Ann. Acad. Med. Siles. (online) 2015; 69: 132–137
eISSN 1734-025X
DOI: 10.18794/aams/35718

PRACA ORYGINALNA
ORIGINAL PAPER

Influence of histamine H_3 receptors on pressor effect of leptin administered centrally in haemorrhage-shocked rats

Wpływ receptorów histaminowych H_3 na reakcję presyjną wywołaną przez leptynę podawaną ośrodkowo u szczurów we wstrząsie krwotocznym

Karolina Jasikowska, Aleksandra Klose, Izabela Kozieł-Kokosińska, Jerzy Jochem

Department of Basic Medical Sciences, School of Public Health in Bytom, Medical University of Silesia

ABSTRACT

INTRODUCTION: Leptin administered intracerebroventricularly (icv) evokes the resuscitating effect in haemorrhage--shocked rats, and the action is associated with activation of the histaminergic system. The aim of the present study was to examine the possible role of the histamine H3 receptor in leptin-evoked cardiovascular effects.
MATERIALS AND METHODS: Studies were performed in male Wistar rats subjected to irreversible haemorrhagic shock (0% survival at 2 h) with a mean arterial pressure (MAP) of 20–25 mmHg that were anaesthetized with ketamine/xylazine (100 mg/kg + 10 mg/kg, intraperitoneally). At 5 minutes of critical hypotension the animals were injected icv with leptin (20 μg) or 0.9% NaCl (5 μl).
RESULTS: Haemorrhage resulted in a decrease in pulse pressure (PP) and heart rate (HR). Leptin evoked long-lasting rises in MAP, PP and HR with 100% survival at 2 h. Pre-treatment with histamine H3 receptor inverse agonist/H4 partial agonist clobenpropit (42.5 nmol, icv), but not with H3 receptor neutral antagonist VUF 5681 (50 nmol, icv), inhibited MAP and PP changes evoked by leptin, however, without an influence on HR or survival rate at 2 h.
CONCLUSIONS: The histamine H3 receptor can influence the centrally-acting leptin-induced resuscitating effect in haemorrhagic shock in rats.

KEY WORDS
histamine, H3 receptor, leptin, haemorrhagic shock, rats

STRESZCZENIE

WSTĘP: Leptyna podawana do komory bocznej mózgu (icv) wywołuje efekt resuscytacyjny u szczurów we wstrząsie krwotocznym; w działaniu tym uczestniczy układ histaminergiczny. Celem obecnej pracy było zbadanie możliwego udziału receptorów histaminowych H3 w wywoływanym przez leptynę wpływie na układ krążenia we wstrząsie.

Received: 21.12.2014 **Revised:** 30.12.2014 **Accepted:** 30.12.2014 **Published online:** 15.10.2015

Adres do korespondencji: Prof. dr hab. n. med. Jerzy Jochem, Katedra i Zakład Podstawowych Nauk Medycznych Wydziału Zdrowia Publicznego Śląskiego Uniwersytetu Medycznego w Katowicach, ul. Piekarska 18, 41-902 Bytom, tel. +48 600 246 536, e-mail: jjochem@poczta.onet.pl

MATERIAŁ I METODY: Badania przeprowadzono u szczurów, samców szczepu Wistar w znieczuleniu ogólnym przy użyciu ketaminy i ksylazyny (100 mg/kg + 10 mg/kg dootrzewnowo), u których wywołano nieodwracalny wstrząs krwotoczny ze średnim ciśnieniem tętniczym (MAP) 20–25 mmHg (wskaźnik przeżycia dwugodzinnego: 0%). W 5 min krytycznej hipotensji zwierzętom podawano icv leptynę (20 μg) bądź 0,9% roztwór NaCl (5 μl).
WYNIKI: Utrata krwi prowadziła do obniżenia ciśnienia tętna (PP) i częstości rytmu serca (HR). Leptyna wywoływała długotrwałe wzrosty MAP, PP i HR, a także podwyższenie do 100% wskaźnika przeżycia dwugodzinnego. Premedykacja odwrotnym agonistą receptorów H3/częściowym agonistą receptorów H4 klobenpropitem (42,5 nmol, icv), ale nie neutralnym antagonistą receptorów H3 VUF 5681 (50 nmol, icv), hamowała zmiany MAP i PP wywoływane przez leptynę, jednak bez wpływu na wskaźnik przeżycia dwugodzinnego we wstrząsie.
WNIOSKI: Receptory histaminowe H3 mogą wpływać na efekt resuscytacyjny wywoływany przez ośrodkowo działającą leptynę we wstrząsie krwotocznym u szczurów.

SŁOWA KLUCZOWE
histamina, receptor H3, leptyna, wstrząs krwotoczny, szczury

INTRODUCTION

Haemorrhagic shock is a life-threatening condition characterized by inadequate tissue perfusion resulting from blood loss. It is the most frequent preventable cause of early death after traumatic injuries [1]. High frequencies of haemorrhage and haemorrhagic shock are common in war conditions, i.e. during the wars in Georgia and Iraq, in 30–40% of patients with traumatic injuries haemorrhagic shock occurred [2,3]. Moreover, haemorrhage contributes to death in the prehospital period in 33–56% of cases [4]. Therefore, studies on the mechanisms responsible for the maintenance of blood pressure in critical haemorrhagic hypovolaemia are of essential importance.

There are two phases of neurohormonal response to blood loss: the first one is characterized by an increase in the sympathetic nervous system activity (the sympathoexcitatory phase). In the second phase, a Bezold-Jarisch reflex initiates a decrease in sympathetic activity (the sympathoinhibitory phase) [5]. The central neuronal systems involved in cardiovascular regulation in haemorrhagic hypotension can be functionally divided into two groups [6]. The first group includes opioidergic neurons which, generally, inhibit the activity of rostral ventro-lateral medulla neurones, while the second one consists of non-opioid systems demonstrating anti-shock properties and includes the melanocortinergic, histaminergic, serotonergic and cholinergic systems [6,7,8,9].

The histaminergic system consists of neurons located at the tuberomammillary nuclei of the posterior hypothalamus [10]. They send axons to many parts of the central nervous system, including the cerebral cortex, subcortical nuclei, structures of the limbic system, cerebellum and the brain stem. Histaminergic neurons are able to affect a variety of central nervous system functions, such as learning and memory, pain perception, feeding behaviour, hypothalamic hormone secretion as well as cardiovascular and respiratory control [10]. In normotension, histamine acting centrally induces a pressor effect with bradycardia in conscious animals [11] and tachycardia in anaesthetized animals [12]. Our previous studies demonstrated a few fold higher increases in mean arterial pressure (MAP) and heart rate (HR), with improvement of the survival rate, elicited by histamine in rats subjected to critical haemorrhagic hypotension compared to normovolaemic animals [7]. The resuscitating effect is accompanied by increases in peripheral blood flows [13] and partial normalization of blood gas and acid-base parameters [14]. The mechanisms activated by histamine in shock include the sympathetic and renin-angiotensin systems, as well as the secretion of arginine vasopressin (AVP) and proopiomelanocortin (POMC)-derived peptides [15].

Leptin is a peptide hormone produced by adipocytes and playing an essential role in the central regulation of feeding behaviour [16]. Apart from the role in energy homeostasis, it is also able to affect cardiovascular regulation. Leptin, acting centrally as a neuromodulator, activates the sympathetic nervous system and thus, influences the cardiovascular system [17]. Experimental studies show that after administration into the brain lateral ventricle (*icv*), it induces an increase in MAP in normotensive rats [18]. Interestingly, our recently published data suggest that leptin has anti-shock properties in haemorrhagic shock [19]. Since leptin is able to stimulate histaminergic neurons [20], and both histamine and leptin have a common mechanism involved in resuscitating action (activation of the sympathetic nervous system), the purpose of the study was to examine the possible role of presynaptic histamine H_3 receptors in the leptin-mediated resuscitating effect in haemorrhagic shock.

METHODS

Animals

All the procedures were performed in accordance to EU directives and reviewed by the Local Ethics Committee, Katowice, Poland (Notifications No. 23/2010, 09/2011 and 84/2014). Studies were carried out in male Wistar rats weighing 240–290 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 (*ip*), supplemented if required), the rats were implanted with catheters filled with heparinised saline (100 IU/ml) in the right carotid artery and the right jugular vein. MAP and HR were measured using a TAM-A transducer amplifier module and an ECGA amplifier (Hugo Sachs Elektronik, Germany), respectively.
For *icv* treatment, the rats were prepared 3–7 days before the experiment by stereotaxic implantation, under ketamine/xylazine anaesthesia, with polyethylene cannulae into the right brain lateral ventricle as previously described [7]. All *icv* injections were made in the volume of 5.0 µl. The correctness of the injections was verified as previously described in [7].

Experimental protocol

Irreversible haemorrhagic shock, according to the method by Guarini et al. [21], was produced by intermittent blood withdrawal from the catheter inserted into the right jugular vein over a period of 15–25 min, until MAP decreased to and stabilised at 20––25 mmHg.
Immediately after inducing critical MAP, the animals were pre-treated *icv* with histamine H_3 receptor neutral antagonist VUF 5681 (50 nmol), H_3 receptor inverse agonist/H_4 partial agonist clobenpropit (42.5 nmol) or saline (5 µl). Five minutes later, the rats were injected *icv* with leptin (20 µg) or saline (5 µl). The doses of leptin and clobenpropit were taken from the literature [19,22], whereas VUF 5681 was administered at an equimolar dose to the previously used thioperamide and H_3 receptor inverse agonist/H_4 antagonist [7]. 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 ± 0.5ºC using heating lamps throughout the experiment. All the experiments were performed between 8:00 and 14:00.
According to the recommendations of the Local Ethics Committee, to avoid duplicating studies performed at our laboratory with the same rat strain, using the same experimental protocol [19], we did not repeat experiments in the control saline *icv*-pre-treated groups treated with saline and leptin, but cited and discussed previously published results.

Drugs

The following drugs were used: leptin (rat, recombinant), clobenpropit dihydrobromide (Sigma-Aldrich, USA), VUF 5681 dihydrobromide (Tocris Bioscience, UK), ketamine hydrochloride, xylazine (Biowet Sp. z o. o., Poland), heparin (Polfa, Poland). All the drug solutions were freshly prepared on the day of the experiment.

Statistics

All the values are given as means ± standard deviation, with $p < 0.05$ considered as the level of significance. Fisher's exact test was used to examine the statistical differences in survival. Statistical evaluation of the other results was performed using the analysis of variance (ANOVA) and the Student-Newman-Keuls post-ANOVA test.

RESULTS

The initial pre-bleeding values of MAP (Fig. 1A), pulse pressure (PP) (Fig. 1B) and HR (Fig. 1C) in all the groups did not reveal significant differences. The total bleeding volume necessary for the induction of critical MAP in all the animals was 2.52 ± 0.39 ml/100 g body weight. In the control saline--treated group, bleeding from MAP 85.7 ± 5.2 mmHg to 23.3 ± 0.8 mmHg was associated with decreases in PP from 38.2 ± 5.1 mmHg to 12.3 ± 3.2 mmHg and in HR from 355 ± 16 beats/min to 218 ± 26 beats/min [19]. There were no differences among any of the studied groups in post-bleeding values of MAP, PP and HR (Fig. 1A–C).
Leptin administered to haemorrhage-shocked rats induced an increase in MAP, PP and HR (Fig. 1A–C). The effects started within 10–15 min after leptin injection, were long-lasting and associated with a 100% survival rate at 2 h ($p < 0.05$ vs. control saline-treated animals; Fisher's exact test) [19].
Clobenpropit inhibited MAP and PP changes were evoked by leptin (Fig. 1A–B), however, without an influence on HR (Fig. 1C) or the survival rate at 2 h

(100%). The antagonist given alone did not affect the measured cardiovascular parameters (Fig. 1) or the survival rate at 2 h (0%). In contrast, VUF 5681 did not influence the measured cardiovascular parameters (Fig. 1A-C) or survival rates in the leptin- and saline-treated groups.

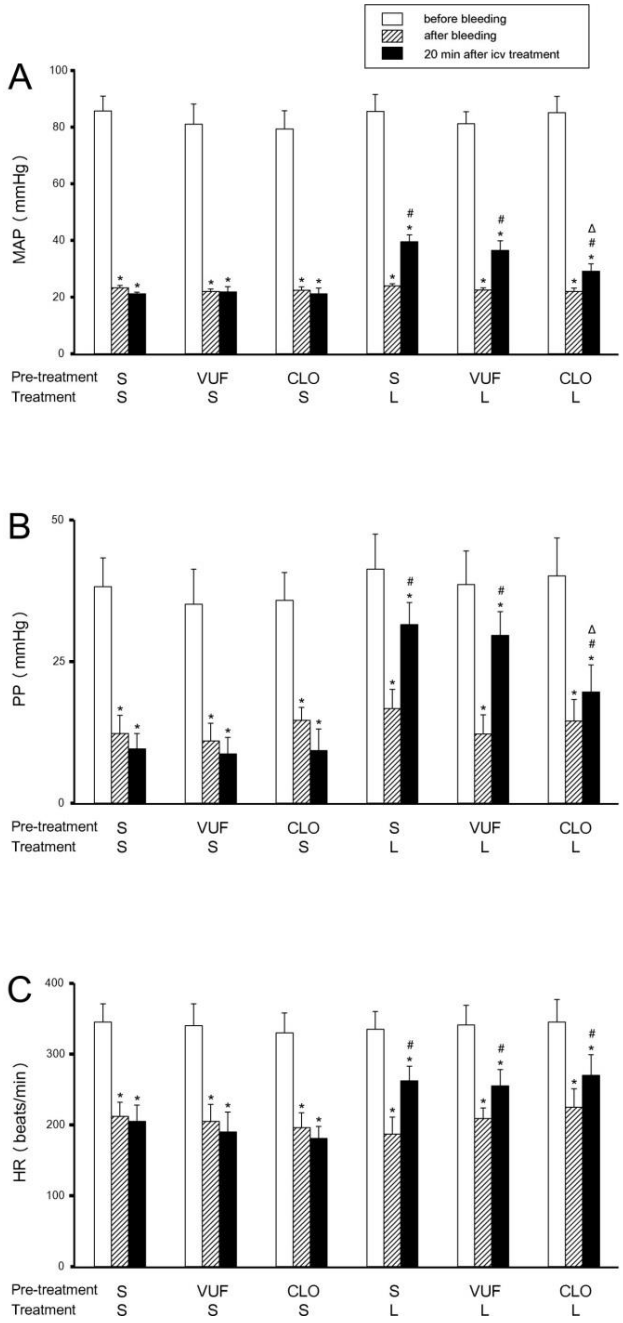

Fig. 1. Influence of *icv* pre-treatment with VUF 5681 (50 nmol), clobenpropit (42.5 nmol) and saline (5 µl) on MAP (A), PP (B) and HR (C) before and after bleeding and 20 min after leptin (20 µg, *icv*) or saline (5 µl) administration; means ± SD; 6 animals per group. * $p < 0.05$ vs. pre-bleeding value; # $p < 0.05$ vs. corresponding value in saline-treated group; in studied H_3 receptor ligands-pre-treated groups, $^{\Delta}$ $p < 0.05$ vs. saline-pre-treated leptin-injected group; all data in control saline *icv*-pre-treated groups treated with saline and leptin are cited from [19].

Ryc. 1. Wpływ premedykacji icv VUF 5681 (50 nmol), klobenpropitem (42.5 nmol) i 0,9% roztworem NaCl (5 µl) na MAP (A), PP (B) i HR (C) przed i po krwotoku oraz 20 min po podaniu leptyny (20 µg, *icv*) bądź 0,9% roztwou NaCl (5 µl); średnie ± SD; n = 6. * $p < 0,05$ w porównaniu z wartością sprzed krwotoku; # $p < 0,05$ w porównaniu z odpowiednią wartością w grupie, w której podawano 0,9% roztwór NaCl; w grupach badanych $^{\Delta}$ $p < 0,05$ w porównaniu z grupą, w której podawano 0,9% roztwór NaCl, a następnie leptynę; dane w grupach kontrolnych, w których podawano 0,9% roztwór NaCl i leptynę zacytowano z [19].

DISCUSSION

The results of the present study demonstrate for the first time the possible influence of histamine H_3 receptors on centrally-acting leptin-mediated cardiovascular effects in critical hypovolaemia. Thus, we extend the evidence for interactions between leptin and the histaminergic system in maintening circulatory homeostasis.

Centrally acting leptin, *via* the sympathetic nervous system, influences cardiovascular regulation both in normotension [17] and critical haemorrhagic hypotension [19]. After *icv* administration, it induces an increase in lumbar sympathetic nerve activity and MAP which results from an increase in regional vascular resistance in the splanchnic and skeletal muscle vascular beds in normotensive rats [23]. On the other hand, studies with peripherally administered α_1- and α_2-adrenoceptor antagonists confirmed leptin-evoked peripheral vascular resistance changes, leading to mobilisation of blood from venous reservoirs in critical hypovolaemia [19]. We hypothesized that leptin-induced changes in peripheral vascular resistance are crucial for arterial pressure regulation in haemorrhagic shock [19]. Similar haemodynamic mechanisms are responsible for the resuscitating action of centrally acting histamine [15] and peripherally administered endothelin 1 [24]. The increases in noradrenalin concentrations after leptin treatment further confirm the predominant role of the sympathetic system in the resuscitating action [19].

To study the possible role of H_3 receptors in the activation of the sympathetic system by leptin, we used two H_3 receptor ligands with different pharmacological profiles: VUF 5681 is a silent H_3 antagonist, while clobenpropit is an H_3 receptor inverse agonist/H_4 partial agonist. By using these two ligands, we were able to deeply explore the role of H_3 auto-/heteroceptors, especially since the histaminergic neurons of the tuberomammillary nucleus are innervated by melanocyte stimulating hormone α (α-MSH)-containing neurons of the arcuate nucleus, and, on the other hand, these neurons are influenced by leptin [25,26,27]. The involvement of melanocortinergic neurons in the activation of the histaminergic system can be confirmed by an increase in histamine release at the anterior hypothalamus after peripheral injection of leptin in rats [20].

We demonstrated previously the interactions between leptin and the histaminergic system, since H_1 receptor antagonist chlorpheniramine inhibits the leptin-evoked pressor effect in haemorrhage-shocked rats [28]. These data are in line with our previous studies in which we presented the involvement of the H_1 receptor in the resuscitating effect of centrally acting exogenous histamine [7]. H_1 receptors are also involved in the mediation of the pressor effect of centrally acting cholinergic and serotonergic ligands – cytidine 5'-diphosphocholine [29] and 8-OH-DPAT [8], respectively.

Presynaptic H_3 receptors mediate autoinhibition of the synthesis/release of histamine and other neurotransmitters/neuromodulators [10]. Tanida et al. [30] demonstrated the involvement of the H_3 receptor in the suppression of renal sympathetic nerve activity and decrease in MAP in normotensive rats, since thioperamide inhibits the effects mediated by centrally administered histamine (0.0001 nmol, *icv*). Interestingly, clobenpropit evokes an increase in histamine release from hypothalamic neurons; however, in contrast to leptin, it did not reduce 12 h-energy intake [31]. Although we did not find the influence of clobenpropit or VUF 5681 administered alone on the central cardiovascular regulation in haemorrhagic shock, we give here the evidence that clobenpropit, but not VUF 5681, is able to inhibit the haemodynamic effects of leptin. We can hypothesize that the difference can result from the pharmacological profile of both ligands and is related to the clobenpropit-mediated influence on other neuronal systems, for example GABAergic neurons. Indeed, earlier studies demonstrated that clobenpropit enhances GABA release [32]. On the other hand, leptin working directly on presynaptic GABAergic neurons has been shown to reduce the inhibitory tone on postsynaptic POMC neurons [33]. Therefore, the observed influence of clobenpropit can be the result of changes in GABA release at the POMC neurons. In contrast to clobenpropit, VUF 5681 – the silent H_3 receptor antagonist, does not affect the central cardiovascular regulation in the leptin-injected group.

Although the functional expression of histamine H_4 receptors on neurons has been demonstrated in a single study [34], and clobenpropit is able to activate H_4 receptors, these action mechanisms seem to be without importance, because there has been no evidence so far for the role of H_4 receptors in central nervous system activities.

Despite the evidence for the possible involvement of H_3 receptors in leptin action in shock, we can suggest the limitations of the study. Firstly, in addition to the melanocortinergic and histaminergic systems, the possible involvement of other neurotransmitters/neurmodulators (thyrotropin-releasing hormone, AVP) cannot be excluded. Secondly, we administered leptin and histamine receptor ligands centrally because of their low permeability of the blood-brain barrier, which is not possible in clinical conditions. Finally, we cannot exclude the involvement of H_3 receptors in the regulation of other neuronal system activities.

CONCLUSION

The histamine H_3 receptor can influence the centrally-acting leptin-induced resuscitating effect in haemorrhagic shock in rats.

The study was supported by a grant of the Medical University of Silesia, Katowice, Poland (KNW-1--065/P/2/0) and by COST Action BM0806 "Recent advances in histamine receptor H4R research".

Author's contribution

Study designe – K. Jasikowska, J. Jochem
Data collection – K. Jasikowska, J. Jochem
Data interpretation – K. Jasikowska, A. Klose, I. Kozieł-Kokosińska, J. Jochem
Statistical analysis – A. Klose, I. Kozieł-Kokosińska, J. Jochem
Manuscript preparation – K. Jasikowska, A. Klose, I. Kozieł-Kokosińska, J. Jochem
Literature research – K. Jasikowska, A. Klose, I. Kozieł-Kokosińska, J. Jochem

REFERENCES

1. Kauvar D.S., Lefering R., Wade C.E. Impact of hemorrhage on trauma outcome: an overview of epidemiology, clinical presentations, and therapeutic considerations. J. Trauma 2006; 60(6 Suppl): S3–S11.

2. Nanobashvili J., Kopadze T., Tvaladze M., Buachidze T., Nazvlishvili G. War injuries of major extremity arteries. World J. Surg. 2003; 27: 134–139.

3. Spinella P.C., Perkins J.G., Grathwohl K.W. et al. Fresh whole blood transfusions in coalition military, foreign national, and enemy combatant patients during Operation Iraqi Freedom at a U.S. combat support hospital. World J. Surg. 2008; 32: 2–6.

4. Sauaia A., Moore F.A., Moore E.E. et al. Epidemiology of trauma deaths: a reassessment. J. Trauma 1995; 38: 185–193.

5. Schadt J.C., Ludbrook J. Hemodynamic and neurohumoral responses to acute hypovolemia in conscious mammals. Am. J. Physiol. 1991; 260: 305–318.

6. Bertollini A. The opioid/anti-opioid balance in shock: a new target for therapy in resuscitation. Resuscitation 1995; 30: 29–42.

7. Jochem J. Cardiovascular effects of histamine administered intracerebroventricularly in critical haemorrhagic hypotension in rats. J. Physiol. Pharmacol. 2000; 51: 229–239.

8. Jochem J., Żak A., Rybczyk R., Irman-Florjanc T. Interactions between the serotonergic and histaminergic systems in the central cardiovascular regulation in haemorrhage-shocked rats: involvement of 5-HT1A receptors. Inflamm. Res. 2009; 58(Suppl 1): 38–40.

9. Ulus I.H., Arslan B.Y., Savci V., Kiran B.K. Restoration of blood pressure by choline treatment in rats made hypotensive by haemorrhage. Br. J. Pharmacol. 1995; 116: 1911–1917.

10. Brown R.E., Stevens D.R., Haas H.L. The physiology of brain histamine. Prog. Neurobiol. 2001; 63: 637–672.

11. Klein M.C., Gertner S.B. Studies on the mechanism of the cardiovascular action of central injections of histamine. Neuropharmacology 1983; 22: 1109–1115.

12. Finch L., Hicks P.E. Involvement of hypothalamic histamine-receptors in the central cardiovascular actions of histamine. Neuropharmacology 1977; 16: 211–218.

13. Jochem J. Central histamine-induced reversal of critical haemorrhagic hypotension in rats – haemodynamic studies. J. Physiol. Pharmacol. 2002; 53: 75–84.

14. Jochem J. Haematological, blood gas and acid-base effects of central histamine-induced reversal of critical haemorrhagic hypotension in rats. J. Physiol. Pharmacol. 2001; 52: 447–58.

15. Jochem J., Kasperska-Zając A. The role of the histaminergic system in the central cardiovascular regulation in haemorrhagic hypotension. Folia Med. Cracov. 2012; 52: 31–41.

16. Dardeno T.A., Chou S.H., Moon H.S., Chamberland J.P., Fiorenza C.G., Mantzoros C.S. Leptin in human physiology and therapeutics. Front. Neuroendocrinol. 2010; 31: 377–393.

17. Dunbar J.C., Lu H. Leptin-induced increase in sympathetic nervous and cardiovascular tone is mediated by proopiomelanocortin (POMC) products. Brain Res. Bull. 1999; 50: 215–221.

18. Rao S.P., Dunbar J.C. A role for the central histaminergic system in the leptin-mediated increase in cardiovascular dynamics. Brain Res. Bull. 2005; 64: 425–432.

19. Jochem J., Kalarus Z., Spaccapelo L. et al. Centrally acting leptin induces a resuscitating effect in haemorrhagic shock in rats. Regul. Pept. 2012; 176: 45–50.

20. Morimoto T., Yamamoto Y., Yamatodani A. Leptin facilitates histamine release from the hypothalamus in rats. Brain Res. 2000; 868: 367–369.

21. Guarini S., Bini A., Bazzani C. et al. Adrenocorticotropin normalizes the blood levels of nitric oxide in hemorrhage-shocked rats. Eur. J. Pharmacol. 1997; 336: 15–21.

22. Chen Z. Effect of clobenpropit on regional cerebral blood flow in rat hippocampus. Acta Pharmacol. Sin. 2001; 22: 355–360.

23. Dunbar J.C., Hu Y., Lu H. Intracerebroventricular leptin increases lumbar and renal sympathetic nerve activity and blood pressure in normal rats. Diabetes 1997; 46: 2040–2043.

24. Jochem J., Żwirska-Korczala K., Gwóźdź B., Walichiewicz P., Joško J. Cardiac and regional haemodynamic effects of endothelin-1 in rats subjected to critical haemorrhagic hypotension. J. Physiol. Pharmacol. 2003; 54: 383–396.

25. Shi Z., Brooks V.L. Leptin differentially increases sympathetic nerve activity and its baroreflex regulation in female rats: role of oestrogen. J. Physiol. 2014; 593: 1633–1647.

26. Guarini S., Cainazzo M.M., Giuliani D. et al. Adrenocorticotropin reverses hemorrhagic shock in anesthetized rats through the rapid activation of a vagal anti-inflammatory pathway. Cardiovasc. Res. 2004; 63: 357–365.

27. Fekete C., Liposits Z. Histamine-immunoreactive neurons of the tuberomammillary nucleus are innervated by alpha-melanocyte stimulating hormone-containing axons. Generation of a new histamine antiserum for ultrastructural studies. Brain Res. 2003; 969: 70–77.

28. Jochem J. Centrally-acting leptin-induced resuscitating effect in haemorrhagic shock in rats – a role of the histaminergic system. COST Action MC & WG1-4 Meeting „Progress in the research on histamine H3 & H4 receptors". Krakow 28–29 March 2011, Poland.

29. Jochem J., Savci V., Filiz N., Rybus-Kalinowska B., Fogel W.A., Yalcin M. Involvement of the histaminergic system in cytidine 5'-diphosphocholine-induced reversal of critical haemorrhagic hypotension in rats. J. Physiol. Pharmacol. 2010; 61: 37–43.

30. Tanida M., Kaneko H., Shen J., Nagai K. Involvement of the histaminergic system in renal sympathetic and cardiovascular responses to leptin and ghrelin. Neurosci. Lett. 2007; 413: 88–92.

31. Ishizuka T., Hatano K., Murotani T., Yamatodani A. Comparison of the effect of an H(3)-inverse agonist on energy intake and hypothalamic histamine release in normal mice and leptin resistant mice with high fat diet-induced obesity. Behav. Brain Res. 2008; 188: 250–254.

32. Dai H., Fu Q., Shen Y. et al. The histamine H_3 receptor antagonist clobenpropit enhances GABA release to protect against NMDA-induced excitotoxicity through the cAMP/protein kinase A pathway in cultured cortical neurons. Eur. J. Pharmacol. 2007; 563: 117–123.

33. Vong L., Ye C., Yang Z., Choi B., Chua S. Jr., Lowell B.B. Leptin action on GABAergic neurons prevents obesity and reduces inhibitory tone to POMC neurons. Neuron 2011; 71: 142–154.

34. Connelly W.M., Shenton F.C., Lethbridge N. et al. The histamine H_4 receptor is functionally expressed on neurons in the mammalian CNS. Br. J. Pharmacol. 2009; 157: 55–63.