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PRACA ORYGINALNA
ORIGINAL PAPER

The dopaminergic system is able to modulate the central histamine-induced pressor effect in hemorrhage-shocked rats

Układ dopaminergiczny może wpływać na reakcję presyjną ośrodkowo działającej histaminy u szczurów we wstrząsie krwotocznym

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ABSTRACT

INTRODUCTION: Histamine administered intracerebroventricularly (icv) induces a resuscitating effect in hemorrhage--shocked rats. Dopamine receptors are present in neuronal pathways involved in central cardiovascular regulation; therefore, the aim of the study was to examine the effects of pre-treatment with dopamine receptor antagonists on histamine-induced cardiovascular effects in hemorrhagic shock.

MATERIAL AND METHODS: Male Wistar rats subjected to a reversible hemorrhagic hypotension with mean arterial pressure (MAP) of 30–35 mmHg were anaesthetized with ketamine/xylazine (100 mg/kg + 10 mg/kg, intraperitoneally). Immediately after bleeding terminated, the animals were pre-treated icv with dopamine receptor antagonists or saline; 5 min later they were treated icv with histamine (50 nmol) or saline.

RESULTS: Hemorrhagic hypotension was accompanied by decreases in pulse pressure (PP), heart rate (HR), and mesenteric blood flow (MBF). Histamine induced increases in MAP, HR, and MBF, with a decrease in PP as compared to the control group. Pre-treatment with the dopamine D_4 receptor antagonist L-745,870 potentiated histamine-induced MAP and MBF changes, with no influence on PP or HR. There were neither the influence of the other dopamine receptor antagonists on histamine-mediated action nor the effects of dopamine receptor antagonists given alone in the control groups.

CONCLUSIONS: Dopamine, acting via D_4 receptors, is able to modulate the central histamine-induced pressor effect in hemorrhage-shocked rats.

KEYWORDS

dopamine, histaminergic system, hemorrhagic shock, rats

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STRESZCZENIE

WSTĘP: Histamina podawana do komory bocznej mózgu (*intracerebroventricular* – icv) wywołuje efekt resuscytacyjny u szczurów we wstrząsie krwotocznym. Receptory dopaminowe występują w drogach neuronalnych związanych z ośrodkową regulacją układu krążenia, dlatego celem pracy było zbadanie wpływu zablokowania receptorów dopaminowych na efekty działania histaminy we wstrząsie krwotocznym.

MATERIAŁ I METODY: Badania przeprowadzono u znieczulonych ketaminą/ksylazyną (100 mg/kg + 10 mg/kg, dootrzewnowo) samców szczurów szczepu Wistar, u których indukowano odwracalną hipotensję krwotoczną ze średnim ciśnieniem tętniczym krwi (*mean arterial pressure* – MAP) 30–35 mmHg. Niezwłocznie po zakończeniu krwotoku u zwierząt stosowano icv premedykację antagonistami receptorów dopaminowych lub 0,9-proc. roztworem NaCl; 5 minut później podawano icv histaminę (50 nmol) bądź 0,9-proc. roztwór NaCl.

WYNIKI: Hipotensji krwotocznej towarzyszyło obniżenie ciśnienia tętna (*pulse pressure* – PP), częstości rytmu serca (*heart rate* – HR) i krezkowego przepływu krwi (*mesenteric blood flow* – MBF). Histamina wywołała wzrosty MAP, HR i MBF, pozostając bez wpływu na PP. Premedykacja antagonistą receptorów dopaminowych D_4 L-745,870 nasilała wywoływane przez histaminę zmiany MAP i MBF, nie miała natomiast wpływu na PP i HR. Nie stwierdzono ani wpływu antagonistów innych receptorów dopaminowych na działanie histaminy, ani efektów samodzielnego działania blokerów receptorów dopaminowych w grupach kontrolnych.

WNIOSKI: Dopamina, działając poprzez receptory D_4, jest zdolna do modulowania reakcji presyjnej, wywoływanej przez ośrodkowo działającą histaminę u szczurów we wstrząsie krwotocznym.

SŁOWA KLUCZOWE

dopamina, układ histaminergiczny, wstrząs krwotoczny, szczury

INTRODUCTION

Hemorrhagic shock is a consequence of inadequate tissue perfusion following blood loss. It is one of the most frequent preventable causes of death in humans [1]. Taking into account hemodynamic changes, there are two phases of the response to massive hemorrhage. The initial phase results from baroreflex inhibition and is characterized by an increase in sympathetic nervous system activity (the sympathoexcitatory phase) and in total peripheral resistance (TPR) and heart rate (HR). In the second phase, there is a withdrawal of the sympathetic tone (the sympathoinhibitory phase), with decreases in cardiac output, TPR, and HR [2]. Both phases correspond to the pathophysiological/therapeutic hemorrhagic shock classification proposed in 2012, in which moderate and mild phases of shock are generally characterized by sympathoexcitation, while severe and critical shock phases – by sympathoinhibition [3].

The activity of the sympathetic nervous system originates in pre-sympathetic neurons, located mainly in the rostral ventrolateral medulla (RVLM). These neurons play a crucial role in cardiovascular regulation, in both normo- and hypotension. In hemorrhage-induced hypotension, the function of RVLM neurons is influenced by many neurotransmitters/neuromodulators. According to the classic work by Bertolini [4], opioid peptides are generally able to inhibit the activity of RVLM neurons, while non-opioid neurotransmitters/neuromodulators prolong the sympathoexcitatory phase.

In our previous studies, we clearly demonstrated a resuscitating effect of centrally acting exogenous and endogenous histamines in experimental models of hemorrhagic shock in rats [5,6,7]. Interestingly, in hemorrhagic shock conditions, histamine-induced rises in mean arterial pressure (MAP) and HR after the administration of equal doses of the amine are a few times higher than in normovolemic animals [5]. This finding allowed us to classify histamine as a central non-opioid neurotransmitter with anti-shock properties.

Dopaminergic neurons are located mainly in the substantia nigra pars compacta and the ventral tegmental area of the midbrain and form the nigrostriatal, mesocortical, and mesolimbic projections. The degeneration of dopaminergic neurons of the substantia nigra, with subsequent decreased dopamine secretion in the striatum, is responsible for the development of Parkinson's disease, the best known result of dopaminergic system dysfunction [8]. However, centrally acting dopamine also plays a role in numerous brain functions, including cognitive processes [9], motivation and reward-related behavior [10], appetite control [11], hormone secretion [12], and addiction mechanisms [13]. Moreover, dopaminergic neurons are able to influence central cardiovascular regulation. An initial study by Granata and Woodruff [14] has demonstrated increases in MAP and HR resulting from bilateral microinjections of dopamine into the area of the nucleus of the solitary tract (nucleus tractus solitarii – NTS). Since dopamine receptors are present in the NTS and are able to affect the baroreflex activity/pathway, the aim of this study

was to examine the effects of dopamine receptor blockage on the central histamine-induced pressor reaction in hemorrhage-shocked rats.

MATERIAL AND METHODS

Animals

All procedures were carried out in accordance with EU directives and were reviewed by the Local Ethics Committee in Katowice, Poland (Notification 47/2018). Male Wistar rats weighing 255–295 g (3––6 months old), housed in an animal colony under controlled conditions (temperature: 20–22 °C; humidity: 60%–70%; and 12 h light/dark cycle), and provided with standard food and water *ad libitum* were used in the experiment.

Surgical preparation

After the induction of general anesthesia with ketamine/xylazine (100 mg/kg + 10 mg/kg intraperitoneally [ip], supplemented if required), the rats were implanted in the right femoral artery and vein with catheters filled with heparinized saline (100 IU/ml). MAP, pulse pressure (PP), and HR were measured using a TAM-A transducer amplifier module and an ECGA amplifier (Hugo Sachs Elektronik, Germany), respectively.
To monitor mesenteric blood flow (MBF; transit time flowmeter module, Transonic Systems Inc., USA), an electromagnetic perivascular probe (type 1RB, Hugo Sachs Elektronik, Germany) was implanted around the superior mesenteric artery. All cardiovascular measurements started after the adaptation period (30 min).

Experimental protocol

The animals were prepared for intracerebroventricular (icv) treatment 3–5 days before the experiment by stereotaxic implantation of polyethylene cannulae into the right brain lateral ventricle under ketamine/xylazine anesthesia, as previously described [5]. All icv injections were made at a volume of 5.0 µl. The correctness of the injections was verified after experiments [5].
Reversible hemorrhagic hypotension was induced by intermittent blood withdrawal (up to 0.5 ml/min) from the catheter in the right femoral vein over a period of 15–25 min, until MAP was stabilized at 30–35 mmHg. Immediately after MAP stabilization, the animals in separate groups (each n = 6) were icv pre-treated with dopamine $D_{1/5}$, D_2, D_3, and D_4 receptor antagonists: SCH-23390 (0.1 µg), remoxipride (1 µg), U-99194 (0.16 µg), and L-745,870 (0.13 µg), respectively. After 5 min, the rats were icv injected with histamine (50 nmol) or 0.9% NaCl solution. The dosages for the dopamine receptor antagonists were taken from the literature [15,16,17]. According to the recommendations of the Local Ethics Committee, and to implement 4R principles and avoid unnecessary duplication of studies performed previously on the same rat strain using the same experimental protocol, we did not repeat experiments in the control saline--injected group and the saline-pre-treated histamine--injected group, instead citing previously published results [18,19].
Animals, always under anesthesia, were continuously monitored for 2 h after treatment to evaluate mortality. Body temperature was monitored by a rectal thermometer and was maintained at 37 ± 0.5 °C using a heat lamp throughout the experiment. The experiments were performed between 9:00 am and 2:00 pm.

Drugs

The following drugs were used: heparin (Polfa, Poland), histamine hydrochloride, U-99194 maleate (Sigma-Aldrich, USA), L-745,870 trihydrochloride, remoxipride hydrochloride, SCH-23390 hydrochloride (Tocris Bioscience, UK), ketamine hydrochloride, and xylazine (Biowet Sp. z o.o., Poland). All drug solutions were prepared on the day of the experiment.

Statistics

All values are given as means ± SD and $p < 0.05$ was considered the level of significance. Statistical evaluation of the other results entailed analysis of variance (ANOVA) and the post-ANOVA Student––Newman–Keuls test.

RESULTS

Initial, pre-bleeding values of MAP, PP, HR, and MBF did not reveal significant differences between the groups (in the control group: MAP: 87.46 ± 4.36 mmHg; PP: 23.43 ± 5.88 mmHg; HR: 215 ± 30 beats/min; and MBF: 8.15 ± 1.88 ml/min; Table I) [18,19].

Table I. Cardiovascular parameters in animals pre-treated with dopamine receptor antagonists/saline and treated with histamine/saline

Pre-treatment (icv)	Treatment (icv)	Before bleeding	After bleeding	20 min after treatment
MAP (mmHg)				
saline	saline	87.46 ± 4.36	32.88 ± 1.5*	54.73 ± 5.18* [18,19]
saline	histamine	82.65 ± 6.93	32.55 ± 1.22*	84.7 ± 4.27# [18,19]
SCH-23390	saline	88.23 ± 7.53	32.45 ± 1.12*	51.96 ± 3.91*
SCH-23390	histamine	88.31 ± 6.66	32.16 ± 1.15*	85.43 ± 5.59#
remoxipride	saline	89.01 ± 4.61	32.77 ± 1.23*	52.31 ± 5.8*
remoxipride	histamine	86.3 ± 6.52	32.16 ± 1.12*	82.9 ± 4.75#
U-99194	saline	89.61 ± 7.32	32.21 ± 1.38*	56.03 ± 7.74*
U-99194	histamine	87.98 ± 7.87	32.38 ± 1.01*	81.8 ± 5.66#
L-745,870	saline	90.3 ± 7.96	32.31 ± 1.49*	52.45 ± 6.72*
L-745,870	histamine	89.25 ± 6.36	31.66 ± 0.75*	94.43 ± 3.61#^
PP (mmHg)				
saline	saline	23.43 ± 5.88	8.49 ± 2.36*	22.74 ± 3.85 [18,19]
saline	histamine	22.23 ± 4.57	6.98 ± 2.13*	17.48 ± 3.1*# [18,19]
SCH-23390	saline	21.54 ± 3.52	8.91 ± 0.94*	20.56 ± 1.72
SCH-23390	histamine	21.68 ± 5.23	7.56 ± 2.79*	19.95 ± 3.22
remoxipride	saline	21.17 ± 4.93	9.53 ± 1.19*	20.84 ± 4.31
remoxipride	histamine	23.58 ± 5.32	7.95 ± 1.78*	20.29 ± 3.18
U-99194	saline	20.75 ± 4.47	9.41 ± 1.83*	21.67 ± 2.34
U-99194	histamine	20.92 ± 4.7	7.68 ± 2.29*	18.56 ± 3.94
L-745,870	saline	20.84 ± 6.99	9.01 ± 2.0*	19.7 ± 3.0
L-745,870	histamine	19.34 ± 3.41	8.25 ± 3.37*	19.8 ± 5.76
HR (beats/min)				
saline	saline	215 ± 30	145 ± 27*	107 ± 35* [18,19]
saline	histamine	218 ± 34	162 ± 27*	181 ± 37# [18,19]
SCH-23390	saline	214 ± 29	139 ± 29*	112 ± 26*
SCH-23390	histamine	204 ± 34	149 ± 35*	176 ± 28#
remoxipride	saline	206 ± 38	140 ± 28*	113 ± 32*
remoxipride	histamine	208 ± 25	144 ± 26*	170 ± 32#
U-99194	saline	204 ± 36	130 ± 27*	117 ± 18*
U-99194	histamine	212 ± 31	152 ± 33*	188 ± 17#
L-745,870	saline	199 ± 33	145 ± 24*	120 ± 21*
L-745,870	histamine	209 ± 34	133 ± 32*	172 ± 24#
MBF (ml/min)				
saline	saline	8.15 ± 1.88	1.62 ± 0.39*	1.48 ± 0.78* [18,19]
saline	histamine	8.82 ± 1.95	1.51 ± 0.31*	2.25 ± 0.57*# [18,19]
SCH-23390	saline	8.51 ± 1.86	1.48 ± 0.2*	1.27 ± 0.49*
SCH-23390	histamine	8.25 ± 1.39	1.16 ± 0.26*	2.03 ± 0.33*#
remoxipride	saline	9.53 ± 1.8	1.43 ± 0.42*	1.36 ± 0.56*
remoxipride	histamine	8.79 ± 1.01	1.21 ± 0.45*	2.09 ± 0.2*#
U-99194	saline	8.95 ± 1.65	1.44 ± 0.31*	1.28 ± 0.54*
U-99194	histamine	8.41 ± 1.62	1.22 ± 0.45*	2.17 ± 0.35*#
L-745,870	saline	8.89 ± 1.57	1.62 ± 0.39*	1.33 ± 0.41*
L-745,870	histamine	9.0 ± 0.78	1.2 ± 0.35*	2.73 ± 0.24*#^

Dopamine receptor antagonists: SCH-23390 ($D_{1/5}$), remoxipride (D_2), U-99194 (D_3), and L-745,870 (D_4);

six animals per group; *p < 0.05 vs. pre-bleeding value; #p < 0.05 vs. corresponding value in the saline-treated group; in animals pre-treated with dopamine antagonist: ^p < 0.05 vs. group pre-treated with saline and injected with histamine.

The total bleeding volume necessary for the induction of hypotension (30–35 mmHg) in all animals was 1.95 ± 0.18 ml/100 g of body weight. In the control (saline-treated) group, the induction of hypotension was associated with decreases in PP, HR, and MBF to 8.49 ± 2.36 mmHg, 145 ± 27 beats/min, and 1.62 ± 0.39 ml/min, respectively (Table I) [18,19].

There was a spontaneous partial recovery in MAP as measured 20 min after treatment in the saline-treated group (Table I). The animals in all groups survived 2 h [18,19].

In the histamine-treated group pre-treated with saline, MAP, HR, and MBF were significantly higher and PP was lower compared to the control group as measured 20 min after treatment (Table I) [18,19]. Pre-treatment with L-745,870 potentiated histamine-induced MAP and MBF changes, with no influence on PP and HR. In contrast, SCH-23390, remoxipride, and U-99194 did not affect histamine action (Table I).

In the control animals, dopamine receptor antagonists did not affect the measured cardiovascular parameters (Table I).

DISCUSSION

The results of our study demonstrate for the first time functional interactions between the histaminergic and dopaminergic systems in central cardiovascular regulation in a rat model of hemorrhagic hypotension. According to the hypothesis by Brown et al. [20], the central histaminergic system is involved in the maintenance of multisystemic homeostasis. Histamine, acting as a neurotransmitter secreted from neurons in the tuberomammillary nuclei of the posterior hypothalamus, seems to activate different compensatory mechanisms, leading to at least partial recovery of homeostatic balance. Our results are in line with this hypothesis, since we confirmed a histamine-induced pressor effect leading to MAP and HR normalization within 20 min of treatment in a model of reversible hemorrhagic hypotension. This model, in which a smaller volume of blood is withdrawn and reflex-induced bradycardia occurs, is more relevant to clinical conditions in humans than the previous model of irreversible shock with lower initial blood pressure (MAP: 20–25 mmHg) and 100% mortality within 30 min in the control group [3,5]. In contrast, in this model, all control animals survived for 2 h, with a spontaneous increase in MAP. Similar cardiovascular changes are observed in the post-bleeding period after non-fatal blood loss in humans [3].

The hypothalamic histaminergic neurons are activated in response to different kinds of stress, including dehydration and hypovolemia, as immunohistochemical studies demonstrate [21]. On the other hand, an increase in endogenous histamine content within the central nervous system after the inhibition of histamine N-methyltransferase, the enzyme responsible for histamine catabolism, leads to the activation of the sympathetic and the renin-angiotensin systems, as well as increased release of arginine vasopressin, and proopiomelanocortin-derived peptides in hemorrhage-shocked rats [22]. Hemodynamic effects elicited by centrally acting histamine include the mobilization of blood from venous reservoirs, with subsequent increases in peripheral blood flows – especially in the renal and skeletal muscle vascular beds – and long-lasting vasoconstriction, with a relatively lower increase in the perfusion of the mesenteric region [23]. Our results confirm persistently reduced MBF after histamine treatment, despite a complete recovery of MAP and HR to the pre-bleeding values at 20 min, which confirms the centralized circulation in conditions of hypovolemia.

Previous studies demonstrate functional interactions between the histaminergic and other neuronal systems, such as the cholinergic [24], adrenergic [25], and serotonergic systems [26], in the central cardiovascular regulation in experimental models of hemorrhagic hypotension in rats. In this study, we decided to verify possible interactions between the histaminergic and dopaminergic systems under these conditions. We used antagonists of dopamine receptors which in mammals are divided into two families: D_1-like and D_2-like receptors. D_1-like receptors consist of D_1 and D_5 receptors, while D_2-like receptors are comprised of D_2, D_3, and D_4 receptors [27]. The studies show an augmented histamine-induced pressor effect after D_4 receptor blockage with L-745,870. In contrast, we did not find an influence of the other dopamine receptor antagonists through histamine-mediated action on the measured cardiovascular parameters, nor did we observe any effects of the dopamine receptor antagonists when administered to the animals pre-treated with saline.

Dopamine D_4 receptors are involved in addictive behaviors related to alcohol [28], morphine [29], and nicotine [30] intake, the regulation of food intake [31], and copulatory behavior [32]. In addition, D_4 receptors are able to influence the cardiovascular responses to stress. A study by Sato et al. [33] demonstrated the pressor effect accompanied by bradycardia following the stimulation of neurons located in the lateral habenula (LHb), which is an essential structure for the activation of the response to stressful stimuli [34]. Interestingly, intravenous pre-treatment with L-745,870 (0.1 mg/kg) decreased the pressor effect resulting from LHb neuron stimulation [33]. However, the effect may be dose-dependent, since a selective D_4 receptor antagonist (L-741742) at a low dosage (0.025 µg) administered locally into the LHb induced a short-lived decrease in the firing rate of the LHb

neurons, followed by a prolonged excitatory effect [35]. Interestingly, L-741742 at a high dosage (0.1 µg) evoked only a brief decrease in the firing rate of LHb neurons [35]. The effect of L-741742 (0.25 µg) was accompanied by an increased release of GABA, dopamine, and glutamate in the LHb; the action of D_4 receptors located pre- and post-synaptically was demonstrated [35]. Since LHb neurons project directly to hypothalamic histaminergic neurons [36], dopamine D_4 receptor antagonist-mediated activation of LHb neurons may be involved in the enhanced histamine--induced pressor effect observed in our study.

Interestingly, a study by Bazzani et al. [15] showed the involvement of dopamine D_1-like receptors in ACTH-induced reversal of hemorrhagic shock in rats. We suggest that since ACTH-mediated anti-shock effect is associated with the activation of the cholinergic anti-inflammatory pathway [37], and the activation of the sympathetic nervous system plays a predominant role in the histamine-induced resuscitating effect in hemorrhagic shock [7], therefore, different types of dopamine receptors may participate in these mechanisms.

Although we demonstrated the potentiation of the central histamine-induced pressor effect in hemorrhagic hypotension after pre-treatment with a dopamine D_4 receptor antagonist, we are aware of the limitations of this study. Firstly, since the dopamine receptor antagonists and histamine were administered icv, we are unable to precisely determine the location of the neurons involved. Secondly, at this stage of the studies, we cannot show particular mechanisms involved in the dopamine D_4 receptor-mediated modulatory effect. However, a LHb neuron-involved pathway can be postulated.

CONCLUSION

The central dopaminergic system, via D_4 receptors, is able to modify a histamine-induced pressor effect in hemorrhagic hypotension in rats.

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Authors' contribution

Study design – J. Jochem, D. Giuliani, A. Ottani, S. Guarini
Data collection – K. Jasikowska
Data interpretation – K. Jasikowska, J. Jochem, A. Ottani, D. Giuliani
Statistical analysis – K. Jasikowska
Manuscript preparation – J. Jochem, M. Zając, A. Ottani, D. Giuliani, S. Guarini
Literature research – M. Zając, J. Jochem

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