ACTH INHIBITS DEVELOPMENT OF PRIMARY DECOMPENSATION OF THE SYSTEMIC AND PORTAL CIRCULATION IN RATS WITH ACUTE BLOOD LOSS

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The writers previously demonstrated two types of response of the cardiovascular system to acute massive blood loss: primary decompensated, with rapid and irreversible decline of parameters of the systemic and organic hemodynamics, and by the development of lasting pathological constriction of the microvessels of the intestine and liver, and compensated, with distinct phasic changes of the systemic BP and the macro- and microcirculation of the blood [2]. In most animals the decompensated course of the posthemorrhagic period becomes compensated after administration of naloxone [3], which, in its pharmacologic properties, is predominantly a β-endophin antagonist [6, 9]. During exposure of the body to extremal factors β-endorphin is formed in the pituitary gland in equimolar amounts with ACTH, a hormone belonging to the group of endogenous peptide antagonists [1, 9].

The aim of this investigation was to study the effect of the ACTH-(1-24) fragment and the (4-10) fragment which has no specific hormonal activity [4], on the systemic and portal circulation in rats with acute massive blood loss.

EXPERIMENTAL METHOD

Experiments were carried out on 52 male Wistar rats weighing 200-250 g. A comprehensive method of assessing the systemic and portal circulation, suggested by the writers previously [2], was used. Under urethane anesthesia the microcirculation in the liver and intestine was studied periodically by contact luminescence biomicroscopy. Simultaneously the mean and pulse BP (in mm Hg) was recorded by means of a micromanometer in the carotid artery, and the volume velocity of the blood flow in the portal vein of the liver (in ml/min) and the linear velocity of the blood flow in the hepatic artery (in cm/sec) were measured by means of an ultrasonic transducer of bandage type. A miniature piezoelectric crystal 0.5 mm^2 in area, with operating frequency of 26.8 MHz, was used as the sensitive element of the transducer. Acute blood loss was produced by a single withdrawal of blood from the femoral artery in an amount of 2.5% of body weight in the course of 5 min. The animal was not previously heparinized. ACTH-(1-24) (Synacthen from "Ciba") and ACTH-(4-10), in a dose of 200 mg/kg and in a volume of 0.1 ml/100 g body weight, or in the same volume of 0.9% sodium chloride solution, was injected intravenously into the animals 15 min after the end of blood loss. The state of the systemic and portal circulation was monitored for 2 h after injection of the preparation. The numerical results were subjected to statistical analysis by the Fisher–Student method.

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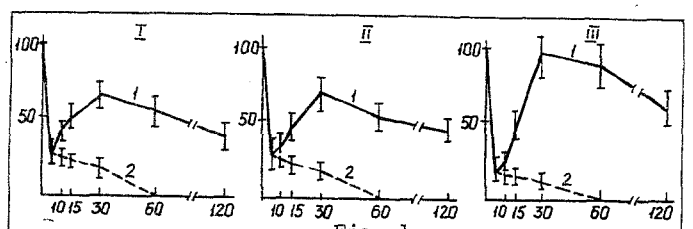

Fig. 1

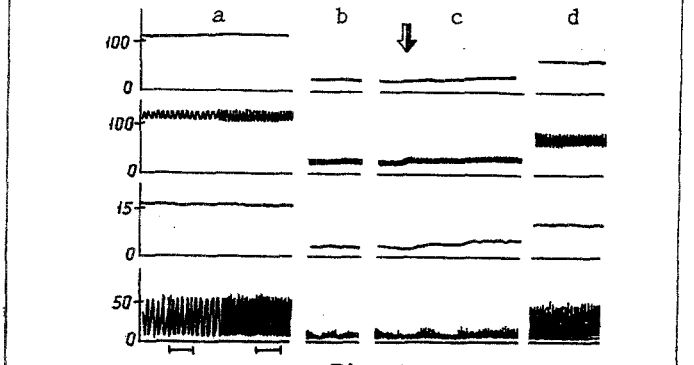

Fig. 2

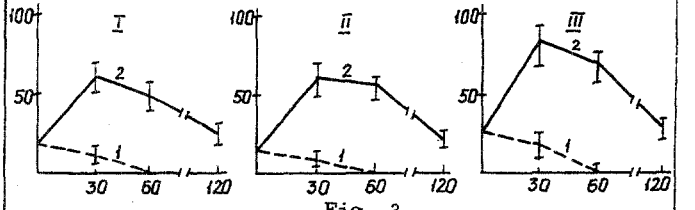

Fig. 3

Fig. 1. Dynamics of mean BP (I) and of blood flow rate in portal vein (II) and hepatic artery (III) in rats with compensated (1) and decompensated (2) type of course of posthemorrhagic period. Abscissa, time after end of blood loss (in min); ordinate, parameter (in per cent of initial value).

Fig. 2. Effect of ACTH-(1-24) on BP and portal and hepatic blood flow in rats with decompensated blood loss. From top to bottom: mean BP, pulse BP, volume velocity of blood flow in portal vein, linear velocity of blood flow in hepatic artery. From left to right: a) before blood loss, b) 15 min after blood loss, c) immediately after intravenous injection of ACTH-(1-24) in a dose of 200 mg/kg, d) 5 min after injection of preparation. Time marker 1 and 10 sec. Arrow indicates beginning of injection of ACTH-(1-24).

Fig. 3. Dynamics of mean BP (I) and blood flow rate in portal vein (II) and hepatic artery (III) in rats with decompensated blood loss after intravenous injection of 0.9% sodium chloride solution (1) and ACTH(4-10) in a dose of 200 mg/kg (2). Abscissa, time after injection of preparation (in min); ordinate, parameter studied (in per cent of initial value).

EXPERIMENTAL RESULTS

Blood equivalent in volume of 2.5% of body weight led to a fall in BP of all the rats to 20-25 mm Hg, and to a decrease in the blood flow rate in the portal vein and hepatic artery to 20-25% of the original value. At the microcirculatory level constriction of the superficial intestinal and hepatic microvessels was observed, with a significant fall of the blood flow velocity in the microvessels and reduction of the total blood volume in the terminal vascu-

lar bed of the two organs. During the first 15 min after termination of blood loss, the hemodynamic parameters, after being depressed as a result of exsanguination, began to recover in the majority of animals (60-70% of cases; compensated blood loss). Values of BP and the arterial and portal blood flow rates reached a maximum 30 min after the end of the procedure, at 60-70, 100-110, and 70-80% of the initial values recorded before blood loss respectively. The state of the hepatic and intestinal microcirculation improved considerably, constriction of the hepatic and intestinal microvessels was reduced, and the volume and linear velocity of the microvascular blood flow increased. The phase of temporary relative compensation of parameters of the systemic and portal circulation was subsequently replaced by a phase of secondary, irreversible decline (secondary irreversible decompensation), and 2 h later all the hemodynamic parameters studied were appreciably depressed (Fig. 1). In the liver at this time of the investigation marked focal disturbances of the microcirculation developed, in the form of microstasis and microthrombosis in individual sinusoids or fragments of them, and generalized erythrocytic aggregation could be seen biomicroscopically in the microvessels of the liver and intestine.

In rats in which the parameters of the systemic and portal circulation, depressed during blood loss, did not increase during the first 15 min of the posthemorrhagic period, the course of the blood loss was one of primary decompensation of the cardiovascular system (decompensated blood loss). BP of these animals 30 min after the end of blood loss did not exceed 20 mm Hg, and the velocities of the portal and arterial blood flows did not exceed 15-20% of their initial values before blood loss (Fig. 1). The terminal microvessels of the liver and intestine were considerably constricted, and their blood flow rate was slowed. The blood volume in the microcirculatory bed of the unpaired abdominal organs remained reduced. All animals with primary decompensated blood loss died during the first hour of the experiment, in agreement with our previous observations [2].

Intravenous injection of 0.9% sodium chloride solution in a volume of 0.1 ml/100 g, and also of fragments ACTH-(1-24) and ACTH-(4-10) in dose of 200 mg/kg into animals with compensated blood loss had no effect on the character of the course of the process. The BP level and the hepatic blood flow rate, and the time course of their changes in the posthemorrhagic period in these animals did not differ significantly from changes in the corresponding parameters in untreated animals with acute blood loss. In rats with the compensated type of posthemorrhagic course, ACTH-(1-24) and (4-10) did not prevent the development of posthemorrhagic disturbances of the hepatic microcirculation in the form of local foci of microstasis and microthrombosis, and generalized erythrocytic aggregation.

Injection of ACTH-(1-24) and (4-10) into animals with decompensated blood loss had a marked beneficial action on the systemic and portal circulation, and converted the decompensated course of the process into compensated and lengthened the survival of the animals in this group by 2-3 times. The systemic BP 15 sec after injection of the ACTH fragments rose by 3-5 mm Hg and the velocity of the portal and arterial blood flows rose by 10-20% (Fig. 2). The hemodynamic changes recorded at the time of injection of the fragments were not specific and were virtually indistinguishable from changes observed after injection of the corresponding volume of 0.9% sodium chloride solution. Later, in the group of animals receiving the ACTH preparation, further growth of the recorded parameters was observed, and was unconnected with the volume of fluid infused. For instance, 5 min after injection of the hormone, BP amounted to 40-50% of the control level, the blood flow rate in the portal vein rose on average to 60%, and in the hepatic artery to 80% of the initial value of this parameter (Fig. 2). The hemodynamic parameters studied 30 min after injection of the ACTH fragment reached their maximum, as follows: BP 64 ± 5.3 mm Hg, portal blood flow 65 ± 9%, arterial blood flow 85 ± 15% of the control (Fig. 3). At the microcirculatory level, constriction of the intestinal and hepatic microvessels was reduced during this period, and the linear velocity of the blood flow in them was increased. Later the values of BP and the portal macro- and microcirculatory parameters began to fall gradually, so that 2 h after treatment they did not exceed 20-30% of their value recorded before blood loss (Fig. 2).

Thus in animals with the compensated type of course of the posthemorrhagic period the ACTH fragment studied had no appreciable effect on the course of the process. Meanwhile, the ACTH-(1-24) fragment improved the state of the portal macro- and microcirculation and reduced posthemorrhagic generalized constriction of the microvessels of the liver and intestine in animals with primary posthemorrhagic decompensation of the cardiovascular system. The ACTH-(4-10) fragment, which has no specific corticoid activity, also possessed a similar action. This suggests that the positive action of ACTH on the systemic and portal circulation, which we found in the early stages of development of acute blood loss, is not realized through hormones of the adrenal cortex, whose antishock effect is linked with their ability to inhibit lipid peroxidation in the tissues, to stabilize cell membranes, and to influence metabolism [5, 7, 8]. In our view, the vascular effect of ACTH which we discovered in rats with primary posthemor-

rhagic compensation of the cardiovascular system may be connected with its action as an endogenous antagonist of the opiate receptors of the brain, weakening the action of endorphins [1]. This conclusion is indirectly confirmed by the results of our previous study [3], which showed that naloxone, if injected intravenously in doses able to pass through the blood-brain barrier, exerts a positive action on the portal and systemic circulation in rats with decompensated blood loss, and also by experimental results proving that the antishock hemodynamic effects of naloxone are associated with central opiate receptor blockade [6, 9]. The results of the present investigation suggest that in primary posthemorrhagic decompensation of the cardiovascular system there is a disturbance of regulation concerning production of ACTEI and β-endorphin in equimolar quantities. Deficiency of ACTH, which has the ability to inhibit the antishock effect of β-endorphin, leads to the development of opiate-dependent inhibition of central endogenous homeostatic mechanisms responsible for self-compensation of the BP and also for the improvement of the portal macro- and microcirculation in the early posthemorrhagic period.

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REFERENCES

1. V. M. Bulaev, Progress in Science and Technology. Series: Pharmacology [in Russian], Vol. 13, Moscow (1982), p. 101.
2. N. Ya. Kovalenko D. D. Matsievskii, Yu. M. Shtykhno, Byull. Éksp. Biol. Med., No. 10, 34 (1982).
3. N. Ya. Kovalenko and D.D. Matsievskii, Byull. Éksp. Biol. Med., No. 5, 547 (1989).
4. M. A. Ponamorev et al., Khim.-Farm. Zh., No. 7, 790 (1984).
5. V. I. Nigulianu (ed.), Traumatic Shock: Pathogenesis, Clinical Features, and Treatment [in Russian], Kishinev (1983).
6. E. W. Bernton, J. B. Long, and J. W. Holaday, Fed. Proc., **44**, No. 2, 290 (1985).
7. J. M. Braughler and E. D. Hall, J. Neurosurg., **62**, 806 (1985).
8. E. D. Hall, P. A. Jonkers, and J. M. McCall, Eur. J. Pharmacol., **147**, 299 (1988).
9. S. Sacamoto, C. K. Stone, P. D. Woolf, et al., Circulat. Res., **65**, 103 (1989).