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PRACA ORYGINALNA
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Bombesin-like peptides are able to affect central histamine--induced resuscitating effect in haemorrhage-shocked rats

Peptydy bombezynopodobne mogą wpływać na efekt resuscytacyjny ośrodkowo działającej histaminy we wstrząsie krwotocznym u szczurów

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ABSTRACT

INTRODUCTION: Activation of the central histaminergic system induces a resuscitating effect in haemorrhage-shocked rats. Since peripherally administered bombesin evokes a similar action, and bombesin receptors are present in the central nervous system regions responsible for cardiovascular regulation, the aim of the study was to examine the effects of bombesin receptor blockage on histamine-induced cardiovascular effects in haemorrhagic shock.
MATERIAL AND METHODS: Studies were carried out in male Wistar rats anaesthetized with ketamine/xylazine (100 mg/kg + 10 mg/kg, intraperitoneally) and then subjected to reversible haemorrhagic shock with a mean arterial pressure (MAP) of 30–35 mmHg. Immediately after terminating bleeding, the animals were pre-treated intracerebroventricularly (icv) with bombesin receptor antagonists/0.9% NaCl solution, and 5 min later – treated via the same route with histamine (50 nmol) or 0.9% NaCl solution.
RESULTS: Haemorrhage led to decreases in the pulse pressure (PP), heart rate (HR) and mesenteric blood flow (MBF). Histamine induced a pressor effect, with a significant increase in PP and MBF. The effect was inhibited by both [D-Phe12,Leu14]-bombesin and BIM 23042, non-selective and selective bombesin 1 (BB1) receptor antagonists, respectively. In the control groups the antagonists had no effect.
CONCLUSIONS: Endogenous bombesin-like peptides, acting via BB1 receptors, are able to affect a histamine-induced pressor effect in haemorrhage-shocked rats.

KEY WORDS

bombesin receptors, histaminergic system, rats, haemorrhagic shock

STRESZCZENIE

WSTĘP: Pobudzenie ośrodkowego układu histaminergicznego wywołuje działanie resuscytacyjne u szczurów we wstrząsie krwotocznym. Skoro podawana dożylnie bombezyna wykazuje podobne działanie, a receptory bombezynowe są obecne w strukturach ośrodkowego układu nerwowego, odpowiedzialnych za regulację czynności układu krążenia, celem pracy było zbadanie wpływu zablokowania receptorów bombezynowych na efekty krążeniowe wynikające z podania do komory bocznej mózgu (icv) histaminy we wstrząsie krwotocznym u szczurów.

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MATERIAŁ I METODY: Badania przeprowadzono u szczurów, samców szczepu Wistar w znieczuleniu ogólnym (ketamina 100 mg/kg + ksylazyna 10 mg/kg, dootrzewnowo). Zastosowano model odwracalnego wstrząsu krwotocznego ze średnim ciśnieniem tętniczym (MAP) 30–35 mmHg. Niezwłocznie po zakończeniu krwawienia podawano icv antagonistów receptorów bombezynowych/0,9% roztwór NaCl, a 5 min później tą samą drogą histaminę (50 nmol) bądź 0,9% roztwór NaCl.
WYNIKI: Utrata krwi prowadziła do obniżenia ciśnienia tętna (PP), częstości rytmu serca (HR) i przepływu krezkowego krwi (MBF). Histamina wywoływała działanie presyjne ze wzrostem PP i MBF. Efekty działania histaminy były częściowo hamowane przez [D-Phe12,Leu14]-bombezynę i BIM 23042, odpowiednio nieselektywnego antagonistę receptorów bombezynowych oraz selektywnego blokera receptorów bombezynowych typu 1 (BB1). W grupach kontrolnych nie stwierdzono wpływu antagonistów receptorów bombezynowych na mierzone parametry układu krążenia.
WNIOSKI: Endogenne peptydy bombezynopodobne, działając poprzez receptory BB1, mogą wpływać na wywoływane przez ośrodkowo działającą histaminę działanie resuscytacyjne we wstrząsie krwotocznym u szczurów.

SŁOWA KLUCZOWE

receptory bombezynowe, szczury, wstrząs krwotoczny, układ histaminergiczny

INTRODUCTION

Haemorrhagic shock is a life-threatening condition which results from inadequate tissue perfusion due to a massive blood loss. It is, after injuries, the most frequent preventable cause of early death in humans [1].
According to the fundamental study by Barcroft et al. [2] carried out on a group of healthy volunteers, there are two phases of haemodynamic response to blood loss. The first one is characterized by an increase in sympathetic nervous system activity with rises in the total peripheral resistance (TPR) and heart rate (HR) (the sympathoexcitatory phase). In the second phase, after a loss of approximately 20% of the total blood volume, the withdrawal of sympathetic activity leads to decreases in cardiac output, TPR and HR [2]. Later experimental studies revealed the possibility of the existence of a third phase of regulation characterized by a transient increase in sympathetic activity and HR [3].
Histamine belongs to biogenic amines widely distributed in mammalian tissues. It is synthesised and released by mast cells, basophils, enterochromaffin-like cells of the stomach, neutrophils, histaminergic neurons and other types of cells [4]. The histaminergic system consists of neurons located at the tuberomammillary nuclei of the hypothalamus and send axons to many parts of the central nervous system, including the cerebral cortex, subcortical nuclei, structures of the limbic system, brain stem and cerebellum [5,6]. Histaminergic neurons are able to affect many of the central nervous system functions, including cardiovascular regulation [7]. In normotension, histamine acting centrally as a neurotransmitter induces a pressor effect with bradycardia in conscious animals and tachycardia in anaesthetized animals [7]. Our previous studies demonstrate a few fold higher increases in mean arterial pressure (MAP) and HR elicited by exogenous histamine administered intracerebroventricularly (icv) in rats subjected to critical haemorrhagic hypotension in comparison to normotensive animals [8].The histamine-induced resuscitating effect is accompanied by increases in peripheral blood flows [9] and partial normalization of blood gas and acid-base parameters [10]. Our results are in line with the hypothesis by Brown et al. [6] concerning activation of the central histaminergic system in response to disturbances of homeostasis. As we suggested, in these conditions, histamine may mobilize compensatory mechanisms responsible for the recovery of circulatory homeostasis [11].
Bombesin is a tetradecapeptide isolated for the first time from the skin of the European frog *Bombina bombina* [12]. In mammals, bombesin activates three types of G-protein-coupled receptors – bombesin receptor 1 (BB_1), bombesin receptor 2 (BB_2) and bombesin receptor 3 (BB_3). Neuromedin B and gastrin-releasing peptide (GRP) are natural ligands of the BB_1 and BB_2 receptors, respectively, whereas a natural ligand of the BB_3 receptor is still unknown [13]. Endogenous ligands of bombesin receptors are known as bombesin-like peptides.
Bombesin receptors are involved in regulating food intake, generating circadian rhythms, memory mechanisms and many behaviours [14]. They are widely distributed in the central nervous system and are present in regions associated with central cardiovascular regulation, such as hypothalamic nuclei, the nucleus of the solitary tract (NTS) and the rostral ventrolateral medulla (RVLM) [14,15]. Since Guarini et al. [16] showed the resuscitating effect of peripherally administered bombesin in haemorrhagic shock, the aim of the present study was to examine possible functional interactions between the histaminergic system and bombesin-like peptides in cardiovascular regulation in haemorrhage-shocked rats.

MATERIAL AND METHODS

Animals

All the procedures were performed in accordance with EU directives and reviewed by the Local Ethics Committee, Katowice, Poland (Notification No 50/2018). Studies were performed in male Wistar rats weighing 265––315 g (4–6 months old), housed in individual cages in the animal colony, under controlled conditions (temperature 20–22°C, humidity 60–70%, 12 h light/dark cycle) and provided with food and water *ad libitum*.

Surgical preparation

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

Experimental protocol

For icv treatment, the rats were prepared 3–5 days before the experiment by stereotaxic implantation, under ketamine/xylazine anaesthesia, of polyethylene cannulae into the right brain lateral ventricle as previously described [8]. All icv injections were made in the volume of 5.0 µl. The correctness of the injections was verified as previously described [8].
Reversible haemorrhagic shock was produced by intermittent blood withdrawal from a catheter inserted into the right femoral vein over a period of 15–25 min, until MAP decreased to and stabilised at 30–35 mmHg. Immediately after the termination of bleeding and stabilisation of MAP, the animals were pre-treated icv with bombesin receptor antagonists – [D-Phe^{12},Leu^{14}]--bombesin (25 nmol) or BIM 23042 (25 nmol), and 5 min later – injected with histamine (50 nmol) or an 0.9% NaCl solution. In the control histamine-treated animals, pre-treatment with the 0.9% NaCl solution was performed. Each group consisted of 6 animals.
The animals were continuously monitored for 2 h after treatment. Body temperature was monitored by a rectal thermometer and maintained at 37 ± 0.5°C using heating lamps throughout the experiment. All the experiments were performed between 9.00 am and 2.00 pm.
According to recommendations of the Local Ethics Committee, to avoid the duplication of studies performed at our laboratory with the same rat strain, using the same experimental protocol of haemorrhagic shock, we did not repeat experiments in the control saline-treated group and we cited and discussed previously presented results [17].

Drugs

The following drugs were used: heparin (Polfa, Poland), histamine (Sigma-Aldrich, USA), [D-Phe^{12},Leu^{14}]-bombesin, BIM 23042 (Tocris Bioscience, UK), ketamine hydrochloride, xylazine (Biowet Sp. z o.o., Poland). All the drug solutions were prepared freshly on the day of the experiment.

Statistics

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

RESULTS

The initial pre-bleeding values of MAP, pulse pressure (PP), HR and MBF did not reveal significant differences between the groups, the values in the control saline-treated group were: 87.46 ± 4.36 mmHg, 23.43 ± 5.88 mmHg, 215 ± 30 beats/min and 8.15 ± 1.88 ml/min, respectively [17].
The total bleeding volume necessary to induce hypotension of 30–35 mmHg in all the animals was 2.04 ± 0.29 ml/100 g body weight.
In the control saline-pre-treated group, the induction of hypotension of 30–35 mmHg 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. There were spontaneous increases in MAP, PP and MBF after shock induction in that group, and all the animals survived 2 h.
Histamine induced a long-lasting pressor effect with a rise in HR, PP and MBF (Tab. I). Pre-treatment with both [D-Phe^{12},Leu^{14}]-bombesin and BIM 23042 partially inhibited histamine-induced changes in MAP, PP and MBF (Tab. I). There were no differences between the saline-, [D-Phe^{12},Leu^{14}]-bombesin- and BIM 23042-pre-treated rats in the control saline-treated animals regarding MAP, PP, HR and MBF as measured 20 min after treatment (Tab. I) [17]. In all the groups, the survival rate of 2 h was 100%.

Table I. Influence of icv pre-treatment with [D-Phe^{12},Leu^{14}]-bombesin (25 nmol), BIM 23042 (25 nmol) or saline (5 µl) on cardiovascular effects elicited by icv histamine (50 nmol) or saline (5 µl) in haemorrhage-shocked rats

Tabela I. Wpływ premedykacji icv [D-Phe^{12},Leu^{14}]-bombezyną (25 nmol), BIM 23042 (25 nmol) i 0,9% roztworem NaCl (5 µl) na zmiany parametrów układu krążenia po podaniu icv histaminy (50 nmol) bądź 0,9% roztworu NaCl (5 µl)

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*
Saline	Histamine	82.65 ± 6.93	32.55 ± 1.22*	84.7 ± 4.28#
[D-Phe^{12},Leu^{14}]-bombesin	Saline	85.71 ± 4.38	32.6 ± 1.15*	57.1 ± 4.28*
[D-Phe^{12},Leu^{14}]-bombesin	Histamine	84.58 ± 7.36	32.91 ± 1.11*	66.23 ± 4.19*#^
BIM 23042	Saline	87.93 ± 6.37	33.51 ± 1.18*	64.6 ± 7.07*#^
PP (mmHg)				
Saline	Saline	23.43 ± 5.88	8.49 ± 2.36*	22.74 ± 3.85
Saline	Histamine	22.23 ± 4.57	6.98 ± 2.13*	17.48 ± 3.1*#
[D-Phe^{12},Leu^{14}]-bombesin	Saline	24.86 ± 5.91	8.58 ± 2.81*	23.33 ± 3.21
[D-Phe^{12},Leu^{14}]-bombesin	Histamine	25.15 ± 4.22	8.71 ± 2.27*	24.85 ± 2.74^
BIM 23042	Saline	27.83 ± 4.74	8.21 ± 3.39*	22.35 ± 2.23*
BIM 23042	Histamine	27.33 ± 4.57	8.84 ± 3.62*	24.65 ± 3.15^
HR (beats/min)				
Saline	Saline	215 ± 30	145 ± 27*	107 ± 35*
Saline	Histamine	218 ± 34	162 ± 27*	181 ± 37#
[D-Phe^{12},Leu^{14}]-bombesin	Saline	204 ± 32	168 ± 20*	117 ± 19*
[D-Phe^{12},Leu^{14}]-bombesin	Histamine	191 ± 30	156 ± 18*	138 ± 21*^
BIM 23042	Saline	190 ± 27	153 ± 39*	104 ± 13*
BIM 23042	Histamine	181 ± 37	139 ± 36*	116 ± 24*^
MBF (ml/min)				
Saline	Saline	8.15 ± 1.88	1.62 ± 0.39*	1.48 ± 0.78*
Saline	Histamine	8.82 ± 1.95	1.51 ± 0.31*	2.25 ± 0.57*#
[D-Phe^{12},Leu^{14}]-bombesin	Saline	7.83 ± 2.89	1.57 ± 0.39*	1.62 ± 0.27*
[D-Phe^{12},Leu^{14}]-bombesin	Histamine	8.15 ± 1.99	1.68 ± 0.46*	1.88 ± 0.35*^
BIM 23042	Saline	7.85 ± 1.03	1.23 ± 0.38*	1.35 ± 0.39*
BIM 23042	Histamine	9.02 ± 2.03	1.04 ± 0.21*	1.42 ± 0.63*^

n = 6; * $p < 0.05$ vs. pre-bleeding value, in comparison to post-bleeding values; # $p < 0.05$ vs. corresponding value in saline-treated group; in bombesin antagonists pre-treated animals ^ $p < 0.05$ vs. saline-pre-treated histamine-injected group

DISCUSSION

The central cardiovascular regulation in haemorrhagic shock is influenced by many neuronal systems. Generally, according to the hypothesis by Bertolini [18], they can be divided into opioid and non-opioid (anti-opioid) systems. Non-opioid neurotransmitters/neuromodulators are able to prolong the sympathoexcitatory phase of regulation and, therefore, may provide the time necessary to start appropriate treatment of haemorrhage-induced hypotension. As we demonstrated previously, the central histaminergic system belongs to non-opioid neurotransmitters [11].

In the present study, we used a model of reversible haemorrhagic shock which is more similar to clinical conditions in humans. In all the groups, the post-bleeding values of PP, HR and MBF were significantly lower in comparison to the pre-bleeding conditions. As we demonstrate, all the animals in the control group survived 2 h, with a spontaneous increase in MAP, PP and MBF. Similar haemodynamic changes are observed in the post-bleeding period after non-fatal blood loss in humans.

The presented results confirm the resuscitating effect of centrally acting histamine in haemorrhage-shocked rats. The values of MAP, PP and MBF 20 min after histamine treatment were higher in comparison to the post-bleeding values by 160%, 150% and 49%, respectively. As we previously reported, endogenous histamine, acting as a neurotransmitter, is able to activate the sympathetic and the renin-angiotensin systems, as well as to increase the release of arginine vasopressin (AVP) and proopiomelanocortin (POMC)-derived peptides [11]. Activation of these mechanisms leads to a long-lasting pressor effect, especially in the mesenteric region [9], as confirmed in the present study.

The central histaminergic system sends axons to almost all the brain regions and there are many interactions between the histaminergic and other neuronal systems, in cardiovascular regulation. We demonstrated previously such a type of interactions with the noradrenergic [19], serotonergic [20], cholinergic [21] and angiotensinergic systems [22]. In the present study, we decided to verify the possible influences of bombesin-like peptides on the histamine-induced resuscitating effect of haemorrhagic shock.

Bombesin receptors and bombesin-like peptides are present in many central nervous system areas involved in cardiovascular regulation in normotensive conditions. Initial studies demonstrate a bombesin-induced increase in blood pressure with bradycardia in rats [23] and GRP (BB_1 receptor agonist)-induced increases in MAP, HR and the ventilation rate in trout [24]. Localization of the neurons involved suggests possible different regions of bombesin-like peptide action. Bombesin administered directly into RVLM induces increases in MAP both in normotensive and spontaneously hypertensive rats (SHR), and BIM-23127 reduces MAP and renal sympathetic nerve activity in SHR but not in normal rats [25]. On the other hand, the studies by Lateef et al. [26] show an increase in sympathetic nervous system activity, with subsequent pressor and tachycardic effects, after the activation of hypothalamic BB_3 receptors. Finally, bombesin evokes a sympathoexcitatory effect at thoracic spinal segments, acting on the sympathetic preganglionic neurons in rats [27].

The peripheral (intravenous) administration of bombesin also induces a pressor effect resulting from activation of the sympathetic nervous system [28]. The studies by Guarini et al. [16] demonstrate a similar action in haemorrhage-shocked rats, however, the authors suggested that the effect is peripherally mediated. Since the bombesin receptor-mediated increase in sympathetic system activity and pressor effects are well documented, we decided here to study the possible interactions between bombesin-like peptides and the histaminergic system in central cardiovascular regulation in critical hypotension. We used two commercially available antagonists of bombesin receptors – [D-Phe^{12},Leu^{14}]-bombesin which is a non-selective antagonist, and BIM 23042 – a selective BB_1 receptor blocker. Both antagonists inhibited histamine induced increases in MAP, PP and MBF, without differences between the groups. Therefore, we suggest that the effect is mediated – predominantly – by BB_1 receptors. Interestingly, neither antagonist given alone affected spontaneous recovery of the measured cardiovascular parameters in the control groups.

We hypothesize that the action may be associated with activation/modulation of the histaminergic system. The studies by Okuma et al. [29] suggest that bombesin-induced central activation of sympatho-adrenomedullary outflow is, at least in part, mediated via histaminergic neurons. On the other hand, we know that activation of the sympathetic system is a predominant mechanism activated in response to histaminergic system stimulation and is mainly responsible for the resuscitating effect in rats [30]. Therefore, we suggest that endogenous bombesin-like peptides may enhance the cardiovascular response to centrally administered histamine in haemorrhage-shocked rats.

Although we demonstrated the inhibitory effect of the BB_1 receptor antagonist on histamine-induced resuscitating action, we can suggest the limitations of our study. Firstly, we cannot exclude the involvement of other types of bombesin receptors in the effect. Moreover, we do not precisely identify the region of bombesin-like peptide action. Finally, we did not study the particular histamine-activated effectory mechanisms (the sympathetic nervous system, the renin-angiotensin system, AVP, POMC-derived peptides) influenced by bombesin-like peptides.

In conclusion, endogenous bombesin-like peptides, acting via BB_1 receptors, are able to modify the histamine-induced resuscitating effect in haemorrhage-shocked rats.

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Author's contribution

Study design – K. Jasikowska, J. Jochem
Data collection – K. Jasikowska, J. Jochem
Data interpretation – K. Jasikowska, J. Jochem
Statistical analysis – A. Klose, D. Nowak
Manuscript preparation – K. Jasikowska, B. Rybus-Kalinowska, J. Jochem
Literature research – J. Jochem, A. Klose, D. Nowak

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