CENTRAL HISTAMINE-INDUCED REVERSAL OF CRITICAL HAEMORRHAGIC HYPOTENSION IN RATS – HAEMODYNAMIC STUDIES

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Volume-controlled irreversible haemorrhagic shock in rats produced by blood withdrawal until stabilisation of critical mean arterial pressure (MAP) 20-25 mmHg is associated with an extreme decrease in cardiac index (CI) and an increase in total peripheral resistance index (TPRI), with reductions in renal (RBF), hindquarters (HBF) and mesenteric blood flow (MBF), and leads to the death of all control animals within 30 min. Histamine (100 nmol) injected intracerebroventricularly (i.c.v.) in the early phase of critical hypotension produces a prompt and long-lasting increase in MAP and heart rate, with a 100% survival for 2 h after treatment. The effects are associated with the rise in the circulating blood volume and CI, and the decrease in TPRI, with the increase in RBF and HBF, and persistently lowered MBF. Both splenectomy and ligation of the suprahepatic veins inhibit histamine-induced increase in circulating blood volume as well as cardiac and regional haemodynamic effects. It can be concluded that histamine administered icv activates central endogenous compensatory mechanisms, which leads to the reversal of haemorrhagic shock conditions due to the mobilisation of blood from venous reservoirs, the increase in circulating blood volume and its redistribution. Moreover, histamine evokes the rises in CI and perfusion of the renal and skeletal muscle vascular regions.

Key words: histamine, haemorrhagic shock, cardiac and regional haemodynamics, rat

INTRODUCTION

Histaminergic system is implicated in central cardiovascular regulation since blockade of histamine N-methyltransferase, and thus inhibition of endogenous histamine catabolism, leads to the pressor effect in normotensive animals (1). Similarly, exogenous histamine administered intracerebroventricularly (i.c.v.) to anaesthetised normotensive rats evokes a dose-related, lasting 5-30 min., increase in mean arterial pressure (MAP) and heart rate (HR) as a result of the stimulation of central \( H_1 \) and \( H_2 \) histamine receptors (2, 3). The mechanisms of the effects are the activation of the sympathetic system and the secretion of arginine vasopressin (AVP) (2, 4).

The previous studies by the author reveal that in irreversible experimental volume-
controlled haemorrhagic shock produced by withdrawal of approximately 50% of total blood volume and resulting in the death of all control rats within 30 min., histamine given icv produces few times higher increases in MAP and HR in comparison to normovolaemic animals (5). Moreover, the pressor effect in these conditions is long lasting and associated with a 100% survival for 2 h after histamine (100 nmol) treatment. The action is due to stimulation of central H₁ histamine receptors, since H₁ receptor antagonist chlorpheniramine inhibits the effects. In contrast, pre-treatment with both H₂ receptor blocker ranitidine and H₃ receptor antagonist thioperamide fails to influence cardiovascular changes produced by histamine (5). It is postulated that differences in central histamine-induced cardiovascular effects between normotensive and hypotensive animals are due to its action antagonistic to endogenous opioid system which becomes activated in pre-terminal conditions of haemorrhagic shock and which inhibits cardiovascular centre function (6, 7). Studies of Guarini et al. demonstrate that also other anti-analgesic (non-opioid) neurotransmitters, including adrenocorticotrophin (ACTH) and many ACTH-fragments, α-melanocyte stimulating hormone (α-MSH) and thyrotropin-releasing hormone (TRH), at doses which show little or no activity in normotensive animals, reveal the resuscitating effects in haemorrhagic shock (8, 9).

The study was undertaken to examine central histamine-induced cardiac and regional haemodynamic effects in critical haemorrhagic hypotension. Splenectomy and ligation of the suprahepatic veins were performed to assess the importance of blood mobilisation from venous reservoirs and its redistribution. Similarly to the previous studies (5, 10), the experimental haemorrhagic shock model by Guarini et al. (8) was chosen to examine histamine action at constant initial values of both the critical MAP and the volume of circulating blood. The preliminary data were in part presented at the XXIXth Annual Meeting of the European Histamine Research Society (11).

MATERIAL AND METHODS

Animals

Male Wistar rats weighing 230-250 g (5-6 months old) were used in all experiments. The animals were housed five per cage, under controlled conditions of temperature (20-22°C), humidity (60-70%), lighting (12 h light/dark cycle) and provided with food and water ad libitum. All procedures were carried out according to EU directives and reviewed by local ethical committee.

Surgical procedure

After induction of general anaesthesia with ethylurethane (1.25 g/kg intraperitoneally) and heparinisation (Heparinum, 600 IU/kg iv), rats were implanted with catheters in the right carotid artery and the right jugular vein. MAP and HR were measured using the pressure transducer RMN-201 (Temed, Poland) and the electrocardiograph Diascope 2 (Unitra Biazet, Poland),
respectively. For icv treatment rats were prepared 5-7 days before the experiment by stereotaxic implantation, under ethylurethane anaesthesia, of polyethylene cannula into the right brain lateral ventricle as described previously (4). All icv injections were made in 5.0 µl of saline vehicle.

Electromagnetic probes (Type 1RB2006, Hugo Sachs Elektronik, Germany) were implanted around the right renal and superior mesenteric arteries to monitor renal (RBF) and mesenteric (MBF) blood flow and around the distal abdominal aorta, below the level of the ileoceleal artery, to monitor perfusion of the hindquarters (HBF) (12) using Transit Time Flowmeter Type 700 (Hugo Sachs Elektronik, Germany; Transonic System Inc., USA).

In separate groups of artificially ventilated animals (Harvard Rodent Ventilator model 683, Harvard Apparatus, USA), with frequency of 60 breaths/min and tidal volume 2.0-2.5 ml, the electromagnetic probe (Type 2.5SB379, Hugo Sachs Elektronik, Germany) was implanted around ascending aorta to monitor cardiac output (CO). Cardiac index (CI) and total peripheral resistance index (TPRI) were calculated by dividing CO (ml/min) by body weight, and MAP (mmHg) by CI (ml/min/100 g b.w.), respectively. All measurements of blood flow were started after a 30 min. adaptation period to avoid influences of probes implantation.

Drugs

The following drugs were used: histamine dihydrochloride (Research Biochemicals Incorporated, USA), ethylurethane (Riedel-de Haën, Germany), heparinum (Polfa, Poland). All drug solutions were prepared fresh on the day of the experiment.

Experimental protocol

Irreversible haemorrhagic shock, according to the modified method of Guarini et al. (8), was produced by intermittent blood withdrawal from the catheter inserted into the right jugular vein over a period of 15-25 min., until MAP decreased to and stabilised at 20 - 25 mmHg. Five minutes after the termination of bleeding, haemorrhage-shocked rats were injected icv with histamine (100 nmol) or saline (5 µl) 5 min. after ligation of the suprahepatic veins, after splenectomy performed 7 days earlier or in sham-operated animals. The 100 nmol dose of histamine was chosen since in the earlier studies by the author, in the same experimental model, it produced a complete reversal of haemorrhagic hypotension and long-lasting survival (5, 10). The animals were monitored continuously for 2 h after treatment, or until death if it occurred earlier. Body temperature was monitored by a rectal thermometer and maintained at 36.5-37.5°C using the heating lamp throughout the experiment. All the experiments were performed between 8.00 and 12.00.

In separate groups (n=6), circulating blood volume was measured 20 min. after i.c.v. injection in histamine-treated groups and in saline-treated sham-operated group, according to the method used by Guarini et al. (13), by bleeding from the arterial catheter.

Statistical analysis

All data are given as means ± SEM with p<0.05 considered as the level of significance. Differences between groups were analysed using a one-way analysis of variance (ANOVA). Significance of differences within groups over time was tested with a paired Student’s t-test. The Fisher’s exact probability test was used to examine significant differences in survival rates.
RESULTS

The pre-haemorrhage values of MAP and HR in all groups did not reveal significant differences. Similarly, there were no differences among the groups with respect to CI, TPRI and peripheral blood flows.

The total bleeding volume for the induction of critical hypotension was $2.24 \pm 0.16 \text{ ml/100g body weight}$. Bleeding from MAP $85 \pm 6 \text{ mmHg}$ to 20-25 mmHg was associated with a decrease in HR from $347 \pm 21 \text{ beats/min}$ to $226 \pm 24 \text{ beats/min}$ (Fig. 1). Haemorrhage produced in all groups a decrease in CI from $25.34 \pm 1.28 \text{ ml/min/100g b.w.}$ to $4.24 \pm 0.52 \text{ ml/min/100g b.w.}$ and an increase in TPRI from $3.35 \pm 0.21 \text{ mmHg/ml/min/100g b.w.}$ to $5.66 \pm 0.77 \text{ mmHg/ml/min/100g b.w.}$ (Fig. 2). The effects were accompanied by a significant decrease in RBF from $5.92 \pm 0.48 \text{ ml/min}$ to $0.89 \pm 0.08 \text{ ml/min}$, HBF from $4.48 \pm 0.76 \text{ ml/min}$ to $0.84 \pm 0.11 \text{ ml/min}$ and MBF from $5.15 \pm 0.83 \text{ ml/min}$ to $0.79 \pm 0.12 \text{ ml/min}$, with no differences between groups (Fig. 3).

Fig. 1. Changes in MAP and HR in rats subjected to haemorrhagic shock after histamine treatment (0 min, arrows) and splenectomy (●), ligation of the suprahepatic veins (●) and in the sham-operated group (■), and in saline-treated (0 min., arrows) animals after splenectomy (◇), ligation of the suprahepatic veins (◇) and in the sham-operated group (□); six animals per group; from 5 min. in all groups $p<0.05$ vs. corresponding values in the sham-operated histamine-treated group.
Effects of centrally administered histamine on MAP, HR and the survival rate in haemorrhagic hypotension

In the control icv saline-treated animals no significant changes in MAP and HR were noted (Fig. 1), and all the animals died within 30 min.

In the sham-operated group histamine (100 nmol i.c.v.) caused a rapid long-lasting increase in MAP and HR which started within first minute after injection, reached a maximum within 5-15 min. and lasted to the end of the experiment (Fig. 1). All animals in this group were still alive 2 h after treatment with MAP and HR values being 79 ± 8 mmHg and 321 ± 19 beats/min, respectively, not significantly different from the pre-bleeding values. In animals after splenectomy histamine-induced rises in MAP and HR were significantly lower (Fig. 1), and the survival rate was 83% (not different from the sham-operated group; Fisher’s exact probability test). In contrast, in the group after ligation of the suprahepatic veins...
Fig. 3. Changes in regional blood flows in rats subjected to haemorrhagic shock after histamine treatment (0 min., arrows) and splenectomy (●), ligation of the suprahepatic veins (◆) and in the sham-operated group (■), and in saline-treated (0 min., arrows) animals after splenectomy (◇), ligation of the suprahepatic veins (○) and in the sham-operated group (□); six animals per group; for RBF and HBF from 5 min. and for MBF from 20 min. in all groups p<0.05 vs. corresponding values in the sham-operated histamine-treated group.
veins histamine induced only short-lasting increases in MAP and HR (Fig. 1) with the survival ratio 0% (p<0.05 vs. the sham-operated group, Fisher’s exact probability test).

**Cardiac and regional haemodynamic effects associated with histamine-induced reversal of haemorrhagic hypotension**

In the sham-operated group histamine produced a long-lasting increase in CI and a decrease in TPRI (Fig. 2), with associated rises in RBF and HBF (Fig. 3) which started within 1 min. of the icv treatment and persisted to the end of experiment (2 h). In contrast, there were no changes in MBF within first 15 min. after treatment, and the increase started between 15 and 20 min. (Fig. 3). Both splenectomy and ligation of the suprahepatic veins significantly inhibited histamine-induced cardiac and regional haemodynamic effects (Fig. 2-3). In saline icv injected animals no CI, TPRI and regional blood flow changes were observed (Fig. 2-3).

**Changes in circulating blood volume associated with histamine-induced reversal of haemorrhagic hypotension**

In the saline-treated sham-operated group the volume of circulating blood was 0.77 ± 0.14 ml/100 g b.w. In contrast, in the sham-operated group 20 min. after histamine icv treatment there was a significant increase in the circulating blood volume to 1.62 ± 0.22 ml/100 g b.w. In histamine-treated rats after splenectomy and ligation of the suprahepatic veins the values were significantly lower, being 1.16 ± 0.15 ml/100 g b.w. and 0.72 ± 0.28 ml/100 g b.w., respectively.

**DISCUSSION**

The present study in a rat model of irreversible haemorrhagic shock demonstrates for the first time cardiac and regional haemodynamic effects elicited by centrally administered histamine which lead to the restoration of circulatory function. Moreover, the major role of blood mobilisation from venous reservoirs and its redistribution in histamine-induced reversal of haemorrhagic hypotension is presented.

Critical haemorrhagic hypovolaemia is associated with the extreme decrease in CI due to lowering of circulating blood volume as well as reflex-induced bradycardia elicited from left ventricular unmyelinated nerve fibres (14). Integrated neural, humoral and local mechanisms which become activated in haemorrhagic shock conditions lead to centralisation of the circulation due to redistribution of circulating blood, mainly by the increase in the sympathetic nervous system activity, the secretion of AVP and the activation of renin-angiotensin system (14). Therefore, the vascular
resistance increases, with concomitant blood flow reduction in vascular beds with the dense $\alpha$-adrenergic receptor expression. The reduced circulating blood volume is shunted to regions with lower regional vascular resistance, mainly to the cerebral and coronary circulation. This results in an increased TPRI, and that is why the strongly reduced cardiac output is sufficient to perfuse the vital organs with an appropriate amount of blood to maintain their function. The present study confirms the increase in TPRI, with decreased RBF, HBF and MBF, associated with the extremely low CI value in post-bleeding period.

According to the earlier studies (5, 10), histamine (100 nmol) given centrally in irreversible haemorrhagic shock in rats produces the pressor effect with the recovery of MAP to pre-haemorrhage value. The mechanisms involved in histamine action include the central activation of the sympathetic nervous system (11) and the secretion of AVP (15). There are two ways of histamine-induced release of AVP – directly, via activation of vasopresinergic neurones of supraoptic and paraventricular nuclei, and indirectly, via local release of norepinephrine (2). In addition, there is a postulated another mechanism – the increase in the secretion of ACTH and its resuscitating properties (8, 9). CRH and AVP, whose release is increased by central histamine, belong to activators of the pituitary-adrenal system and stimulate synergistically the release of ACTH (16-18). Moreover, AVP, via a histaminergic mechanism located in hypothalamus and hippocampus, is involved in stimulation of the ACTH secretion (19). Therefore, central histamine action may involve activation of direct and indirect mechanisms leading to reversal of haemorrhagic hypotension.

The present study demonstrates that histamine-induced normalisation of MAP is associated with the significant rise in CI and the decrease in TPRI, with the increases in regional blood flows, especially in RBF and HBF, whereas MBF is persistently lowered. Prolonged vasoconstriction in the mesenteric vascular bed demonstrates the mobilisation of blood from venous reservoirs, and thus the increase in circulating blood volume and its redistribution. Indeed, histamine evokes over a 100% increase of circulating blood volume 20 min. after treatment, and both splenectomy and ligation of the suprahepatic veins diminish the haemodynamic effects. The present study confirms the fact that the mobilisation of blood from reservoirs in the venous part of circulatory system is of essential importance in reversal of haemorrhagic shock, which was previously concluded by Guarini et al. in the same haemorrhagic shock model (13, 20-22).

Histamine-induced increase in CI results not only from the rise in circulating blood volume due to its mobilisation. The earlier studies by the author demonstrate that central histamine is able to reverse reflex-induced bradycardia associated with critical hypovolaemia (5, 10). Also in the present study the normalisation of HR within 5-10 min. after icv histamine treatment has been observed. Moreover, the previous studies by the author show that central histamine-induced reversal of haemorrhagic hypotension in rats is accompanied by an increase in residual blood volume at the
end of the experiment (2 h), probably as a result of the transfer of fluid from the extravascular to the intravascular compartment (10). The effects are associated with the decrease in haematocrit value, haemoglobin concentration, erythrocyte and platelet count due to haemodilution. Probably all three mechanisms, the increase in circulating blood volume, the reversal of reflex-induced bradycardia and the transfer of fluid to the intravascular compartment participate in histamine-induced rise in CI, and secondary in the improvement in peripheral tissues perfusion.

In the previous study (10) it was demonstrated that central histamine action in haemorrhagic shock includes not only improvement of cardiovascular system function but also respiratory compensation. In conditions of critical hypotension histamine evokes a long-lasting rise in respiratory rate which, together with circulatory compensation, leads to biphasic blood acid-base changes – the initial increase of metabolic acidosis with the decrease in arterial and venous pH, bicarbonate concentration and base excess (BE), followed by almost a complete recovery of blood gas and acid-base parameters to the pre-bleeding values, with normalisation of arterial and venous pH, \( \text{Pco}_2 \), bicarbonate concentration and BE at the end of the experiment (10).

In conclusion, the present results demonstrate that activation of central histamine receptors in rats subjected to critical haemorrhagic hypotension leads to reversal of shock conditions due to improvement in circulatory functions resulting from the mobilisation of blood, especially from venous reservoirs, and its redistribution. Histamine-induced effects are associated with the increase in CI and the decrease in TPRI, which causes the improvement in the perfusion of peripheral tissues, especially in renal and skeletal muscle vascular beds.

REFERENCES


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