EFFECT OF OPIATE RECEPTOR AGONISTS ON MYOCARDIAL ENERGY METABOLISM IN RATS WITH HEMORRHAGIC SHOCK

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A disturbance of myocardial energy metabolism is one cause of the hemodynamic disorders associated with shock, including hemorrhagic shock [6], and this necessitates a search for substances which can promote restoration of the energy state of the heart muscle. Endogenous opioid peptides (enkephalins) restore the energy potential in the liver after acute blood loss [2]. Opiate receptors have been found in the myocardium of animals [9], and the contractile function of the heart is enhanced in rabbits with shock under the influence of dalargin [3], a synthetic enkephalin analog; taken together, these facts may indicate the possibility of exerting a beneficial influence on myocardial energy metabolism in response to administration of exogenous enkephalins.

The aim of this investigation was to study the effect of synthetic Leu-enkephalin analogs (agonists of μ- and Δ-opiate receptors) on the energy state of the myocardium in rats with hemorrhagic shock.

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar albino rats weighing 320-350 g. The animals were anesthetized by intraperitoneal injection of pentobarbital sodium in a dose of 50 mg/kg body weight. The femoral artery was catheterized. Fractional hemorrhage was induced by means of a DR-2 peristaltic pump (East Germany) at the rate of 0.8 ml/kg·min, until 30% of the circulating blood volume (CBV). After blood loss equivalent in volume to 7.5% of CBV, the enkephalins were injected intravenously in a dose of 100 μg/kg, diluted in 0.6 ml physiological saline. The following Leu-enkephalin analogs were used: DADL (D-Ala^2-D-Leu^5), DAGO (D-Ala^2-N and Phe^4-Gly^5), and dalargin (D-Ala^2-Arg^6), synthesized by Professor M. I. Titov. In the control series 0.6 ml of physiological saline was injected intravenously. The mean blood pressure (MBP) was recorded in the femoral artery by means of a BMT 401 biomonitor (East Germany) on the 3 NEK-1 automatic writer (East Germany). Heart tissue samples were taken 1 h after hemorrhage with cooled forceps, and transferred into liquid nitrogen. Concentrations of adenine nucleotides (ADN), of lactic and pyruvic acids (lactate and pyruvate), and glucose were determined with the aid of kits from "Boehringer Mannheim" (West Germany), on a Specord M-40 spectrograph. Creatine phosphate and glycogen were determined spectrophotometrically [7]. The total content of ADN was calculated. The results were subjected to statistical analysis on a personal computer.

EXPERIMENTAL RESULTS

The time course of MBP for the different groups of rats is shown in Table 1. Since the response of MBP in rats after an initial blood loss of 7.5% by volume was variable, subsequently values of MBP were calculated as percentages of this value, which was taken as 100%

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TABLE 1. Time Course of MBP in Rats with Hemorrhagic Shock Receiving Preparations (M ± m)

Period of observation	Hemorrhage + physiological saline (n = 10)	Hemorrhage + DADL (n = 9)	Hemorrhage + DAGO (n = 9)	Hemorrhage + dalargin (n = 10)
Initial value	103±7	99±5	109±4	97±6
Fraction of CBV taken, %				
7,5	92±7 (100)	74±8 (100)	80±7 (100)	61±6 (100)
Injection of preparations:				
15	59±5** (64±6)	55±8 (74±12)	70±6 (88±8)	39±3** (64±5)
30	28±3** (30±4)	26±5** (35±7)	44±5** (55±6)	17±2** (28±3)
Posthemorrhagic period, min:				
15	63±7* (68±5)	52±6* (70±10)	55±7* (69±7)	42±4 (70±7)
60	74±6 (80±7)	85±5 (115±11)	78±7 (98±9)	61±5 (100±9)

Legend. *p < 0.05, **p < 0.001 compared with period after 7.5% hemorrhage MBP shown in parentheses (in %).

TABLE 2. Myocardial Energy Parameters in Rats with Hemorrhagic Shock (M ± m)

Metabolite	Control	Hemorrhage + physiological saline	Hemorrhage + DADL	Hemorrhage + DAGO	Hemorrhage + dalargin
ATP	4,59±0,45 (8)	4,27±0,44 (8)	4,42±0,38 (7)	3,73±0,38 (7)	4,84±0,65 (7)
ADP	1,31±0,10 (7)	0,61±0,06 (7)*	1,13±0,25 (8)**	1,16±0,34 (8)**	1,18±0,14 (7)**
AMP	0,70±0,09 (7)	0,45±0,08 (8)*	0,46±0,10 (7)*	0,54±0,13 (8)	0,47±0,09 (7)*
ATP/ADP	3,25±0,51 (7)	7,31±1,26 (7)*	4,38±1,08 (8)**	3,32±1,02 (8)**	3,92±0,42 (8)**
ATP/AMP	5,85±1,11 (7)	9,87±1,61 (8)*	10,04±2,23 (8)*	7,41±2,03 (7)	9,74±1,74 (8)*
ADN	6,63±0,25 (7)	5,37±0,29 (8)*	6,08±0,28 (7)	5,68±0,26 (7)	6,58±0,40 (7)
Lactate	2,48±0,37 (8)	3,71±0,47 (6)*	3,45±0,38 (8)*	3,90±0,51 (6)*	3,89±1,03 (7)*
Glycogen	28±2 (7)	30±3 (7)	31±4 (7)	30±3 (7)	32±4 (5)
Pyruvate	0,09±0,03 (8)	0,09±0,03 (8)	0,07±0,03 (4)	0,14±0,03 (6)	0,08±0,03 (5)
Creatine phosphate	5,56±1,02 (8)	3,49±0,70 (7)*	3,49±1,08 (8)*	3,12±0,51 (6)*	4,00±0,50 (7)*

Legend. *p < 0.05 Compared with control, **p < 0.05 compared with group with hemorrhage.

Injection of DAGO reduced the rate of fall of MBP during blood loss in both absolute and relative terms. The highest rate of fall of MBP was noted in response to injection of dalargin. In the posthemorrhagic period, after 60 min, MBP of all the animals was restored up to the level observed before injection of the peptides, although in relative terms the values of MBP in rats receiving physiological saline were nevertheless 20-30% lower than in animals receiving the enkephalins (Table 1).

In rats treated with physiological saline, disturbances of energy metabolism were observed in the myocardium, namely reduction of the concentrations of ADP, AMP, creatine phosphate, and ADN, and an increase in the values of the ATP/ADP and ATP/AMP ratios and the lactate level (Table 2).

Injection of all the enkephalin analogs studied restored the original parameters of ADN metabolism to some degree or other, but did not affect the lactate level, which remained high. It was noted that when dalargin was injected, the ATP concentration in the myocardium rose a little by comparison with intact animals, the total ADN concentration was virtually unchanged, and the creatine phosphate concentration remained at a higher level (by 15-20%; Table 2).

Thus opioid peptides delay the rate of development of hypotension after acute blood loss. Agonists of μ-opiate receptors, including DAGO, are more effective in this respect. In the posthemorrhagic period the rate of normalization of MBP is accelerated by a greater degree by agonists of Δ-opiate receptors, including DADL and dalargin. The positive effect of synthetic enkephalin analogs on the hemodynamics can be explained on the grounds that the energy reserves of the myocardium and, in particular, the system of high-energy compounds (ADN), are preserved to a greater degree as a result of their action. Since it has been shown that the contractility of the heart is enhanced by enkephalins [3, 5], preservation of the energy reserves of the myocardium discovered in the present investigation provides an explanation of the possible

mechanism of this enhancement, which leads to diminution of the hypotension and which contributes to some degree to the reduction of mortality of the animals from hemorrhagic shock [8]. The greater degree of preservation of ATP under the influence of dalargin in the myocardium also has been found in the liver tissue of animals receiving the peptide after traumatic shock [2].

The results indicate that synthetic analogs of enkephalins may be useful preparations for the treatment of hemorrhagic and traumatic shock, although this is by no means always true for toxic-infectious shock [1, 4].

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EFFECT OF LOW CALCIUM AND MAGNESIUM CONCENTRATIONS IN DRINKING WATER ON MONOVALENT CATIONIC AND CALCIUM TRANSPORT IN ERYTHROCYTES OF NORMOTENSIVE RATS

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In essential hypertension in man and spontaneous genetic hypertension in rats changes are present in the ion-transporting systems in the membranes of various cells [7]. There is evidence of negative correlation between the incidence of cardiovascular diseases, including arterial hypertension, and the hardness of the drinking water [8-11]. However, there is a complete absence of physiological and biochemical studies of the possible effect of low and normal concentrations of calcium and magnesium ions in the drinking water on cationic transport across cell membranes, in the literature.

The aim of this investigation was to study the effect of low and normal concentrations of these cations in drinking water on transport of monovalent cations and of calcium in rat erythrocytes.

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