DOSE-DEPENDENT ACTION OF NALOXONE ON THE SYSTEMIC AND PORTAL CIRCULATION IN ACUTE BLOOD LOSS IN RATS

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KEY WORDS: blood loss; naloxone; circulation; biomicroscopy; ultrasound

Investigators studying shock and acute blood loss in recent years have had their attention drawn to the endogenous opioid peptide system. An antishock effect of naloxone and also of other selective blockers of opiate receptors has been demonstrated on several different models of shock [3, 5, 7, 9]. However, some workers have obtained results showing that naloxone does not change, or may even worsen, the course of shock and acute blood loss [4, 6, 8]. In previous publications devoted to the study of the role of opiate receptor antagonists in the development and correction of shock, no information is given on their influence on the portal macro- and microcirculation, which plays the key role in the development of irreversible shock disturbances [2].

The aim of this investigation was to study the dose-dependent action of naloxone on the state of the systemic and portal circulation in rats with acute blood loss.

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar albino rats weighing 200-250 g. A method of combined assessment of the systemic and portal circulation, suggested previously [1], was used. The microcirculation in the liver and intestine of an animal anesthetized with urethane was studied over a period of time by contact luminescence biomicroscopy. The average and pulse arterial pressure (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 recorded by means of an ultrasonic transducer of bandage type. Acute blood loss was induced by a single bleeding from the femoral artery to the extent of 2.5% of the animal's body weight in the course of 5 min. The animals were not given a preliminary injection of heparin. Naloxone hydrochloride ("Sigma") was injected intravenously into the animals 15 min after the end of blood loss, in a dose of 0.1, 1, and 5 mg/kg in a volume of 0.1 ml/100 g body weight (41 rats), or the same volume of 0.9% sodium chloride solution was injected (11 rats). The control series of experiments was carried out on animals with acute blood loss, not followed by injection of the above preparations (14 rats). The state of the systemic and portal circulation was observed for 2 h after injection of the preparation. The numerical data were subjected to statistical analysis by the Fisher–Student method.

EXPERIMENTAL RESULTS

Blood loss caused BP of all the rats to fall to 26 ± 7 mm Hg, while the velocity of the blood flow in the portal vein and hepatic artery fell to 20-30% of their initial levels (Fig. 1). At the microcirculatory level, constriction of the superficial vessels of the intestine and liver was observed, with a marked reduction of the linear velocity of the blood flow in them and a decrease in the total blood volume in the terminal vascular bed of the respective organs. During the first 15 min after the end of blood loss the hemodynamic parameters, which were reduced during blood loss, began to recover in the majority of animals (60-70% of cases) (compensated blood loss). The BP level and the velocity of the hepatic portal and arterial blood flows 30 min after the end of blood loss were 66 ± 9, 75 ± 11, and 105 ± 15% respectively of the values recorded before blood loss. The state of the hepato-intestinal microcirculation was much improved. The phase of temporary compensation of the parameters of the systemic and portal circulation gave way to a phase of their secondary, irreversible

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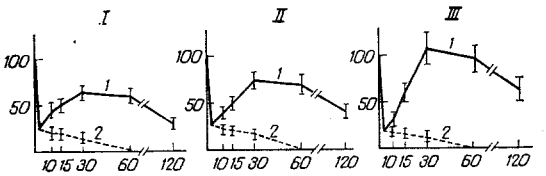

Fig. 1. Time course of average BP (I) and blood velocity of blood flow in portal vein (II) and hepatic artery (III) in rats with compensated (1) and decompensated (2) type of course of posthemorrhagic period. Abscissa, time after end of blood loss (in min); ordinate, value of parameter studied (in % of initial value).

decompensation, and after 2 h all the hemodynamic parameters studied were considerably lowered. In the liver during this period of investigation marked focal disturbances of the microcirculation developed, in the form of microstases and microthromboses in individual sinusoids or fragments of them, together with generalized erythrocytic aggregation. In those rats in which the parameters of the systemic and portal circulation, which were reduced during blood loss, did not increase during the first 15 min of the posthemorrhagic period, the course of the blood loss resembled that 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, whereas the velocity of the portal and arterial blood flow was 15-20% of the initial values (Fig. 1). The terminal microvessels of the liver and intestine were considerably constricted and the velocity of the blood flow in them was slowed. The total blood volume of 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 naloxone in doses of 0.1 and 1 mg/kg into animals with compensated and decompensated blood loss did not affect the character of course of the process. The BP, velocity of the hepatic blood flow, state of the microcirculation and time course of these parameters in the posthemorrhagic period of these animals did not differ significantly from changes in the corresponding hemodynamic parameters in animals with acute untreated blood loss. The use of naloxone in large doses (5 mg/kg) in animals with compensated blood loss likewise was ineffective. However, injection of the corresponding dose of the drug into animals with decompensated blood loss had a marked positive action on the cardiovascular system and converted the primary decompensated course of the process into compensated. The pulse BP of these animals 15-20 sec after injection of the drug was increased by 50-60% and the average BP by 3-5 mm Hg. The increase in the volume velocity of the portal blood flow immediately after injection of the drug amounted to 10-15%, whereas the linear velocity of the hepatic arterial blood flow rose sharply, being increased by 100-150% (Fig. 2). Later a further increase in the hemodynamic parameters was recorded. The BP level 30 min after injection of the drug was 65 ± 7 mm Hg, and the arterial blood flow by this time of the investigation reached 96 ± 18, and the portal blood flow 70 ± 12% of the control value (Fig. 3). At the microcirculatory level during this period constriction of the intestinal and hepatic microvessels was reduced, and the linear velocity of the blood flow in them increased. Later the values of BP and of the parameters of the portal macro- and microcirculation gradually began to fall, and 2 h after treatment they did not exceed 20-30% of the values recorded before blood loss (Fig. 3). In all animals with acute blood loss, irrespective of the type of course of the process and the dose of naloxone used, it did not prevent the development of posthemorrhagic disturbances of the hepatic microcirculation, in the form of local microstases, microthromboses, and generalized erythrocytic aggregation.

The data described above thus show that the mechanism of disturbances of the systemic and portal circulation in animals with a decompensated type of course of acute blood loss is opiate-dependent. The fact that naloxone was effective against decompensated blood loss only in large doses, which if injected intravenously can pass through the blood-brain barrier [5], suggests that the positive effect of the opiate antagonist on BP and the portal macro- and microhemodynamics is linked with blockade of central opiate receptors and abolition of depressor

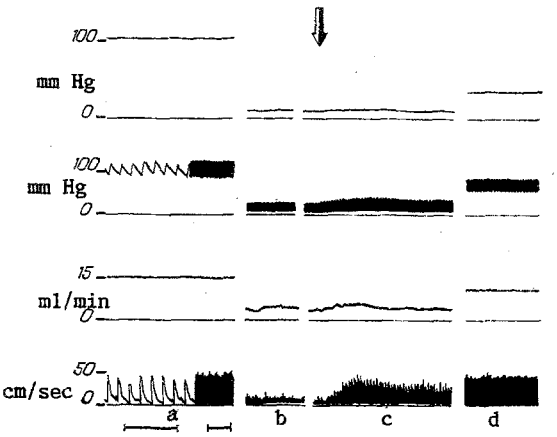

Fig. 2. Effect of naloxone on BP and portal and hepatic blood flow in rats with decompensated blood loss. From top to bottom: average BP, pulse BP, volume velocity of blood flow in portal vein, linear velocity of blood flow in hepatic artery. From left to right: a) before blood loss; b) 15 min after blood loss; c) immediately after intravenous injection of naloxone (5 mg/kg); d) 30 min after injection of naloxone. Time marker 1 and 10 sec. Arrow indicates beginning of injection of naloxone.

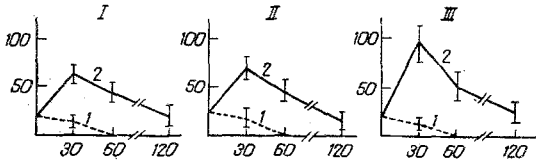

Fig. 3. Time course of average BP (1) and velocity of blood flow in portal vein (II) and hepatic artery (III) in rats with decompensated blood loss after intravenous injection of 0.9% sodium chloride solution (1) and naloxone in a dose of 5 mg/kg (2). Abscissa, time after injection of preparation (in min); ordinate, value of parameter studied (in % of initial value).

and constrictor influences of brain endorphins on the heart and blood vessels of the liver and intestine. In animals with the compensated type of posthemorrhagic period, unlike rats with primary decompensated blood loss, no such activation of central endogenous endorphins evidently takes place. The mechanisms of posthemorrhagic compensation of BP and of the portal circulation in such animals are unconnected with opiate receptors, for which naloxone is a blocker. In the present experiments, when opiate receptors were blocked by naloxone, posthemorrhagic microcirculatory disturbances such as erythrocytic aggregation and local microstases and microthromboses also were preserved in the animals.

On the whole the results suggest that the use of naloxone for the treatment of acute blood loss is effective only in the presence of opiate-dependent inhibition of endogenous homeostatic mechanisms responsible for self-compensation of BP and also for the improvement in the portal macro- and microcirculation in the early posthemorrhagic period.

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LEFT VENTRICULAR PUMPING FUNCTION AND CONTRACTILITY CHANGES AFTER MYOCARDIAL ISCHEMIA EVOKED BY CORONARY ARTERIAL EMBOLIZATION BY MICROSPHERES IN ANESTHETIZED RATS

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Microspheres inserted through a catheter into one coronary artery without thoracotomy are being used on an ever increasing scale in recent years to create a model of myocardial ischemia [4-7]. However, research of this kind has been undertaken only on large animals, such as dogs or pigs, mainly because of the difficulty of catheterizing single coronary arteries in small animals. This paper describes a relatively simple method of inducing a measured degree of embolization of the coronary vessels by means of microspheres in anesthetized rats and gives the results of the study of the effect of measured myocardial ischemia on the pumping function of the heart.

EXPERIMENTAL METHOD

Under pentobarbital anesthesia (40 mg/kg) catheters were inserted into the abdominal aorta of Wistar rats through the femoral artery and into the left ventricle through the right carotid artery. Measured embolization of the coronary vessels was produced with the aid of

TABLE 1. Basic Parameters of BP and of Left Ventricular Function in Control Rats (n = 6) and in Rats with Embolization of the Coronary Vessels (n = 16)

Parameter	Control group	Experimental group
Average BP, mm Hg	117±9	108±4
P_s of LV, mm Hg	135±7	134±4
EDP of LV, mm Hg	3,8±0,9	5,0±0,5
dP/dt_{max}, mm Hg/sec	7625±1284	6974±282
$dP/dt_{max}/P$ (1/sec)	55,5±7,9	51,6±1,5

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