Disturbances in Hormonal Regulation of Vascular Tone during Traumatic Shock

L. M. Kozhevnikova* and P. V. Avdonin*,**

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 141, No. 5, pp. 511-514, May, 2006
Original article submitted June 28, 2005

Changes in hormonal regulation of the vascular tone in Wistar rats were studied on Cannon model of traumatic shock. The pressor response to angiotensin II decreased by 30-40% 3 h after the incidence of trauma. The reaction to vasopressin remained unchanged. However, phenylephrine in medium and high doses produced a more pronounced pressor response under these conditions. One day after trauma we revealed a decrease in vascular sensitivity not only to angiotensin II, but also to vasopressin and α_1-adrenoceptor agonist phenylephrine. The vascular response was observed only after treatment with phenylephrine in maximum doses. Traumatic shock was accompanied by inverse response to serotonin: hypertensive effect instead of blood pressure drop. Our results show that traumatic shock is accompanied by specific changes in vascular reactivity.

Key Words: *shock; blood pressure; vasoconstrictor hormones; neurotransmitters*

Despite much progress in the studies of shock, the pathogenesis of this disorder is poorly understood. Little is known about variations in the function and expression of vascular receptors mediating neurohumoral regulation of blood flow in the early and late stage of shock. The development of arterial hypotension during the torpid phase of septic and burn shock is primarily associated with the decrease in pressor response to vasoconstrictor hormones [5,7,9]. These changes can be related to decreased expression of their receptors on vascular smooth muscle cells (SMC). Septic shock is accompanied by a significant decrease in the content of mRNA for angiotensin II AT1 and vasopressin V1A receptors [3,4]. The function of membrane receptors and intracellular signaling systems in blood vessels during traumatic shock were not studied.

This work was designed to test the hypothesis that traumatic shock is accompanied by a decrease in the vascular response to vasoconstrictor hormones. We studied the effects of peptide hormones angiotensin II and vasopressin, α_1-adrenoceptor agonist phenylephrine, and serotonin on blood pressure (BP) during traumatic shock.

MATERIALS AND METHODS

Traumatic shock in male Wistar rats (250-300 g) was modeled according to Cannon. Trauma of thigh soft tissues was accompanied by a decrease in BP to 40 mm Hg. Mean BP in the femoral artery was measured by the direct method using a Statham 23D sensor (hemodynamic laboratory, Medicor). BP in intact animals was 132±3 mm Hg. The influence of hormones was studied by recording BP increase under basal conditions (before trauma) and 3 or 24 h after the incidence of trauma. We studied the effects of phenylephrine (2, 6, 10, 20, 60, and 100 nmol/kg), arginine vasopressin (20, 60, and 100 pmol/kg), angiotensin II (50, 100, and 300 pmol/kg), and serotonin (20, 60, and 100 nmol/kg). The hormones (purchased from Sigma) were dissolved in 0.9% NaCl and injected into the femoral

*Institute of General Pathology and Pathophysiology, Russian Academy of Medical Sciences; **N. K. Kol'tsov Institute of Developmental Biology, Russian Academy of Sciences, Moscow. ***Address for correspondence:*** avdonin@proxima.idb.ac.ru. P. V. Avdonin

0007-4888/06/1415-0574

artery in a volume of 0.3-0.4 ml. The interval between injections was 15 min. BP returned to the basal level over this period. The effect of each compound was studied in a special series. Each series was performed on 9-10 animals.

The data were processed using Statistica 6.0 software (Student's *t* test). The differences were significant at $p<0.05$.

RESULTS

Intravenous injection of an α_1-adrenoceptor agonist phenylephrine dose-dependently increased BP in intact animals (before trauma, Fig. 1). The drug in various doses had a short-lasting effect. BP rapidly increased, but returned to the basal level 5-10 sec after phenylephrine injection. The maximum BP rise (ΔBP) was observed after injection of phenylephrine in a dose of 60 nmol/kg. Phenylephrine in doses of 60 and 100 nmol/kg increased BP by 65.4±2.3 and 67.8±2.5 mm Hg, respectively.

The effect of phenylephrine was studied 3 h and 2 days after the incidence of trauma. Three hours after trauma, BP in animals was 88±8 mm Hg (*vs*. 138±4 mm Hg before trauma). After treatment with phenylephrine in minimum doses (2 and 6 nmol/kg) the increase in BP during this period did not differ from that observed under basal conditions. However, phenylephrine in medium and high doses produced a greater increase in BP. Phenylephrine in a dose of 100 nmol/kg increased BP by 146% ($p<0.05$ compared to the control). The increased vascular response to phenylephrine in high doses was probably related to hyperkalemia developed over the first hours of shock. Hyperkalemia is accompanied by membrane depolarization in vascular SMC and potentiation of excitation in potential-dependent calcium channels coupled to α_1-adrenoceptors, which leads to potentiation of the effect of phenylephrine.

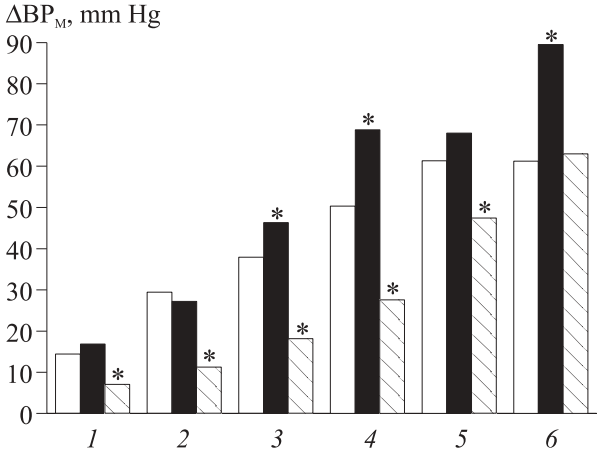

Fig. 1. Blood pressure (BP) elevation under the influence of phenylephrine in increasing doses before and 3 or 24 h after the incidence of trauma. Doses of phenylephrine: 2 (*1*), 6 (*2*), 10 (*3*), 20 (*4*), 60 (*5*), and 100 nmol/kg (*6*). Light bars: before trauma (control); dark bars, 3 h after trauma; shaded bars, 24 h after trauma. Here and in Figs. 2 and 3: *$p<0.05$ compared to the basal value (before trauma).

Severe shock is characterized by serious hemodynamic disturbances manifested in BP drop to 55±12 mm Hg. The animals exhibited a negative response to phenylephrine. Injection of phenylephrine in the lowest (2 nmol/kg) and medium doses (10 nmol/kg) was followed by a sharp deterioration of animal's state. Most rats died over 15-20 min after phenylephrine treatment. The vascular response to phenylephrine was diminished. Three hours after trauma, the degree of BP elevation in response to 6 nmol/kg phenylephrine decreased to 14.7±2.7 mm Hg (*vs*. 25.7±2.1 mm Hg in the control, $p<0.05$). The drug in a dose of 10 nmol/kg produced a 2-fold lower increase in BP compared to the control (14.3±5.4 and 34.3±1.2 mm Hg, $p<0.05$).

On day 2 after trauma mean BP was 102±4.1 mm Hg. The animals had disturbances of moderate severity. Despite relatively high level of BP, these rats exhibited a significant decrease in the vascular response to stimulation with phenylephrine in doses of 2-60 nmol/kg. The drug produced a lower elevation of PB in traumatized rats compared to intact animals (Fig. 1). Twenty-four hours after trauma, the increase in BP in response to phenylephrine in doses of 2, 6, 10, 20, and 60 nmol/kg was 52, 40, 49, 55, and 72% of the control, respectively ($p<0.05$). However, injection of phenylephrine in high dose (100 nmol/kg) was followed by a significant increase in BP (93% of the basal level).

Vasopressin in doses of 20, 60, and 100 nmol/kg produced a dose-dependent increase in BP in intact animals (before trauma). Similarly to phenylephrine, vasopressin had a short-lasting effect. The degree of BP elevation depended on the dose of intravenous vasopressin (by 23.0±2.8, 38.1±3.5, and 47.3±2.8 mm Hg; Fig. 2). Three hours after trauma, BP in these rats was 89±5 mm Hg. During this period the dose-dependent increase in BP of vasopressin-treated animals practically did not differ from that in intact rats (Fig. 2). However, vascular sensitivity to vasopressin significantly decreased on day 2 after trauma. BP elevation in response to vasopressin in doses of 20, 60, and 100 nmol/kg was 56.5, 69.5, and 87% of the control, respectively (Fig. 2).

The decrease in vascular sensitivity to angiotensin II occurred in the earlier period after shock (3 h posttrauma) and was more pronounced compared to that observed in experiments with phenyl-

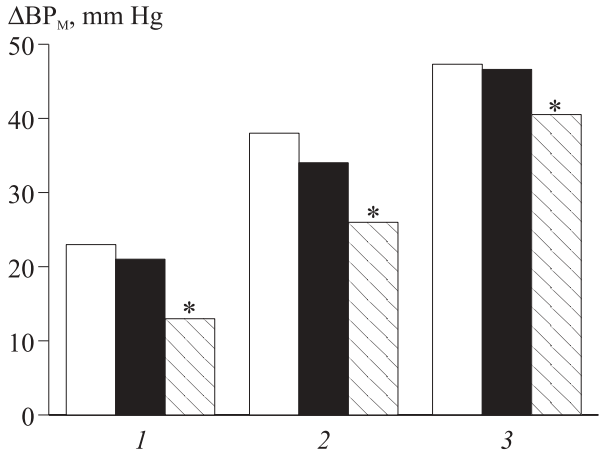

Fig. 2. BP elevation under the influence of vasopressin in doses of 20 (*1*), 60 (*2*), and 100 pmol/kg (*3*) before (light bars) and 3 (dark bars) or 24 h after the incidence of trauma (shaded bars).

ephrine and vasopressin. After trauma, BP elevation produced by intravenous angiotensin II in doses of 50, 100, and 300 pmol/kg was 25-30% lower compared to the control (before trauma, Fig. 3, *a*). The pressor response to angiotensin II decreased by 60-70% 24 h after trauma. We revealed a rightward shift of the dose dependence curve. BP elevation in intact rats receiving angiotensin II in increasing doses was 33.4±4.0, 46.6±5.0, and 63.6±5.2 mm Hg (*vs*. 10.4±1.0, 16.8±1.7, and 27.6±3.2 mm Hg, respectively, 1 day after trauma).

Serotonin induced a transient BP drop in intact animals. Serotonin in doses of 20, 60, and 100 nmol/kg decreased BP by 26.0±1.7, 37.3±3.1, and 46.2±5 mm Hg, respectively (Fig. 3, *b*). By the 3rd hour, BP increased to 89±3 mm Hg (*vs*. 40±2 mm Hg immediately after trauma). It should be emphasized that serotonin injection at this term significantly increased BP by 15.7±7.6, 33.8±2.4, and 39.0±4.2 mm Hg, respectively, in contrast to intact animals responding by BP decrease. In some animals the effect of serotonin in doses of 60 and 100 nmol/kg was biphasic. The initial rise was followed by normalization and short-term decrease in BP. The hypotensive effect of serotonin in traumatized rats was less significant than in intact animals. Serotonin in doses of 60 and 100 nmol/kg decreased BP in traumatized rats by 16.0±1.7 and 18.7±1.4 mm Hg, respectively (*vs*. 37.3±3.1 and 46.2±5.0 mm Hg, respectively, in the control). The vasoconstrictor effect of serotonin persisted 24 h after trauma. Before serotonin treatment, BP in animals of this group was 97±4 mm Hg. Serotonin in doses of 20, 60, and 100 nmol/kg increased BP by 6.8±4.9, 31.0±4.9, and 37.2±5.4 mm Hg, respectively. Hypotensive activity of serotonin in the follow-up period did not exceed 20-60% of the preshock value. Serotonin produced more complex changes than other hormones, which is probably related to the existence of several types of serotonin receptors in the endothelium and SMC of blood vessels [2]. Shock is accompanied by dysfunction of endotheliocytes. Under these conditions serotonin affects primarily SMC, which results in BP elevation.

The decrease in vascular reactivity during traumatic shock can occur due to several reasons. Desensitization of vessels to angiotensin II in the early posttraumatic period is probably related to hyperactivation of the renin-angiotensin system during shock. The decrease in vascular sensitivity to vasoconstrictors over the first hours of traumatic shock can be associated with uncoupling of receptors and intracellular signaling systems due to activation of protein kinase C [1]. Delayed changes (after 1 day) in the regulation of vascular contraction and BP with peptide hormones and biogenic amines prob-

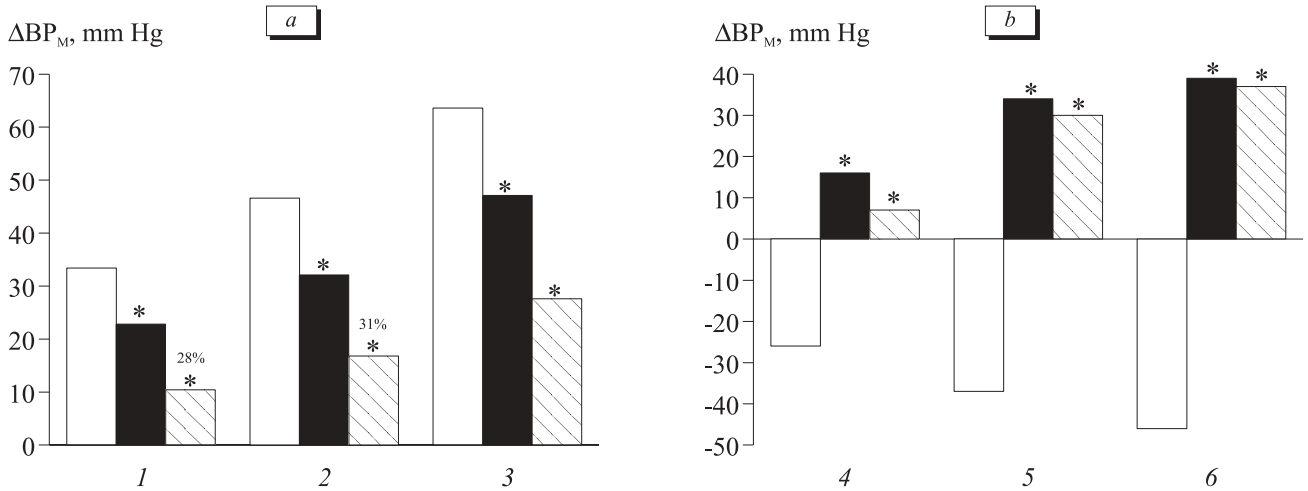

Fig. 3. BP under the influence of angiotensin II and serotonin before (light bars) and 3 (dark bars) or 24 h after the incidence of trauma (shaded bars). Doses of angiotensin II: 50 (*1*), 100 (*2*), and 300 pmol/kg (*3*). Doses of serotonin: 20 (*4*), 60 (*5*), and 100 nmol/kg (*6*).

ably result from variations in receptors and signal systems of SMC. On day 2 we revealed not only the decrease in the response to angiotensin II, vasopressin, and phenylephrine, but also a rightward shift of the dose dependence. These changes are probably associated with a decrease in the number of receptors for these vasoconstrictors in vascular SMC. The half-life of mRNA for vasopressin receptors on vascular SMC is approximately 4 h [6,8]. Therefore, shock can be accompanied by immediate changes in the expression of these receptors.

Our results suggest that traumatic shock is followed by a decrease in the pressor response to vasoconstrictor hormones and neurotransmitters, which results in uncontrolled hypotonia. The knowledge of specific changes in vascular responses to vasoactive compounds is important for the development of new methods for therapy of shock. α_1-Adrenoceptor agonists are of limited use under conditions of severe hypotonia that accompanies serious shock. Treatment with angiotensin II as a hypertensive drug is not justified, since vascular sensitivity to this hormone decreases during traumatic shock. The peptide hormone vasopressin has a mild vasoconstrictor effect. Therefore, vasopressin can be used to increase BP in the torpid phase of shock. Serotonin produces a vasoconstrictor effect during traumatic shock and, therefore, holds promise increasing BP under these conditions.

This work was supported by the Russian Foundation for Basic Research (grants No. 04-04-49054 and 05-04-49166).

REFERENCES

1. P. V. Avdonin and V. A. Tkachuk, *Receptors and Intracellular Calcium* [in Russian], Moscow (1994).
2. P. V. Sergeev, N. L. Shimanovskii, and V. I. Petrov, *Receptors for Physiologically Active Substances* [in Russian], Volgograd (1999).
3. M. Bucher, K. P. Ittner, J. Hobbhahn, *et al*., *Hypertension*, **38**, No. 2, 177-182 (2001).
4. M. Bucher, J. Hobbhahn, K. Taeger, and A. Kurtz, *Am. J. Physiol. Regul. Integr. Comp. Physiol.*, **282**, No. 4, 979-984 (2002).
5. W. G. Cioffi, J. E. DeMeules, and R. L. Gamelli, *Circ. Shock*, **25**, No. 4, 309-317 (1988).
6. F. Cottet-Maire, P. V. Avdonin, E. Roulet, *et al*., *Br. J. Pharmacol*., **132**, No. 4, 909-917 (2001).
7. G. Julou-Schaeffer, G. A. Gray, I. Fleming, *et al*., *Am. J. Physiol*., **259**, No. 4, Pt. 2, H1038-H1043 (1990).
8. S. Murasawa, H. Matsubara, K. Kizima, *et al*., *Hypertension*, **26**, No. 4, 665-669 (1995).
9. D. Pieber, G. Horina, A. Sandner-Kiesling, *et al*., *Cardiovasc. Res*., **44**, No. 1, 166-175 (1999).