# EFFECT OF OPIATE RECEPTOR AGONISTS ON THE COURSE OF HEMORRHAGIC SHOCK IN RATS

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UDC 616-005.1-001.36-085.31:547.95.547.943]-036.8-092.9

KEY WORDS: acute blood loss; opioid peptides; hemodynamics

Experience of the use of narcotic analgesics in the treatment of critical states suggests that opioids may be used in shock [9]. Information on the possibility of using various ligands of opiate receptors in shock is rather contradictory, largely due to the heterogeneity of the opiate receptors [12]. Moreover, the character of effects observed following administration of opioids may depend on the course of the shock process.

The aim of this investigation was to study the effect of agonists of μ- and δ-receptors on hemodynamic parameters after acute one-stage blood loss and after gradual hemorrhage in experiments on rats.

## EXPERIMENTAL METHOD

Experiments were carried out on 93 male Wistar rats weighing 200-250 g. One-stage acute blood loss was simulated by bleeding from the right common carotid artery in a volume of 3% of body weight [6]. In another series of experiments hemorrhagic shock was simulated by fractional withdrawal of blood in a volume of 30% of the circulating blood volume (CBV) in the course of 30 min. The preparations studied, namely the μ-agonist DAGO and the δ-agonist DADL, were injected intravenously in a dose of 1 mg/kg into animals undergoing acute blood loss immediately after the hemodynamic parameters had been recorded at the 10th minute, and into animals undergoing fractional blood loss after withdrawal of 7.5% of CBV. All the operations were performed under ether anesthesia. The arterial blood pressure (BP) was measured by the direct method in the carotid artery by means of a "Salyut" polygraph (USSR), and the heart rate (HR) was calculated from the ECG. The cardiac output (CO) was determined by the thermodilution method [2]. The stroke volume (SV) was calculated. The numerical results were subjected to analysis of variance ($\bar{X} \pm m$) and to the matched pairs test ($\bar{X}_1 - \bar{X}_2 \pm m$).

## EXPERIMENTAL RESULTS

Values of BP (in mm Hg) of intact rats were: systolic BP (SBP) 130 ± 7, diastolic (DBP) 81 ± 5, and pulse (PBP) 49 ± 4. One-stage blood loss quickly led to marked hypotension, but in the early posthemorrhagic period BP rose gradually.

In rats receiving physiological saline (PS), SBP and DBP rose parallel to one another during the first 12 min of observation, and on that account PBP increased statistically significantly compared with its value before injection of PS, but not until the 30th minute of the posthemorrhagic period (Table 1). Administration of the μ-agonist DAGO reduce the degree of increase of SBP and DBP in the early posthemorrhagic period, but the trend of PBP was the same as in the control. Injection of the δ-agonist DADL prevented the rise of DBP and had no significant effect on the course of SBP, so that PBP was increased through the action of the preparation as early as at the 12th minute of the experiment (Table 1).

The selective agonists of μ- and δ-receptors evidently differ in their effect on the time course of BP in rats undergoing one-stage blood loss. To study the mechanisms of action of opioids experiments were carried out on intact animals to study the cardiac output (CO).

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 0007-4888/89/0006-0774$12.50 

TABLE 1. Time Course of Changes in BP Parameters of Animals Undergoing One-Stage Blood Loss and Receiving Physiological Saline (PS; 1), DAGO (2), and DADL (3)

| BP, mm Hg | Time of after blood loss, min | | | |
|---|---|---|---|---|
| | 1 | 10 | 12 | 30 |
| Systolic | | | | |
| 1 | 37±2 | 52±4 | 67±5* | 76±7** |
| 2 | 32±3 | 44±3 | 47±2 | 77±6** |
| 3 | 35±2 | 40±2 | 47±2* | 71±9** |
| Diastolic | | | | |
| 1 | 28±7 | 36±4 | 55±4** | 54±5* |
| 2 | 21±2 | 29±2 | 28±1 | 48±6 |
| 3 | 23±2 | 26±2 | 23±2 | 46±6 |
| Pulse | | | | |
| 1 | 9±1 | 11±2 | 12±2 | 24±3** |
| 2 | 11±2 | 15±1 | 19±2 | 29±3** |
| 3 | 12±2 | 14±2 | 24±2** | 25±2** |

Legend. *p < 0.05, **p < 0.01 compared with corresponding values at 10th minute after blood loss.

TABLE 2. Time Course of Average BP in Rats Undergoing Fractional Blood Loss and Receiving PS, DAGO, and DADL

| Period of observation | PS | DAGO | DADL |
|---|---|---|---|
| Blood loss | | | |
| % OF CBV withdrawn | | | |
| 5 | 92±7 | 80±7 | 74±8 |
| 15 | 59±5** | 70±6 | 55±8 |
| 30 | 28±3** | 36±5** | 26±5** |
| Posthemorrhagic period | | | |
| Time, min | | | |
| 15 | 63±7* | 55±7* | 52±6* |
| 60 | 74±6 | 78±8 | 85±5 |

Legend. *p < 0.05, **p < 0.01 compared with corresponding value before injection of preparations (withdrawal of 5% of CBV).

Injection of DAGO into intact rats caused HR to fall in the 1st minute after injection from 386 to 219 beats/min ($\overline{X}_1 - \overline{X}_2 = 167$; $m = 36$; $p < 0.01$); CO was reduced from 50.4 to 36.3 ml/min ($\overline{X}_1 - \overline{X}_2 = 14.1$; $m = 4$; $p < 0.01$); SV showed no statistically significant change.

Under the influence of DADL, HR fell in the 1st minute of the experiment from 358 to 208 beats/min ($\overline{X}_1 - \overline{X}_2 = 150$; $m = 41$; $p < 0.05$). In the same period, however, there was a marked increase of SV from 0.132 to 0.227 ml ($\overline{X}_1 - \overline{X}_2 = 0.095$; $m = 0.42$; $p < 0.05$), and thereafter until the 5th minute it showed a tendency to rise. Accordingly CO was not reduced after injection of DADL, but by the 5th minute of the experiment, it was actually increased, though not significantly, from 47.4 to 53.2 ml/min ($\overline{X}_1 - \overline{X}_2 = 5.8$; $m = 2.2$; $p < 0.05$).

In these experiments BP was not investigated although we know that both μ- and δ-agonists, injected intravenously, induce short-term hypotension [7]. With intravenous injection, the leading factor among the mechanisms whereby DAGO influences the circulation is bradycardia, inducing a fall of CO and hypotension. The fall of BP in response to injection of DADL [7] is evidently due to a decrease in tone of the resistive vessels and in the total peripheral vascular resistance (TPVR) a characteristic feature of the action of certain opiates [11]. The data explain differences in the time course of the changes in BP under the influence of DAGO and DADL in acute blood loss.

In rats subjected to fractional blood loss and treated with PS a progressive fall of the average BP was observed until the end of bleeding (Table 2). After injection of DAGO the rate of decline of the average BP was less. For instance, after withdrawal of 15% of CBV there was no significant change in BP, and by the end of blood loss it was reduced by only 44% compared with initially. In response to injection of DADL the rate of fall of BP during blood loss also was slower than in the control, but faster than after injection of DAGO (Table 2). In the early posthemorrhagic period, the average value of BP was gradually restored. BP was increased 15 min after the end of blood loss in animals receiving PS by 125%, in those receiving DADL by 100%, and receiving DAGO by 53%. At the 60th minute after hemorrhage the values of BP were closely similar in animals of all three groups (Table 2).

Opioid peptides thus reduce the intensity both of development of hypotension in the course of blood loss and of restoration of BP in the early posthemorrhagic period; the effect of the μ-agonist DAGO, moreover, was more marked than that of the δ-agonist DADL. Differences in the effect of DAGO and DADL and the character of their action on the time course of BP in rats undergoing fractional blood loss are rather difficult to explain by the direct effect of opioids on the cardiovascular system.

The slow rise of BP in the posthemorrhagic period discovered in the present experiments in rats receiving DAGO and DADL can be explained by reduction of hypersecretion of catecholamines, a characteristic feature of the action of opioid peptides [1], for the increase in BP in the early stages after blood loss is largely due to activation of the sympathicoadrenal system [6]. The mechanisms of slowing of the fall of BP under the influence of DAGO and DADL during fractional blood loss are evidently more complex. An important contribution to their understanding may be made by information on the antihypoxid action of opioid peptides [3, 4, 8]. The hypoxia arising after blood loss has a depressor action on function of the cardiovascular system. Accordingly, until the phase of temporary self-compensation arises [5], due to activation of the sympathicoadrenal system [6], signs of posthemorrhagic collapse are as a rule observed [10]. Opioid peptides increase the resistance of the brain and myocardium to hypoxia [3, 4, 8], and may thus have a favorable influence on function of the circulatory system in the early period of acute blood loss. It is pointed out that μ-agonists have a stronger antihypoxic action than δ-agonists [3]. This view is supported by our data showing that DAGO was more effective than DADL in preventing the development of hypotension in the course of hemorrhage.

The data given above allow a number of hypotheses to be put forward, which add greatly to existing views on the effect of opioids on the course of hemorrhagic shock.

Changes in the hemodynamic parameters under the influence of opioid peptides in hemorrhagic shock are largely dependent on the character of blood loss and, in particular, on its duration, and also on the affinity of enkephalins for particular populations of opiate receptors. The direct effect of opioid peptides on hemodynamic parameters both of intact animals and in hemorrhagic shock is of short duration. Nevertheless, enkephalins may have a direct effect on the circulatory system during shock, in whose mechanisms properties of opioids such as their antihypoxic action and their antagonistic relations with the sympathetic nervous system may play an important role.

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# URINARY ENZYME EXCRETION IN RATS DUE TO HEAVY PHYSICAL WORK: EFFECT OF THE ANTIOXIDANT PHENOSAN*

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UDC 616.633.1-092:612.766.1]-085.
272.014.425-036.8-092.9

KEY WORDS: urinary gamma-glutamyl transpeptidase; renal function; physical work; antioxidants

Physical work has a significant effect on the hemodynamics of the kidneys and their excretory function. The renal blood flow is reduced during physical work in proportion to its heaviness (sometimes by 50-60%) due to the redistribution of blood in the body, caused by the increased proportion of it supplying working muscles [6]. Glomerular filtration also is reduced significantly (by 30%), although by a lesser degree. Thus, during heavy physical work, besides general hypoxemia, relative renal ischemia also develops. Of all the structures of the kidney, cells of the proximal tubules are considered to be most susceptible to hypoxia [10]. Damage to the tubular epithelium can evidently explain the increased urinary excretion of gamma-glutamyl transpeptidase (γ-GTP), a marker enzyme of renal ischemia, localized in the membrane of the brush border, which has been observed in athletes after long-distance running [8], and also the disturbance of tubular function after intensive exercises [7]. Activation of lipid peroxidation (LPO) in cell membranes is ascribed an important role in the mechanism of tissue damage during ischemia and hypoxia. The use of antioxidants in physical work has been shown to reduce the accumulation of LPO products in the blood [1], and to stabilize cell membranes, thereby preventing the release of cytosol enzymes into the blood stream [2].

The aim of this investigation was to study γ-GTP activity and the excretory function of the kidneys in rats made to do heavy physical work, and also the effect of the synthetic water-soluble antioxidant phenosan on enzyme and renal function.

## EXPERIMENTAL METHOD

Experiments were carried out on male albino rats weighing initially 190-250 g. The model of physical work consisted of making the rats swim to exhaustion (until they could swim no more) in water at a temperature of 30°C, carrying a load fixed to the base of the tail and equivalent to 10% of body weight. There were five sessions of swimming with intervals of 1-2 days between sessions. Before the rats began their heavily laden swimming sessions (HS) they were adapted to the experimental conditions by swimming for 15 min daily on 3 successive days, carrying a load equivalent to 2% of body weight. At the end of the series of adapative swimming exercises and after each HS the rats were kept for 18 h in metabolism cages in order to collect the urine, and using sodium azide as bacteriostatic agent. There were three series of experiments. In series I, on 47 rats (group 1) the effect of physical work on urinary enzyme excretion, diuresis, urinary creatinine excretion, and creatinine clearance was investigated. In the experiments of series

*Potassium salt of di-tert-butylhydroxyphenylpropionic acid – Translator

Research Institute of Urology, Ministry of Health of the RSFSR. Institute of Chemical Physics, Academy of Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Sciences of the USSR, N. A. Lopatkin.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 107, No. 6, pp. 670-672, June, 1989. Original article submitted May 15, 1988.

  