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CARDIOVASCULAR EFFECTS OF HISTAMINE ADMINISTERED INTRACEREBROVENTRICULARLY IN CRITICAL HAEMORRHAGIC HYPOTENSION IN RATS

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The study was designed to determine the cardiovascular effects of histamine administered intracerebroventricularly (icv) in a rat model of volume-controlled haemorrhagic shock. The withdrawal of approximately 50% of total blood volume resulted in the death of all control saline icv treated animals within 30 min. Icv injection of histamine produced a prompt dose-dependent (0.1—100 nmol) and long-lasting (10—100 nmol) increase in mean arterial pressure (MAP), pulse pressure (PP) and heart rate (HR), with a 100% survival of 2 h after treatment (100 nmol). The increase in MAP and HR after histamine administration in bled rats in comparison to the normovolaemic animals was 2.7—3.3- and 1.3—3.6-fold higher, respectively. Pretreatment with chlorpheniramine (50 nmol icv), H₁ receptor antagonist, inhibited the increase in MAP, PP, HR and survival rate produced by histamine, while chlorpheniramine given alone had no effect. Neither ranitidine (50 nmol icv), H₂ histamine receptor antagonist, nor thiopiramide (50 nmol icv), H₃ receptor blocker, influenced the histamine action, however, when given alone, both evoked the pressor effect with elongation of survival time. It can be concluded that histamine administered icv reverses the haemorrhagic shock conditions, and histamine H₁ receptors are involved.

Key words: histamine, haemorrhagic shock, central cardiovascular regulation, rat

INTRODUCTION

Considerable evidence has accumulated over the years on the role of the central histaminergic system in control of the cardiovascular system function (1). It is postulated that histaminergic neurons which are mainly concentrated in the tuberomammillary nucleus of the posterior hypothalamus innervate and may influence the central cardiovascular regulatory related structures, especially nuclei of the anterior and medial hypothalamus and the nucleus of the solitary tract (1, 2).

The central pressor effect of exogenous histamine, as a result of the increase in sympathetic activity and secretion of arginine vasopressin (AVP), has been widely confirmed in a number of species (3, 4). In normotensive rats histamine
given intracerebroventricularly (icv) evokes a short-lasting rise in blood pressure accompanied by tachycardia in anaesthetized animals and bradycardia in conscious animals (1). Similarly, endogenous histamine influences the cardiovascular centre since the same changes are observed after icv injection of SKF 91488, histamine N-methyltransferase inhibitor, which blocks histamine catabolism, thus elevating its brain levels (5).

Both central H₁ and H₂ histamine receptors participate in the central cardiovascular histamine effects in rats since microinjections of H₁ and H₂ histamine receptor antagonists given icv (6, 7) or into the posterior hypothalamus (8) inhibit the central effects of histamine. On the other hand, involvement of H₃ histamine receptors, which have been identified on histaminergic and non-histaminergic neurons in the central nervous system (9), in cardiovascular regulation in rats is not clear.

There is a general agreement that in pre-terminal conditions of haemorrhagic shock endogenous analgesic (opiodergic) and anti-analgesic (melanocortinergic, cholecystokininergic, thyreoliberinergic) systems in the central nervous system become activated (10). Studies of recent years reveal not only the influence on pain transmission, but also the resuscitating effects on cardiovascular parameters during the haemorrhagic shock of many anti-analgesic (non-opioid) neurotransmitters, including ACTH and many ACTH-fragments, CCK peptides, and thyrotropin-releasing hormone, at doses which show little or no activity under normal conditions (10). It is well known that histamine belongs to the central endogenous neurotransmitters which modulate the information from the nociceptors (11) in a way at least in part independent of endogenous opioids, since it participates in both opioid- and non-opioid-mediated antinociception (12, 13). On the other hand, the increase in the rate of endogenous histamine release from the posterior hypothalamus has been reported to result from a decrease in blood pressure after intravenous injection of sodium nitroprusside and haemorrhage in cats (14). This suggests that histamine may play an important role in the central cardiovascular regulation during the disturbance of circulatory homeostasis in hypovolaemic hypotension. Therefore, the present study was undertaken to examine the circulatory effects of histamine given icv in anaesthetized rats in the model of irreversible haemorrhagic hypovolaemia. The experimental haemorrhagic shock model by Guarini et al. (15) was chosen to study histamine action at constant initial values of both the critical mean arterial pressure (MAP) and the volume of circulating blood in critical hypovolaemia.

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, in controlled conditions of temperature (22 ± 2°C), humidity
(60–70%), lighting (12 h light/dark cycle) and provided with food and water ad libitum. All procedures were approved by the Ethical Committee of the Silesian Medical University.

**Surgical procedure**

After induction of general anaesthesia with ethylurethane (1.25 g/kg intraperitoneally), heparinization (Heparinum, 600 IU/kg iv) and clean dissection rats were implanted with catheters in the right femoral artery and vein. MAP and pulse pressure (PP) were recorded by the pressure transducer RMN—201 (Temed, Poland). Heart rate (HR) was recorded by means of three electrodes implanted subcutaneously on the chest and connected to the electrocardiograph Diacope 2 (Unitra, Poland). For icv treatment rats were prepared 5–7 days before the experiment by stereotaxically implanting, under ethylurethane anaesthesia, polyethylene cannula into the right brain lateral ventricle. A trephine hole was drilled through the skull 1.5 mm lateral to the midline and 1.0 mm posterior to the bregma. The cannula was lowered 4.0–4.5 mm below the skull and was fixed to the skull with acrylic cement. Rats were then kept in individual cages until the time of experiment. All icv injections were made in 5.0 µl of saline vehicle using a Hamilton microsyringe. Correction of icv administration was verified by injecting 10.0 µl of Evans blue dye through the cannula at the end of each experiment, followed by decapitation and dissection of the brain. The results were excluded if the dye did not penetrate the ventricular system.

**Drugs**

The following drugs were used: histamine dihydrochloride, chlorpheniramine maleate, ranitidine hydrochloride, thioperamide maleate (Research Biochemicals Incorporated, USA), ethylurethane (Riedel-de Haën, Germany), heparinum (Pollfa, 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. (15), was produced by intermittent withdrawal of blood from the venous catheter over a period of 15–25 min until MAP, automatically calculated and continuously digitally displayed, decreased to and stabilized at 20 to 25 mmHg. Five minutes after termination of bleeding, haemorrhage-shocked rats were injected icv with: (I) histamine (0.1–100 nmol) five minutes after icv pretreatment with saline, or (II) histamine (100 nmol) five minutes after icv pretreatment with chlorpheniramine (50 nmol), ranitidine (50 nmol) or thioperamide (50 nmol). In control groups normovolaemic rats were injected with (III) histamine (0.1–100 nmol icv) five minutes after pretreatment with saline. The animals were continuously monitored for 2 h after treatment, or until death, if it occurred earlier. Body temperature was monitored by a rectal thermometer and maintained at 37 ± 0.5°C using the heating lamp throughout the experiment. All the experiments were performed between 12.00 and 16.00.

**Statistical analysis**

All data are given as means ± standard error with p < 0.05 considered as the level of significance. Statistical evaluation of MAP, PP and HR values was performed by analysis of variance. Separate comparisons were made for data obtained before bleeding, after bleeding and after treatment. In the case of after-treatment data, ANOVA was followed by Dunnett’s test for multiple comparisons with the control. The Fisher’s exact probability test was used to examine significant differences in survival rates.
RESULTS

The pretreatment baseline values of MAP, PP and HR in experimental groups did not reveal significant differences. The total bleeding volume for the induction of critical hypotension was $2.11 \pm 0.16$ ml/100 g body weight, which is approximately 50% of the estimated total blood volume (16). Bleeding from MAP $92 \pm 7$ mmHg to 20—25 mmHg was associated with the decrease in PP from $24 \pm 8$ mmHg before haemorrhage to $4 \pm 2$ mmHg after shock induction and the decrease in HR from $345 \pm 25$ beats/min to $257 \pm 32$ beats/min. In the control saline-treated group all the bled animals died within 30 min.

Effects of icv administered histamine on MAP, PP, HR and survival rate in haemorrhagic hypotension

The icv histamine administration in rats bled to a critical hypotension caused a dose-dependent (0.1—100 nmol) increase in MAP (Fig. 1A), PP (Fig. 1B) and HR (Fig. 1C) which started immediately after injection and reached a maximum within 10—30 min. The pressor effect after 0.1 and 1 nmol of histamine was short-lasting and MAP, PP and HR returned to the predrug value in approximately 20 min. The mean survival times after 0.1 and 1 nmol of histamine were $28 \pm 5$ and $31 \pm 7$ min, respectively, and were not significantly different in comparison to the control value. In contrast to the above, histamine given at the dose of 10 and 100 nmol produced a long-lasting increase in MAP, PP and HR and elongation of survival time. After administration of 10 nmol of histamine 66% of animals survived to the end of the experiment ($p < 0.05$ vs saline-treated group). In the group injected with 100 nmol of histamine all animals were still alive 2 h after treatment with MAP and HR values ($86 \pm 11$ mmHg and $363 \pm 18$ 1/min, respectively) not significantly different from the prebleeding values.

Effects of icv administered histamine on MAP, PP and HR in normovolaemic rats

In anaesthetized normovolaemic, non-bled rats, histamine injected icv evoked a dose-dependent (1.0—100 nmol) increase in MAP (Fig. 2A) and HR (Fig. 2B). The MAP response began within 1 min of drug administration, reached a maximal increase of $10 \pm 3$ mmHg for 1 nmol, $16 \pm 4$ mmHg for 10 nmol and $28 \pm 6$ mmHg for 100 nmol within 5—10 min and returned to the predrug value in 10—20 min. The increase in HR, similar to changes in MAP, started immediately after histamine administration and reached within 15—20 min the maximal values of $16 \pm 5$, $41 \pm 10$ and $76 \pm 14$ beats/min for doses of 1, 10 and 100 nmol, respectively, and basal values within 20—30 min.
Fig. 1. Influence of icv injection of histamine (0.1 nmol — ■, 1.0 nmol — ○, 10 nmol — ▲, 100 nmol — □) on MAP (A), PP (B) and HR (C) in rats bled to haemorrhagic shock; six animals per group; from 5 min. for all MAP and HR values (0.1—100 nmol) and all PP values (1.0—100 nmol) in histamine-treated groups p < 0.05 versus corresponding values in saline-treated group (×).
Fig. 2. Dose-dependent increase in MAP (A) and HR (B) following icv administration of histamine in normovolaemic rats (■) and in critical haemorrhagic hypotension (●); six animals per group; basal MAP values: 92 ± 7 mmHg and 22 ± 2 mmHg, respectively; basal HR values: 345 ± 25 beats/min and 257 ± 32 beats/min, respectively; increases in MAP and HR after all histamine doses in hypovolaemic rats are significantly different from those in normovolaemic animals.

Effects of icv pretreatment with histamine receptor antagonists on icv histamine-induced changes in MAP, PP and HR in haemorrhagic shock

Intracerebroventricular pretreatment with chlorpheniramine (50 nmol), H₁ histamine receptor antagonist, inhibited the influence of histamine (100 nmol) on MAP (Fig. 3A), PP (Fig. 3B), HR (Fig. 3C) and survival rate in haemorrhagic shock, while chlorpheniramine given alone did not affect MAP, PP, HR and survival time in comparison to the control, saline-treated group.

Pretreatment with ranitidine (50 nmol icv), H₂ histamine receptor blocker, did not influence the central histamine (100 nmol) action on MAP (Fig. 3A), PP (Fig. 3B), HR (Fig. 3C) and survival rate, however, ranitidine given alone produced a hypertensive response with the increase in MAP and PP, positive chronotropic effect and the increase in survival rate to 50% in comparison to the control group (p < 0.05, Fisher’s exact probability test).

Pretreatment with thioperamide (50 nmol icv), H₃ histamine receptor antagonist, had no influence on anti-shock histamine (100 nmol icv) action, whereas, thioperamide alone significantly increased MAP (Fig. 3A), PP (Fig. 3B) and HR (Fig. 3C), without effect on survival rate.
Fig. 3. Influence of icv chlorpheniramine (CHL, 50 nmol), ranitidine (RAN, 50 nmol), thioperamide (THI, 50 nmol) and saline (SAL) administered 5 min before histamine (HI, 100 nmol icv) on MAP (A), PP (B) and HR (C) in haemorrhage-shocked rats; six animals per group; histogram heights indicate values before bleeding (□), after bleeding (□) and 15 min after histamine treatment in experimental groups or saline administration in control groups (□); p < 0.05 versus corresponding values in histamine-treated (*) and saline-treated (**) rats.
The present results demonstrate for the first time that histamine given icv restores the cardiovascular functions and improves the survival rate in rats bled to the critical hypovolaemic hypotension. Intracerebroventricular histamine administration during the experimental volume-controlled haemorrhagic shock evokes prompt dose-dependent, long-lasting increase in MAP, PP, HR (10—100 nmol) up to the complete reversal to the pre-haemorrhage values and 100% survival of 2 h (100 nmol).

In normovolaemic rats histamine injected icv also evokes the pressor effect, however, in contrast to the bled animals, its maximal value after equimolar doses is 2.7—3.3-fold lower. Another difference between the hypertensive effect of icv histamine in normotensive animals and the reversal of the shock conditions is the duration of the effect: in normovolemic animals the increase in blood pressure lasts 10—20 min, while in hypovolaemic rats it is still present 2 h after treatment.

Severe hypovolaemia, as confirmed by the present study, is associated with the reduction in HR due to stimulation of left ventricular unmyelinated nerve fibres causing an increase in parasympathetic and a decrease in sympathetic activity. It has also been found that central histamine can reverse the Betzold-Jarish reflex-induced bradycardia. Moreover, the study has shown that the increase in HR in haemorrhage-shocked rats is 1.3—3.6-fold higher than that in normovolaemic animals.

The present experiments demonstrate that H₁ histamine receptors participate in the central cardiovascular histamine effects in haemorrhagic hypotension, since chlorpheniramine significantly inhibits histamine action on MAP, PP, HR and the survival rate. Similar changes in MAP have been observed after blockade of H₁ central receptors with chlorpheniramine and subsequent histamine icv administration in conscious rats in normotension (6). Moreover, icv administration of pyridylethylamine, selective H₁ histamine receptor agonist, dose-dependently increases MAP in conscious rats (17).

In contrast, pretreatment with ranitidine (50 nmol icv) fails to affect MAP, PP and HR changes evoked by icv histamine in critical haemorrhagic hypotension. Surprisingly, ranitidine itself produces pressor reaction and improvement in survival rate similar to the histamine effect. In normotensive rats activation of H₂ receptors with selective agonist imiprimidine produces a dose-dependent pressor response, which is blocked by BMY—25505, H₂ receptor antagonist (17). However, in some studies H₂ antagonists given icv were found to evoke a hypertensive response (1, 6). This effect may be associated with the blockade of brain stem H₂ histamine receptors, which mediate the hypotensive action (18), or with affinity of H₂ antagonists to H₃ receptors controlling histamine biosynthesis and release (1).
It has been shown that blockade of presynaptic central histamine $H_3$ receptors with thiopental (50 nmol ivc) in haemorrhagic shock results in the pressor reaction, similar to that produced by histamine itself, however, pretreatment with thiopental does not influence histamine action. In contrast, in normotensive conscious guinea pigs activation of central $H_3$ receptors with ivc injected R-α-methylhistamine causes a transient increase in MAP associated with a decrease in HR, followed by a prolonged decrease in MAP and a pronounced decrease in HR, and pretreatment with thiopental attenuates the decrease in MAP and HR (19). The possible mechanism of this reaction is that activation of central $H_3$ receptors in normotensive animals leads to a decrease in the sympathetic drive to the vasculature and to the heart, and on the other hand, it diminishes the release of AVP (19).

The causes of differences in histamine influence on cardiovascular regulation in haemorrhagic shock and in normovolaemia are unclear. In normotensive anaesthetized rats the central histamine action on the cardiovascular system has been reported to be mainly mediated by the activation of central sympathetic mechanisms (7). The evidence is based on the results of studies in which the ganglionic blockade inhibited the centrally-mediated pressor effect after ivc histamine administration (7). This mechanism may also play an important role in central histamine-induced reversal of haemorrhagic hypotension since the sympathetic nerve activity is essential in the maintenance of blood pressure in haemorrhagic shock (20). Another mechanism of ivc histamine action in normotensive rats is associated with the massive increase in AVP secretion due to central norepinephrine release and stimulation of local $\alpha_1$-receptors (1, 21). After exogenous histamine administration ivc or into the paraventricular nuclei of the anterior hypothalamus an increase in the plasma AVP concentration has been reported (1, 21). On the other hand, in haemorrhagic hypotension plasma AVP concentration increases and AVP directly contributes to the peripheral regulation of the blood pressure, which is particularly important in the spontaneous recovery from haemorrhagic hypotension (20). Additional stimulation of AVP secretion after ivc histamine administration may participate in anti-shock central histamine action.

Finally, histamine contributes to the secretion of CRH and AVP, activators of the pituitary-adrenal system (22 — 24). The two peptides synergistically stimulate the release of ACTH, which belongs to the anti-opioid neurotransmitters participating in modulation of information from nociceptors, and demonstrating anti-shock properties (10). Moreover, AVP, via a histaminergic mechanism located in hypothalamus and hippocampus, is involved in stimulation of the ACTH secretion (25). This mechanism also may be associated with the central histamine action in haemorrhagic hypotension.
since exogenous ACTH and ACTH fragments injected intravenously evoke reversal of the haemorrhagic shock conditions (10, 15).

The present results support the hypothesis that the central histaminergic system activation, similarly to other systems associated with non-opioid mediators participating in pain transmission, plays an important role in blood pressure regulation during the haemorrhagic hypovolaemia since histamine given icv produces the long-lasting pressor reaction with an increase in survival rate in the model of irreversible volume-controlled haemorrhagic shock in rats. Histamine H₁ receptor activation is involved in central histamine-induced reversal of haemorrhagic shock, while blockade of both H₂ and H₃ receptors results in action similar to that of histamine.

REFERENCES


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