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Inflammation Research

Cardiac and regional haemodynamic effects of histamine N-methyltransferase inhibitor metoprine in haemorrhage-shocked rats

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Abstract. *Objective and design:* The increase in central histamine concentrations after inhibition of histamine N-methyltransferase (HNMT) activity is associated with the reversal of critical haemorrhagic hypotension, therefore the present study examines cardiac and regional haemodynamic effects of HNMT inhibitor metoprine in haemorrhage-shocked rats.
Material: Cardiovascular parameters were measured in 72 and central histamine concentrations in 12 male Wistar rats anaesthetised with ketamine/xylazine.
Treatment: Metoprine (5, 15 mg/kg) was administered intraperitoneally to normotensive and critically-hypotensive rats with mean arterial pressure (MAP) 20–25 mmHg. Haemorrhage-shocked rats were pre-treated intracerebroventricularly with histamine H_3 receptor agonist R(–)-α-methylhistamine (10 µg) or saline.
Methods: MAP, heart rate (HR) and cardiac and regional haemodynamics were monitored within 2 h after treatment, or to death if it occurred earlier. Histamine concentrations were measured using enzyme immunoassay. ANOVA followed by Neuman-Keules test, and Fisher's exact test were used to compare the results.
Results: Bleeding resulted in an extreme decrease in cardiac index (CI), an increase in total peripheral resistance index (TPRI) and the death of control animals within 30 min. Metoprine induced increases in MAP and HR which were significantly higher in hypotensive than in normotensive animals. The resuscitating effect of metoprine (15 mg/kg) was associated with a rise in CI, a decrease in TPRI, and a 100% survival at 2 h. TPRI changes resulted from decreased renal, hindquarters and mesenteric vascular resistance. R(–)-α-methylhistamine inhibited metoprine-induced increases in endogenous histamine concentrations in the cerebral cortex (0.89 ± 0.12 vs. 1.25 ± 0.29 nmol/g of wet tissue; $P < 0.05$), hypothalamus (4.37 ± 0.42 vs. 5.74 ± 0.47 nmol/g of wet tissue; $P < 0.01$) and medulla oblongata (0.39 ± 0.07 vs. 0.65 ± 0.28 nmol/g of wet tissue; $P < 0.05$), diminished haemodynamic effects and decreased the survival rate at 2 h to 33% ($P < 0.05$ vs. the saline-pre-treated group).
Conclusions: The results support the hypothesis that histaminergic system activation leads to mobilisation of compensatory mechanisms in haemorrhagic hypotension.

Key words: Histaminergic system – Haemorrhagic hypotension – Metoprine – R(–)-α-methylhistamine – rat

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Introduction

There is increasing experimental evidence to support the hypothesis that the histaminergic system is involved in mobilisation of compensatory mechanisms in response to the action of potentially dangerous stimuli which disturb homeostasis, including dehydration, changes in blood pressure, nociceptive stimuli and other kinds of stress [1]. Microdialysis studies confirm that a decrease in mean arterial pressure (MAP) is associated with an increase in histamine release from the posterior hypothalamus in cats [2]. Furthermore, both endogenous [3] and exogenous histamine [4], acting via H_1 receptors, is able to reverse the critical haemorrhagic hypotension and to increase the survival rate at 2 h in a rat model of irreversible haemorrhagic shock.

Inhibition of histamine N-methyltransferase (EC 2.1.1.8; HNMT) activity is a generally accepted pharmacological method used to explore in vivo the biological effects of the histaminergic system [1]. Previous studies demonstrate that in anaesthetised normotensive rats, inhibition of HNMT activity with SKF 91488, similarly to exogenous histamine [4–5], produces a dose-dependent short-lasting pressor effect accompanied by a rise in heart rate (HR) [6–7]. The effect is due to an increase in the sympathetic system activity and a secretion of arginine vasopressin (AVP) [1]. Interestingly, rises in MAP and HR elicited by intracerebroventricularly (icv) administered SKF 91488 or histamine in the early phase of irreversible haemorrhagic hypotension are

long-lasting and significantly higher compared to those in normovolaemic animals [3–4]. These findings indicate an involvement of the histaminergic system in the maintenance of circulatory homeostasis in critical hypotension.

The present paper extends previous studies on the role of the histaminergic system in central cardiovascular regulation in critical haemorrhagic hypotension, with the aim of clarifying the cardiac and regional haemodynamic effects of endogenous central histamine-induced reversal of haemorrhagic shock in rats. Metoprine, a competitive inhibitor of HNMT, was administered intraperitoneally (ip) since, in contrast to SKF 91488, it can pass the blood-brain barrier. In addition to measurements of peripheral haemodynamics, tissue levels of histamine in the cerebral cortex, hypothalamus and medulla oblongata were determined. Moreover, R(–)-α-methylhistamine, an agonist of H_3 receptors which inhibits histamine synthesis and release [8], was used to study the effects of HNMT blockage. The experimental haemorrhagic shock model by Guarini et al. [9] was chosen, as in the previous studies [3–4, 10], to examine histamine action at constant initial values of critical MAP and volume of circulating blood.

Material and methods

Animals

Studies were carried out in 84 male Wistar rats weighing 250–300 g (5–6 months old). The animals were housed in individual cages in the animal colony, 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. Each studied group consisted of six animals. All experimental procedures were performed according to the EU directives and reviewed by the Ethics Committee of the Medical University of Silesia (Notification No 5/03).

Surgical preparations

For icv treatment the rats were prepared 5–7 days before the experiment by stereotaxic implantation, under ketamine/xylazine (100 mg/kg/10 mg/kg; ip) anaesthesia, of polyethylene cannula into the right brain lateral ventricle [4]. All icv injections were made in a volume of 5 µl over a period of 60 s, and the correctness of injections was verified as described previously [4].

On the day of the experiment, after induction of general anaesthesia under ketamine/xylazine, rats were implanted with catheters filled with heparinized saline (300 IU/ml) in the right carotid artery and the right jugular vein.

Cardiovascular parameter measurements

MAP and HR were measured using the pressure transducer RMN-201 (Temed, Zabrze, Poland) and the electrocardiograph Diascope 2 (Unitra Biazet, Bialystok, Poland), respectively. Electromagnetic probes (Type 1RB2006, Hugo Sachs Elektronik, March-Hugstetten, Germany) were implanted around the right renal and superior mesenteric arteries to monitor renal (RBF) and mesenteric blood flow (MBF), and around the distal abdominal aorta, below the level of the ileocaecal artery, to monitor perfusion of the hindquarters (HBF) using Transit Time Flowmeter Type 700 (Hugo Sachs Elektronik, March-Hugstetten, Germany) [11]. Regional vascular resistance was calculated by dividing MAP (mmHg) by regional blood flow (ml/min).

In separate groups of artificially ventilated animals (Harvard Rodent Ventilator model 683, Harvard Apparatus, Inc., Holliston, MA, USA), with frequency of 60 breaths/min and tidal volume 2.0–2.5 ml, the electromagnetic probe (Type 2.5SB379, Hugo Sachs Elektronik, March-Hugstetten, Germany) was implanted around ascending aorta to monitor cardiac output (CO) [11]. Cardiac index (CI) and total peripheral resistance index (TPRI) were calculated by dividing CO (ml/min) by body weight (b.w.), 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 probe implantation.

Haemorrhagic shock protocol

Irreversible haemorrhagic shock, according to the method of Guarini et al. [9], was produced by intermittent blood withdrawal from the catheter inserted into the right jugular vein over a period of 15–25 min, until MAP stabilised at 20–25 mmHg.

Experimental protocol

To study cardiovascular effects of HNMT blockage, metoprine (5 or 15 mg/kg; ip) was injected in two groups of haemorrhage-shocked rats 5 min after termination of bleeding, and in two groups of normovolaemic animals. In two other groups pre-treated just before start of a bleeding period with R(–)-α-methylhistamine (10 µg; icv) or saline (5 µl; icv), metoprine (15 mg/kg; ip) was injected 5 min after bleeding termination. In the control groups, rats were treated with equivalent volumes of 0.9% solution of NaCl (0.5 ml/100 g b.w.; ip).

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 RMN-201 (Temed, Zabrze, Poland) 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 a.m.

Determination of residual blood volume

In haemorrhage-shocked rats, plasma volume was measured 20 min after saline injection, and 20 min and 120 min after metoprine (15 mg/kg) treatment using the Evans blue dye dilution technique [12]. Blood volume was calculated based on haematocrit value which was measured after centrifugation of the blood samples (0.2 ml) collected from the jugular vein.

Drugs

The following drugs were used: metoprine (Burroughs Wellcome Co., Research Triangle Park, NC, USA), R(–)-α-methylhistamine dihydrochloride, xylazine hydrochloride (Research Biochemicals Inc., Natick, MA, USA), ketamine (Gedeon Richter, Budapest, Hungary), heparin (Polfa, Warszawa, Poland), lactic acid, $NaHCO_3$ (POCh, Gliwice, Poland).

To maintain isoosmolarity and to avoid stimulation of osmoreceptors all injected agents, except metoprine, were dissolved in water or hypotonic solutions of NaCl. Osmolarity was measured using osmometer Marcel OS 3000 (Marcel, Bialystok, Poland) based on the freezing-point method. Metoprine was dissolved in 1% lactic acid and was neutralised with $NaHCO_3$. All ip injections were performed at a volume of 0.5 ml/100 g b.w. R(–)-α-methylhistamine and saline were injected icv in a volume of 5 µl over a period of 60 s. All drug solutions were prepared freshly on the day of the experiment.

Histamine assay

Endogenous central histamine concentrations were measured in two groups of haemorrhage-shocked rats pre-treated with R(–)-α-methylhistamine or saline 1 h after injection of metoprine (15 mg/kg; ip). After decapitation of the rats, their brains were rapidly removed and the cerebral cortex, hypothalamus and medulla oblongata were quickly dissected on a glass plate chilled on ice, according to the procedure of Glowinski and Iversen [13]. The samples were homogenised by sonication – the hypothalamus in 0.3 ml, the cerebral cortex and medulla oblongata in 10 volumes (w/v) of ice-cold 0.9% NaCl. After centrifugation (3000 rpm for 20 min at 4 °C), 100 µl of the supernatant was used for measurement of histamine concentration by commercially available enzyme immunoassay (Immunotech, Marseille, France). Similarly, plasma histamine concentrations were measured in blood samples (0.5 ml) taken from the femoral vein before bleeding, after bleeding termination and 20 min after metoprine or saline treatment in saline-pre-treated haemorrhage-shocked rats. The sensitivity of the method was 0.2 nmol/l. The mean recovery of standard histamine was 93% (ranging from 87 to 107%) [3].

Statistics

All values are given as means ± standard deviation with $P < 0.05$ considered as the level of significance. Statistical evaluation was performed by analysis of variance (ANOVA) and the post-ANOVA test of Neuman-Keules. The Fisher's exact test was used to examine significant differences in survival rates.

Results

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

The total bleeding volume for the induction of critical hypotension was 2.36 ± 0.17 ml/100 g b.w. In the control saline icv pre-treated group, bleeding from MAP 85.7 ± 4.2 mmHg to 20–25 mmHg was associated with a decrease in HR from 365 ± 16 beats/min to 219 ± 23 beats/min.

Cardiovascular effects of metoprine in normotensive and critically hypotensive rats

In normotensive animals, metoprine (5, 15 mg/kg; ip) produced dose-dependent increases in MAP (Fig. 1A) and HR (Fig. 1B). The action started 10–30 min after injection and reached a maximum 60–90 min after treatment. The pressor effect was long-lasting, and HR, but not MAP, returned to the initial values within 2 h after injection.

Metoprine administered to rats bled to a critical hypotension caused dose-dependent increases in MAP (Fig. 1A) and HR (Fig. 1B) which were significantly higher compared to those in normovolaemic rats. Metoprine at a dose of 5 mg/kg produced only transient increases in MAP and HR, and the survival rate at 2 h was 50%. In contrast, metoprine given at a dose of 15 mg/kg evoked long-lasting rises in MAP (Fig. 2A) and HR (Fig. 2B) and increased the survival rate at 2 h to 100% ($P < 0.05$ vs. the control saline-treated animals). Since a 15 mg/kg dose of metoprine provided a 100% survival rate at 2 h after treatment, it was chosen in further studies to establish metoprine-induced haemodynamic action.

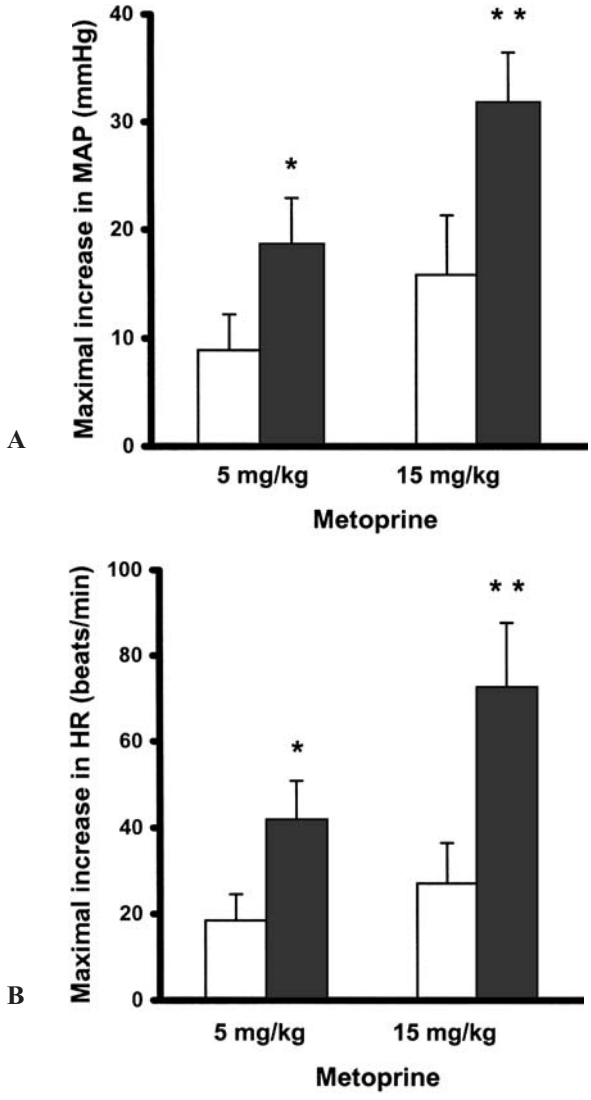

Fig. 1. Metoprine-induced maximal increases in mean arterial pressure (MAP; A) and heart rate (HR; B) within 2 h after ip treatment in normotensive (open columns) and critically hypotensive rats (filled columns). Data are represented as mean ± SD, six animals per dose. Baseline MAP and HR values in all normotensive animals were 87.1 ± 4.5 mmHg and 361 ± 11 beats/min, respectively. Baseline MAP and HR values in critically hypovolaemic rats were 22.3 ± 0.8 mmHg and 231 ± 22 beats/min, respectively. * $P < 0.05$, ** $P < 0.01$ vs. normotensive rats.

Influence of R(–)-α-methylhistamine on cardiac and regional haemodynamic effects associated with metoprine-induced reversal of haemorrhagic hypotension

Changes in MAP, HR and cardiac and regional haemodynamics over time in the metoprine- and saline-treated groups are presented in Fig. 2–4. Haemorrhage produced in the control icv saline-injected group a decrease in CI from 24.0 ± 2 ml/min/100 g b.w. to 4.2 ± 0.6 ml/min/100 g b.w. (Fig. 2C) with an increase in TPRI from 3.5 ± 0.3 mmHg/ml/min/100 g b.w. to 5.3 ± 0.5 mmHg/ml/min/100 g b.w. (Fig. 2D). These effects were associated with decreases in RBF from 5.82 ± 0.51 ml/min to 0.92 ± 0.18 ml/min (Fig. 3A), HBF from 5.09 ± 0.83 ml/min to 0.57 ± 0.19 ml/min (Fig. 3B) and

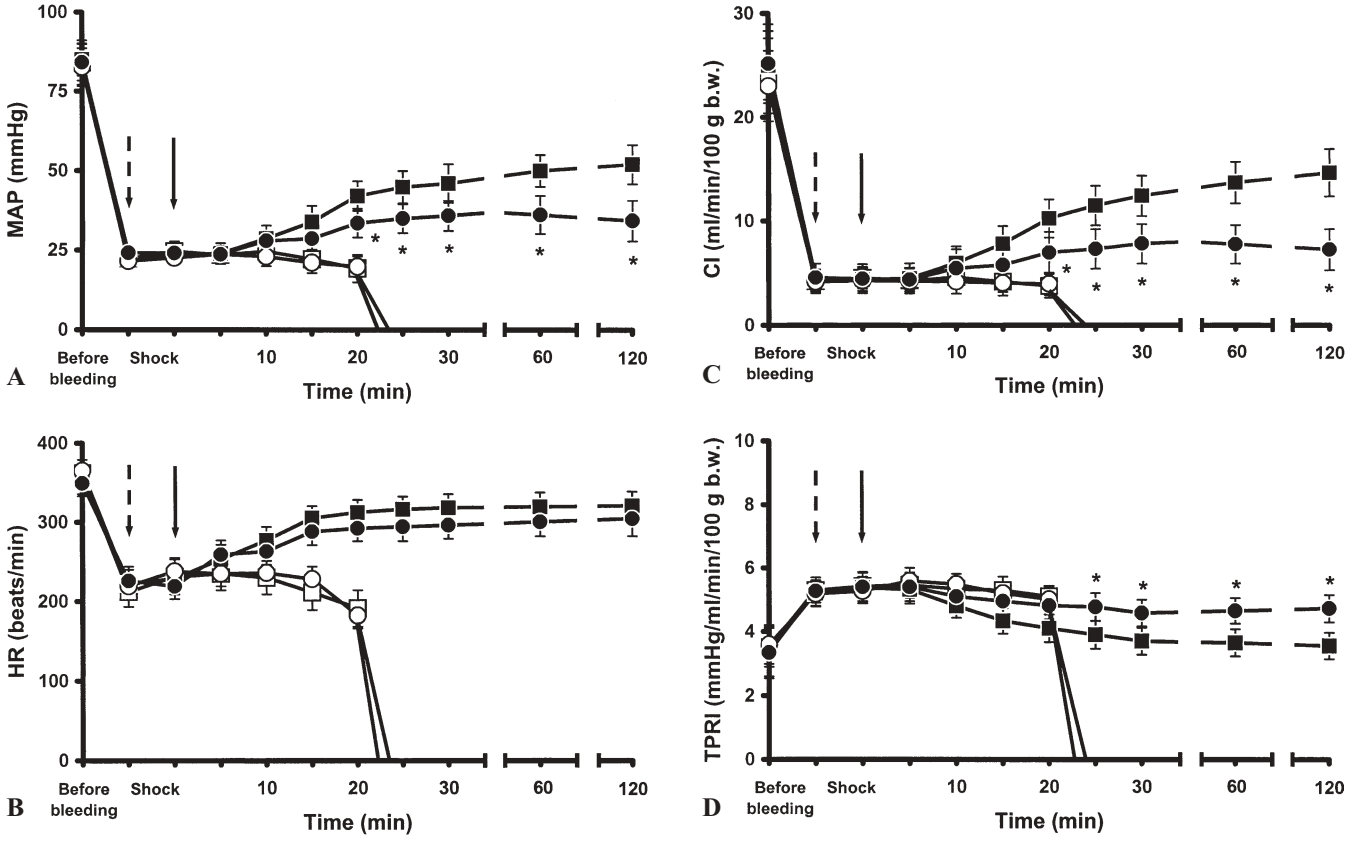

Fig. 2. Influence of icv pre-treatment (–5 min; ↓) with R(–)-α-methylhistamine (10 µg; ●, ○) and saline (5 µl; ■, □) on MAP (A), HR (B), cardiac index (CI; C) and total peripheral resistance index (TPRI; D) changes after ip treatment (0 min; ↓) with metoprine (15 mg/kg; filled symbols) and saline (0.5 ml/100 g b.w.; open symbols). Data are represented as mean ± SD, six animals per group. Since 15 min, for all parameters in saline-treated groups $P < 0.05$ vs. the saline-pre-treated metoprine-injected group. In the R(–)-α-methylhistamine pre-treated group, * $P < 0.05$ vs. the saline pre-treated metoprine-injected group.

MBF from 5.71 ± 0.94 ml/min to 0.64 ± 0.21 ml/min (Fig. 3C) due to increased regional vascular resistance (Fig. 4A–C).

In the saline-pre-treated group, metoprine produced long-lasting increases in MAP (Fig. 2A), HR (Fig. 2B) and CI (Fig. 2C), and a decrease in TPRI (Fig. 2D). Peripheral haemodynamic changes were associated with a decrease in renal (RVR), hindquarters (HVR) and mesenteric vascular resistance (MVR), which led to increases in RBF, HBF and MBF (Fig. 3–4). These effects started within 15 min after treatment and persisted until the end of the experiment (2 h).

Pre-treatment with R(–)-α-methylhistamine significantly inhibited metoprine-induced changes in MAP (Fig. 2A), as well as cardiac and regional haemodynamic effects (Fig. 2C–D, Fig. 3–4). Moreover, histamine H_3 receptor agonist decreased the survival rate at 2 h to 33.33% in the metoprine-treated group ($P < 0.05$ vs. saline-pre-treated metoprine-injected group; Fisher's exact test).

Residual blood volume changes associated with metoprine-induced reversal of haemorrhagic hypotension

Haemorrhage produced a significant decrease in haematocrit values progressing with time, with no differences between metoprine- and saline-treated groups before bleeding and 20 min after treatment, the values in the control saline-treated group were 45 ± 3.2%, and 37.86 ± 3.36%, respectively. There was a further decrease in haematocrit value to 30.88 ± 2.66% 2 h after treatment in the metoprine-injected group.

In both metoprine-treated and control animals 20 min after treatment there were no differences in residual blood volumes, the values being 3.05 ± 0.3 ml/100 g b.w. and 3.13 ± 0.22 ml/100 g b.w., respectively. A significant increase in residual blood volume was noted 2 h after metoprine administration to 4.16 ± 0.48 ml/100 g b.w. ($P < 0.001$ vs. the value in the metoprine-treated group at 20 min after shock induction).

Concentrations of histamine in the cerebral cortex, hypothalamus and medulla oblongata

There were significantly higher histamine concentrations in the saline-pre-treated animals than in the R(–)-α-methylhistamine-pre-treated group in the cerebral cortex (0.89 ± 0.12 vs. 1.25 ± 0.29 nmol/g of wet tissue; $P < 0.05$), hypothalamus (4.37 ± 0.42 vs. 5.74 ± 0.47 nmol/g of wet tissue; $P < 0.01$) and medulla oblongata (0.39 ± 0.07 vs. 0.65 ± 0.28 nmol/g of wet tissue; $P < 0.05$) 1 h after metoprine (15 mg/kg) injection (Fig. 5).

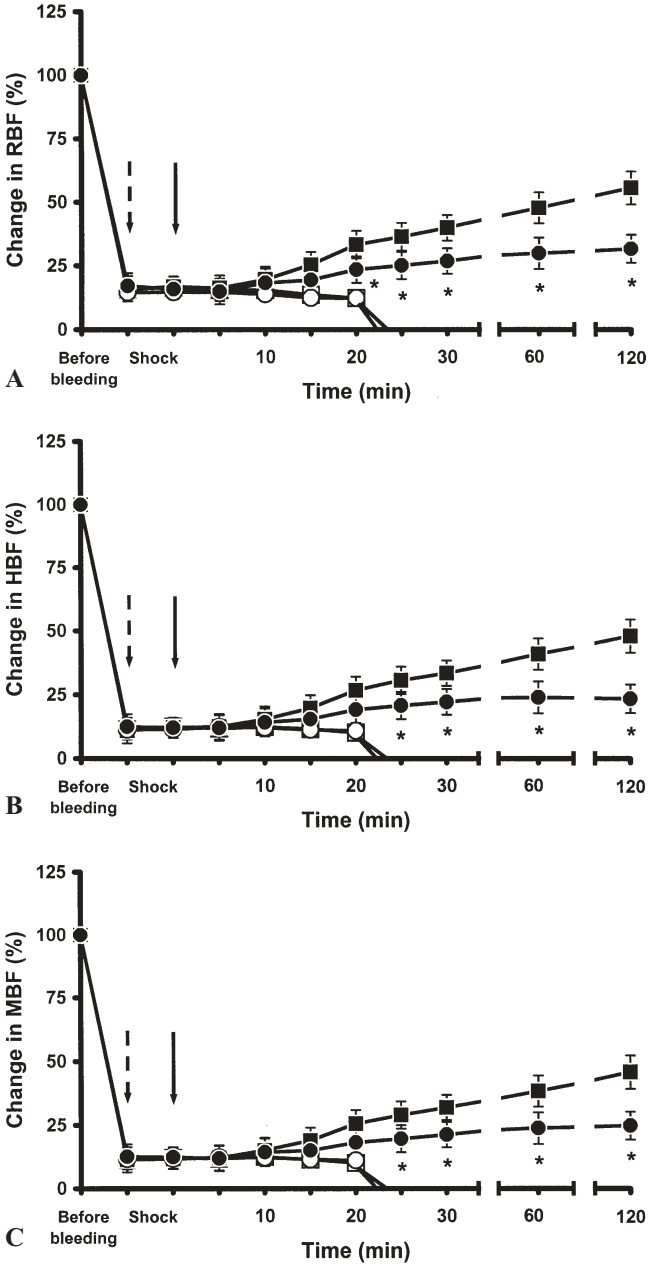

Fig. 3. Influence of icv pre-treatment (–5 min; ↓) with R(–)-α-methylhistamine (10 µg; ●, ○) and saline (5 µl; ■, □) on renal (RBF; A), hindquarters (HBF; B) and mesenteric blood flow (MBF; C) changes after ip treatment (0 min; ↓) with metoprine (15 mg/kg; filled symbols) and saline (0.5 ml/100 g b.w.; open symbols). Data are represented as percent of the initial pre-bleeding value, mean ± SD are given; six animals per group. Initial RBF, HBF and MBF were 5.82 ± 0.51 ml/min, 5.09 ± 0.83 ml/min and 5.71 ± 0.94 ml/min, respectively. In the control groups, for RBF since 15 min, and for HBF and MBF at 20 min $P < 0.05$ vs. saline-pre-treated metoprine-injected group. In the R(–)-α-methylhistamine pre-treated group, * $P < 0.05$ vs. the saline pre-treated metoprine-injected group.

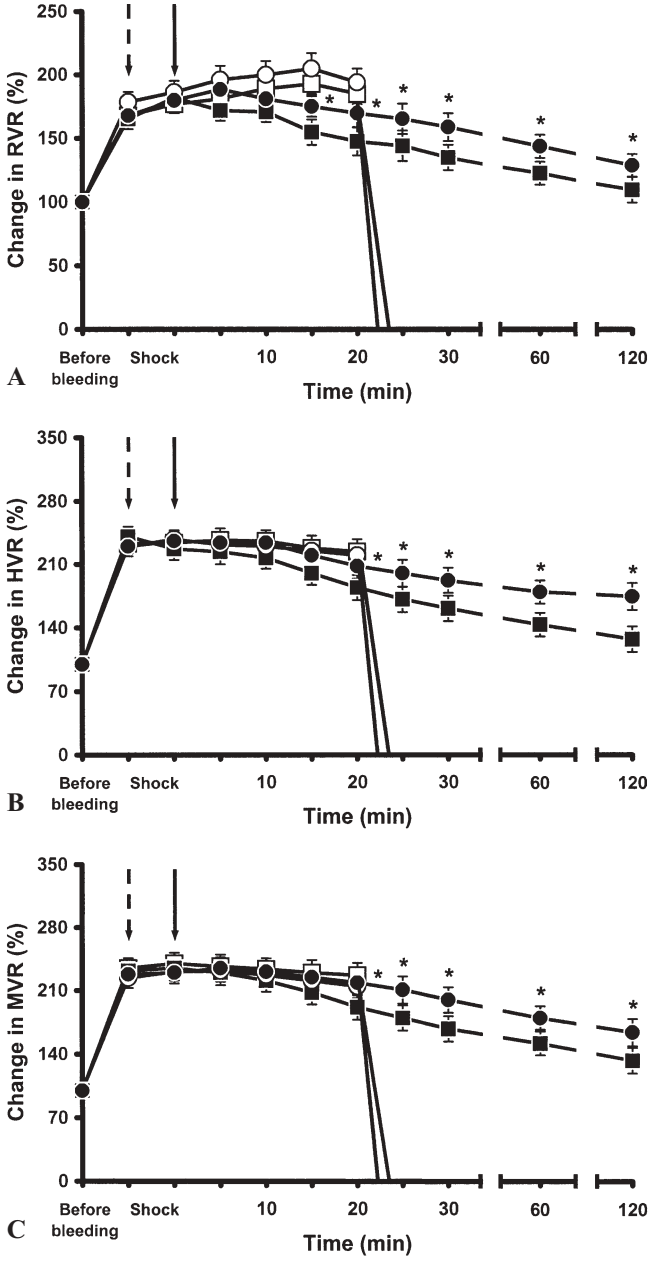

Fig. 4. Influence of icv pre-treatment (–5 min; ↓) with R(–)-α-methylhistamine (10 µg; ●, ○) and saline (5 µl; ■, □) on renal (RVR; A), hindquarters (HVR; B) and mesenteric vascular resistance (MVR; C) changes after ip treatment (0 min; ↓) with metoprine (15 mg/kg; filled symbols) and saline (0.5 ml/100 g b.w.; open symbols). Data are represented as percent of the initial pre-bleeding value, mean ± SD are given; six animals per group. Initial RVR, HVR and MVR were 14.43 ± 4.53 mmHg/ml/min, 16.5 ± 4.92 mmHg/ml/min and 14.71 ± 4.77 mmHg/ml/min, respectively. In the control groups, for RVR and HVR since 15 min, and for MVR at 20 min $P < 0.05$ vs. saline-pre-treated metoprine-injected group. In the R(–)-α-methylhistamine pre-treated group, * $P < 0.05$ vs. the saline pre-treated metoprine-injected group.

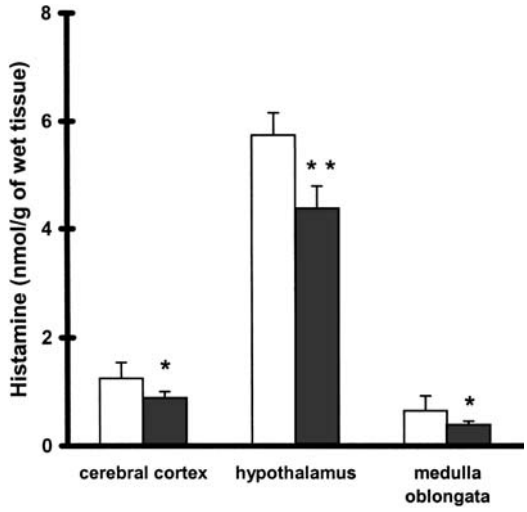

Fig. 5. Concentrations of histamine in the cerebral cortex, hypothalamus and medulla oblongata after metoprine (15 mg/kg; ip) injection and pre-treatment with saline (open columns) and R(–)-α-methylhistamine (filled columns) in haemorrhage-shocked rats. Data are represented as mean ± SD, six animals per group. * $P < 0.05$, ** $P < 0.01$ vs. saline-pre-treated group.

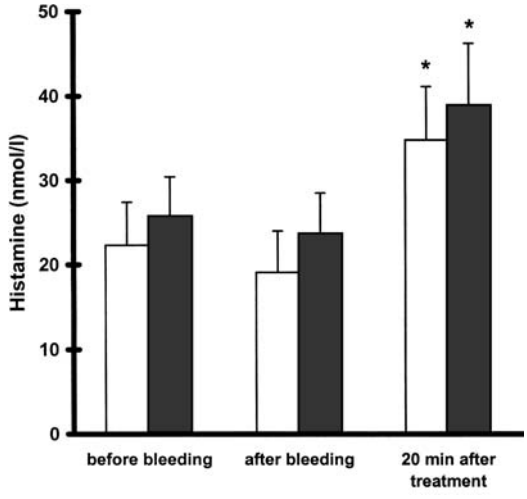

Fig. 6. Plasma histamine concentrations before bleeding, after bleeding termination and 20 min after ip treatment with saline (0.5 ml/100 g b.w.; open symbols) and metoprine (15 mg/kg; filled columns) in icv saline-pre-treated rats. Data are represented as mean ± SD, six animals per group. * $P < 0.05$ vs. pre-bleeding values.

Plasma histamine concentrations

Pre-bleeding and post-bleeding plasma histamine concentrations in the control saline-treated group were 22.3 ± 4.9 nmol/l and 19.1 ± 5.7 nmol/l, respectively, with no differences between groups (Fig. 6). Both in saline-treated and metoprine-treated groups there was an increase in plasma histamine concentration 20 min after shock induction up to 34.8 ± 8.2 nmol/l and 38.9 ± 6.3 nmol/l, respectively, however, without significant differences between groups (Fig. 6).

Discussion

The present study demonstrates for the first time cardiac and regional haemodynamic effects elicited by peripherally administered metoprine which lead to the reversal of critical haemorrhagic hypotension in rats. Moreover, the results show that central pre-treatment with the H_3 histamine receptor agonist R(–)-α-methylhistamine inhibits metoprine-induced effects.

Metoprine is a generally accepted HNMT inhibitor previously used to study the influence of the histaminergic system on pain perception [14], regulation of body water balance [15], anxiety [16] and learning and memory processes [17]. The study by Hough et al. demonstrates that metoprine (10 mg/kg; ip) inhibits HNMT activity in the rat brain by more than 80% [18]. Indeed, the present results show significantly higher histamine concentrations in the cerebral cortex, hypothalamus and medulla oblongata after metoprine treatment compared to those in the saline-injected haemorrhage-shocked rats [3, 19].

A comparison of the maximal metoprine-induced increases in cardiovascular parameters demonstrates that it produces dose-dependent rises in MAP and HR both in normotensive and haemorrhage-shocked rats. Thus, the present study confirms earlier findings by Lecklin et al. [15] that metoprine, by increasing central histamine concentrations, induces a rise in blood pressure in normotensive rats. Interestingly, however, increases in MAP and HR in haemorrhagic hypotension are significantly higher than in normovolaemia. Similar differences between critically hypotensive and normotensive rats have earlier been demonstrated with regard to exogenous histamine administered centrally [4], as well as endogenous histamine [3, 19]. As postulated, the possible explanation is the central histamine-induced activation of compensatory mechanisms in haemorrhagic shock. The previous study based on a rat model of blood volume/blood pressure-controlled haemorrhagic hypotension demonstrates that SKF 91488, at a dose which does not influence cardiovascular regulation in anaesthetised normovolaemic rats, produces an increase in blood volumes necessary to induce hypotension of 40 and 20 mmHg [7]. Furthermore, pre-treatment with histidine decarboxylase inhibitor (S)-α-fluoromethylhistidine, which decreases central histamine concentrations, reduces the volumes of blood required to achieve critical MAP 20–25 mmHg [19].

The chosen pressure-controlled model of shock by Guarini et al. [9] is a model of severe haemorrhage, since it is associated with an early initiation of the sympathoinhibitory phase of cardiovascular regulation, and development of hypoxaemia and severe metabolic acidosis [20–21]. Indeed, critical hypotension is associated with pronounced bradycardia [3–4], which, as postulated, results from the stimulation of left ventricular unmyelinated nerve fibres and a reflex-induced increase in parasympathetic and a decrease in sympathetic activity [22]. The study confirms that hypotension of 20–25 mmHg is associated with an extreme decrease in CI and an increase in TPRI. Rises in regional vascular resistance can be explained by the activation of humoral compensatory mechanisms in the post-bleeding period [22].

The mechanisms of integrated haemodynamic response to hypovolaemia depend on a balance between central opioid

peptides, demonstrating an inhibitory influence on the cardiovascular centre neurones and delaying the activation of the compensatory mechanisms [23–24], and non-opioid neurotransmitters which reveal resuscitating action [25]. There is clear evidence not only for an increase in the release and/or turnover of neuronal histamine in haemorrhagic hypotension [2], but also for its role in mobilisation of compensatory mechanisms in shock [3–4, 11, 19–20]. These mechanisms are complex and may include the activation of the sympathetic nervous system and the renin-angiotensin system, and the secretion of AVP and proopiomelanocortin (POMC)-derived peptides [1]. Indeed, previous studies by the author demonstrate that in haemorrhage-shocked rats, histamine acting centrally is more effective in the resuscitating action than peripheral noradrenaline [26], and similarly effective as AVP [27].

Metoprine-mediated resuscitating action includes both an increase in CI and a decrease in TPRI. The present study confirms previous findings that central histamine is able to reverse reflex-induced bradycardia in critical hypotension [3–4, 11]; however, that effect cannot be responsible for the resuscitating action, especially that HR changes have little influence on MAP in haemorrhagic shock [28]. Therefore, changes in vascular resistance and the volume of circulating blood should be taken into consideration as dominant mechanisms involved in metoprine-induced effects. Interestingly, the present study fails to demonstrate an additional increase in regional vascular resistance in the metoprine-injected group in the post-treatment period. That is probably a result of extremely high RVR, HBR and MVR values, and decreased regional blood flows. Despite that, the metoprine-induced resuscitating effect can be explained by compensatory mechanisms-mediated vasoconstriction of the venous part of the circulatory system, and mobilisation of blood from its reservoirs. The previous study by the author demonstrates that exogenous histamine administered icv in haemorrhagic shock produces over a 100% increase of circulating blood volume 20 min after treatment, and both splenectomy and ligation of the suprahepatic veins diminish the effect [11]. The hepatic vascular bed belongs to the most important blood reservoirs and α_2-adrenoceptor blockage diminishes the mobilisation of blood in response to the activation of the sympathetic system in haemorrhage-shocked rats [29–30]. The earlier study by Guarini et al. reveals an essential importance of blood mobilisation for the POMC-derived peptides-induced reversal of haemorrhagic shock [29]. Furthermore, present results show that central histamine-mediated reversal of hypotension 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.

The demonstrated decrease in regional vascular resistance may result not only from an increase in the volume of circulating blood, but also from peripheral endogenous histamine-induced vasodilatation. The present results confirm the earlier finding [19] that there is an increase in plasma histamine concentration 20 min after induction of haemorrhagic shock. In addition, peripheral histamine after inhibition of its catabolism by metoprine leads, via H_3 receptors of sympathetic neurones innervating resistance vessels, to a decrease in the electrically-induced neurogenic vasopressor response in pithed rats [31]. The present study demonstrates, however, that there are no differences between metoprine- and saline-treated animals in plasma histamine levels 20 min after shock induction, and inhibition of HNMT activity does not induce further increase in the plasma histamine concentrations. Therefore, probably three mechanisms – the mobilisation of blood from venous reservoirs, reversal of reflex-induced bradycardia, and the transfer of fluid to the intravascular compartment participate in the central histamine-induced rise in CI. The improvement in peripheral tissue perfusion resulting from decreased vascular resistance is probably an effect of blood mobilisation and an increase in MAP. However, further studies are needed to establish a possible role of the tissue histamine, which in addition to nitric oxide and/or cyclooxygenase products, may participate in a loss of vascular reactivity in haemorrhagic shock [32].

Since pre-treatment with R(–)-α-methylhistamine not only prevents an increase in central histamine concentrations, but also inhibits metoprine-induced cardiovascular effects, the present study demonstrates the association between elevated central histamine concentrations and the resuscitating action. On the other hand, histamine H_3 receptors participate in regulation of the synthesis and the release not only of histamine, but also of other neurotransmitters and neuromodulators, including noradrenaline, dopamine, glutamate, serotonin, GABA, acetylcholine and biologically active peptides [1, 8]. Therefore, a possible influence of R(–)-α-methylhistamine on non-histaminergic neuronal systems cannot be excluded in the present experiment.

In conclusion, the present study demonstrates that the increase in endogenous central histamine concentrations, after peripheral administration of HNMT inhibitor metoprine in haemorrhage-shocked rats, is accompanied by the reversal of critical hypotension and the improvement in the survival rate at 2 h. The resuscitating effect is associated with the rise in CI and the decrease in TPRI, which together cause an increase in the peripheral tissue perfusion. The results are in agreement with the hypothesis that the histaminergic system activation leads to the mobilisation of compensatory mechanisms in the state of disturbed circulatory homeostasis.

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