kartamyshev, *Fiziol. Zh.*, **82**, No. 1, 93-101 (1996).
2. L. I. Osadthchy, T. V. Balueva, and I. V. Sergeev, *Byull. Eksp. Biol. Med.*, **136**, No. 11, 487-489 (2003).
3. L. I. Osadthchy, T. V. Balueva, and I. V. Sergeev, *Izv. Akad. Nauk. Ser. Biol.*, No. 3, 335-339 (2004).
4. L. I. Osadthchy, T. V. Balueva, and I. V. Sergeev, *Byull. Eksp. Biol. Med.*, **140**, No. 8, 124-126 (2005).
5. *Manual on Physiology of Blood Circulation* [in Russian], Leningrad (1984), Vol. 2.
6. J. Akimoto, T. Horinouchi, M. Shibano, *et al.*, *J. Smooth Muscle Res.*, **38**, Nos. 4-5, 87-99 (2002).
7. M. L. Bea, B. Ghalen, J. F. Gudicelli, and A. Berdeaux, *Br. J. Pharmacol.*, **111**, No. 4, 981-982 (1994).
8. C. Cardillo, C. M. Kilcoyne, A. A. Quyyumi, *et al.*, *Hypertension*, **30**, No. 4, 918-921 (1997).
9. J. P. Dumas, F. Goirand, M. Bardou, *et al.*, *Br. J. Pharmacol.*, **127**, No. 2, 421-428 (1999).
10. J. Graves and L. Poston, *Ibid.*, **108**, No. 3, 631-637 (1993).
11. J. Jordan, J. Tank, M. Stoffels, *et al.*, *J. Clin. Endocrinol. Metab.*, **86**, No. 6, 2803-2810 (2001).
12. A. MacDonald, M. McLean, L. MacAulay, and A. M. Shaw, *J. Auton. Pharmacol.*, **19**, No. 3, 145-149 (1999).