

JERZY JOCHEM¹, ALICJA KASPERSKA-ZAJAC²

THE ROLE OF THE HISTAMINERGIC SYSTEM IN THE CENTRAL CARDIOVASCULAR REGULATION IN HAEMORRHAGIC HYPOTENSION

Abstract: *The role of the histaminergic system in the central cardiovascular regulation in haemorrhagic hypotension*

The histaminergic system consists of neurons located in tuberomammillary nucleus of the posterior hypothalamus. It affects many functions of the central nervous system, including regulation of the brainstem cardiovascular center. In this paper, we present current review of the literature concerning the role of the histaminergic system in the cardiovascular regulation in haemorrhagic hypotension. Experimental studies demonstrate that in both, normotension and critical haemorrhagic hypotension, histamine, acting as a central neurotransmitter, evokes the pressor effect. Interestingly, increases in mean arterial pressure are significantly higher in hypovolaemic than in normovolaemic animals. Many lines of evidence support the hypothesis that in haemorrhagic shock, the histaminergic system is able to activate neural and humoral compensatory mechanisms involving the sympathetic nervous and renin-angiotensin systems, arginine vasopressin and proopiomelanocortin-derived peptides. We suggest that the histaminergic system could be a new target for treatment of haemorrhagic hypotension.

Key words: histamine, cardiovascular center, haemorrhagic hypotension

INTRODUCTION

Haemorrhagic shock is a life-threatening condition characterized by inadequate tissue perfusion due to haemorrhage-induced hypovolaemia. It is the second-leading cause of early deaths in injured patients, with account for 30–40% of all trauma deaths [1]. Only in road crashes worldwide, an estimated 1.2 million people are killed each year and as many as 50 million are injured [2]. Taking into consideration, additionally, the number of people, who die of injuries/haemorrhagic shock due to interpersonal violence, terrorism, wars and occupational accidents, studies concerning the compensatory mechanisms in hypovolaemia and new strategies of haemorrhagic shock treatment are of essential importance.

There are two reflex-induced phases of haemodynamic response to blood loss [3]. In the initial sympathoexcitatory phase, reflex-initiated reaction from arterial

baroreceptors of the systemic circulation and/or low-pressure cardiopulmonary receptors leads to the stimulation of the sympathetic nervous system which results in tachycardia and an increase in vascular resistance, especially in the musculocutaneous and splanchnic vascular beds [4–6]. An increase in plasma noradrenalin concentration, an indicator of the sympathetic system activity, characterizes this phase of regulation [7]. The consequence of the increase in the total vascular resistance is a redistribution of blood from venous reservoirs, which together with a limitation of diuresis, provides the maintenance of blood pressure, despite the fall in cardiac output [3].

After a loss of 20–35% of total blood volume and a critical reduction of central blood volume, the second (sympathoinhibitory) phase develops [3, 8]. The signal from cardiopulmonary afferents, possibly originating in the left ventricle initiates a withdrawal of the vasoconstrictive activity in the whole sympathetic nervous system except for the part innervating the adrenal medulla (a reflex of Bezold-Jarisch) [5, 9]. The fall in arterial pressure is due to a decrease in cardiac output and total peripheral resistance, especially in the renal, gastrointestinal and muscular vasculature. A decrease in heart rate appears to be vagally mediated [3]. Arterial pressure falls abruptly in this phase of regulation, despite the activation of humoral compensatory mechanisms, including the secretion of arginine vasopressin (AVP), adrenaline and proopiomelanocortin (POMC)-derived peptides (Table 1), as well as the activation of the renin-angiotensin system [3]. There is also an activation of local vascular pathways, including the release of endothelin 1 [10]. Notwithstanding the action of all these humoral compensatory mechanisms, the second phase of regulation in haemorrhagic shock is characterized by a decrease in the total peripheral resistance, resulting probably from hyporeactivity to endogenous vasoconstrictive factors [11].

Table 1

Plasma concentrations of adrenalin, noradrenalin, arginine vasopressin, angiotensin II, ACTH and α -MSH before and after shock induction and 20 min after metoprine treatment

Hormone concentration	Before bleeding	Sympathoinhibitory phase of cardiovascular regulation in shock	20 min after treatment with metoprin	Reference
Adrenalin (pg/ml)	145.3 \pm 47.9	717.5 \pm 160.6	1078.6 \pm 203.8	23
Noradrenalin (pg/ml)	91.5 \pm 33.0	165.3 \pm 59.2	359.6 \pm 95.9	23
AVP (pg/ml)	24.1 \pm 14.9	424.6 \pm 126.3	587.5 \pm 98.8	37
Angiotensin II (pg/ml)	245.2 \pm 61.1	975.2 \pm 272.4	1559.3 \pm 265.9	38
ACTH (pg/ml)	180.1 \pm 54.7	583.3 \pm 95.2	781.6 \pm 155.1	39
α -MSH (pg/ml)	197.8 \pm 35.6	329.8 \pm 91.9	432.7 \pm 69.7	39

Central neuronal systems activated in pre-terminal conditions of haemorrhagic shock and involved in the initiation of the sympathoinhibitory phase of cardiovascular regulation can be categorised into two groups — endogenous analgesic (opioidergic) and anti-analgesic (melanocortinergetic, cholecystokininergetic, thyroliberinergetic) systems [12]. Studies of recent years have revealed not only the influence on pain transmission, but also the resuscitating effects of many anti-analgesic (non-opioid) neurotransmitters, among them adrenocorticotropic hormone (ACTH), α -melanocyte stimulating hormone (α -MSH), cholecystokinin peptides and thyrotropin-releasing hormone (TRH) [11], at concentrations which cause little or no activity in normotension. Interestingly, in our previous studies we have demonstrated that many of central neuromodulators participating in food intake regulation, such as leptin [13], orexin A [14], serotonin [15] and histamine [16], are also able to activate compensatory mechanisms in haemorrhagic shock.

Histaminergic neurones are concentrated mainly in the tuberomammillary nucleus of the posterior hypothalamus and can be divided into three groups: (1) medial tuberomammillary subgroup, (2) ventral tuberomammillary subgroup and (3) tuberomammillary diffused neurones [17]. They send innervation, *via* ascending and descending pathways, to almost all parts of the brain, including the medulla oblongata where the cardiovascular complex is located, and may thus directly influence central cardiovascular regulation [17]. According to the hypothesis by Wada *et al.*, histaminergic neurons are able to affect the activity of the whole brain [18]. Indeed, histamine, acting centrally, influences learning and memory, transmission of the information from nociceptors, feeding behavior, hypothalamic hormone secretion and cardiorespiratory control [19]. The purpose of this work is to present a critical review concerning the role of the histaminergic system, the system influencing both pain perception and food intake control, in the central cardiovascular regulation in haemorrhagic shock.

INFLUENCE OF THE HISTAMINERGIC SYSTEM ON CARDIOVASCULAR FUNCTION IN NORMOTENSION

Initial studies concerning the role of histaminergic neurones in cardiovascular regulation were carried out in normotensive animals. Exogenous histamine administered into the brain lateral ventricle (*icv*) in rats evoked short-lasting rises in mean arterial pressure (MAP) associated with tachycardia in anaesthetized, while bradycardia in conscious animals [20–21]. Similarly, histamine *N*-methyltransferase (HNMT) inhibitors, SKF 91488 and metoprine, which produce the increase in extracellular endogenous histamine concentration due to the blockage of its catabolism, evoke the pressor effect in normotensive rats [22–23]. Both effects are due to the central activation of the sympathetic system (predominantly in conscious animals) and the release of AVP (in anaesthetized animals) — Fig. 1 [20–21].

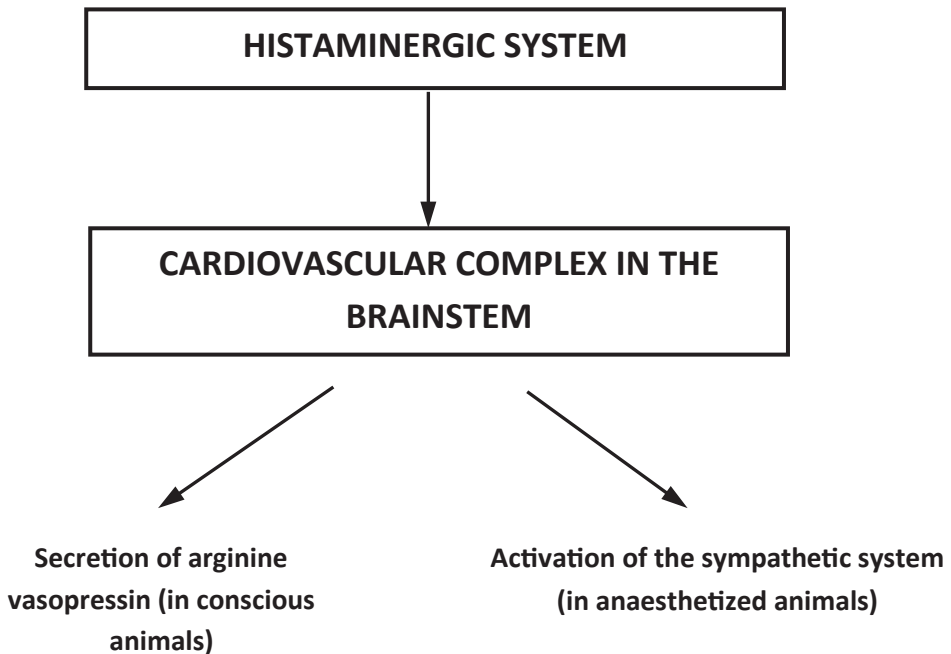


Fig. 1. Function of the histaminergic system in the central cardiovascular regulation in normotension

All four types of histamine receptors (H_1 – H_4) are present in the central nervous system [19, 24], however, only H_1 and H_2 receptors are involved in the central cardiovascular regulation in normotension. Histamine receptor antagonists H_1 and H_2 administered *icv* [21] inhibit histamine action, while selective H_1 and H_2 receptor agonists, pyridylethylamine and impromidine, respectively, produce the pressor effect [21].

In many studies, interactions between the histaminergic and other neuronal systems, such as noradrenergic, opioidergic, angiotensinergic and serotonergic systems, in the central cardiovascular control in normotension have been demonstrated. We have shown that histamine-mediated cardiovascular effects were abolished by neurotoxin of noradrenergic neurons DSP-4 and inhibited by pre-treatment with α_1 - and α_2 -adrenoceptor antagonists [25]. Histamine-induced haemodynamic effects could be inhibited by an antagonist of μ opioid receptors CTOP, but not by δ - and κ -opioid receptor antagonists [26]. Our studies demonstrated also the involvement of the central angiotensin type 1 (AT_1) and type 2 (AT_2) receptors in the effect since captopril, ZD 7155 and PD 123319 — angiotensin converting enzyme inhibitor and AT_1 and AT_2 antagonists, respectively, inhibited histamine-induced changes in MAP [27]. Finally, H_1 receptor antagonist, chlorpheniramine, inhibited MAP and peripheral vascular resistance changes elicited by centrally injected serotonin, which suggests that central serotonin-

induced cardiovascular effects in normotensive rats are in part mediated by the histaminergic system, and histamine H₁ receptors are involved [28].

INFLUENCE OF THE HISTAMINERGIC SYSTEM ON CARDIOVASCULAR FUNCTION IN CRITICAL HYPOTENSION

A large body of evidence suggests that the histaminergic system is especially involved in the initiation of the response to the action of adverse or potentially dangerous stimuli, including dehydration, nociceptive stimuli and other kinds of stress [19]. In these conditions, there is an increase in the release and/or turnover of neuronal histamine leading to activation of compensatory/antinociceptive mechanisms [19].

Philippu *et al.* were the first to demonstrate an increase in the release of endogenous histamine from the posterior hypothalamus in cats as a result of a decrease in blood pressure after intravenous injection of sodium nitroprusside and haemorrhage [29]. Interestingly, the localization differences in activated neurones in response to different kinds of stress have been reported [30]. These findings showed the activation of the central histaminergic system in the state of disturbed circulatory homeostasis, however, the importance of the effect was not clear.

Studies from the beginning of this decade revealed for the first time that histamine administered *icv* in the sympathoinhibitory phase of haemorrhagic shock produces a long-lasting pressor effect, with an increase in MAP and HR up to the pre-haemorrhage values [16]. In comparison to normovolaemic animals, the rises in MAP and HR after histamine injections in critical hypovolaemia are 2.7–3.3- and 1.3–3.6-fold higher, respectively, and are associated with the increase in the survival rate of 2 hrs after treatment [16]. Moreover, the resuscitating effect was accompanied by increases in peripheral blood flows, especially in the renal and hindquarters vascular beds [31]. All these findings suggest an important role of the histaminergic system in the maintenance of circulatory homeostasis in hypovolaemia and have resulted in further studies on the mechanisms responsible for the effect.

Histamine action in haemorrhagic hypotension is due to stimulation of H₁ histamine receptors, since chlorpheniramine inhibits the influence on MAP, HR and decreases the survival rate. In contrast, pre-treatment with ranitidine, H₂ histamine blocker, and thioperamide, H₃ receptor inverse agonist/H₄ antagonist failed to influence cardiovascular changes evoked by histamine [16].

Early treatment (5 min of shock) with histamine (*icv*) was accompanied by almost a complete reversal of hypoperfusion-induced metabolic acidosis, with normalization of arterial and venous Pco₂, bicarbonate concentration, pH and base excess (BE) at 2 hrs [32]. Therefore, the effectiveness of this treatment was similar to standard volume resuscitation [33]. Interestingly, histamine treatment

at 15 min of critical hypotension was associated with lower increase in MAP and decreased survival rate of 2 hrs in comparison to volume-resuscitated animals [33]. Thus, we demonstrated that early treatment with histamine and primary central stimulation of compensatory mechanisms is as effective as volume resuscitation of haemorrhagic shock.

A comparison of the action of different vasoconstrictive agents shows that the pressor effect resulting from histamine treatment (100 nmol, *icv*) was more pronounced than that of AVP (0.25 nmol/kg, intravenously [*iv*]) [34], whereas AVP was more effective than noradrenaline (2 µg/kg, *iv*) [35]. We hypothesize that the differences can be explained by central histamine-induced mobilisation of complex homeostatic mechanisms in haemorrhagic shock, including activation of the sympathetic nervous system and secretion of AVP.

To study the role of the histaminergic system in the central cardiovascular regulation in haemorrhagic shock, two different pharmacological approaches were used to increase the local histamine level — stimulation of the synthesis by administration of its precursor L-histidine as well as inhibition of catabolizing enzyme activity, HNMT. We have shown that L-histidine administered intraperitoneally in 5 min of critical hypotension produced increases in endogenous histamine concentrations in the cerebral cortex, hypothalamus and medulla oblongata and a long-lasting dose-dependent pressor effect, with a 100% survival rate of 2 hrs, whereas in normotensive animals it did not influence cardiovascular parameters [36]. Further, pre-treatment with (S)- α -fluoromethylhistidine, an irreversible inhibitor of L-histidine decarboxylase, produced a decrease in central histamine concentrations, diminished volume of blood required to achieve critical hypotension and prevented L-histidine-induced increases in central histamine concentrations and its resuscitating effect [36].

Inhibitors of HNMT, SKF 91488 and metoprine, similarly to L-histidine, evoked an increase in endogenous central histamine concentrations and produced a more pronounced pressor effect in hypotensive rats than in normotensive animals [23].

To clarify mechanisms activated by centrally acting endogenous histamine during the resuscitating effect in haemorrhagic shock, we administered metoprine centrally and measured peripheral haemodynamic changes after pre-treatment with antagonists of different effector pathways. We demonstrated an involvement of the sympathetic nervous system, the renin-angiotensin system as well as AVP and POMC-derived peptides in central histamine-induced resuscitating action [23, 37–39].

Endogenous histamine-mediated increases in MAP and HR were accompanied by increased plasma concentrations of noradrenaline, adrenaline, AVP, angiotensin II, ACTH and α -MSH (Table 1). We demonstrated that nicotinic cholinergic antagonist hexamethonium decreased MAP and HR changes, whereas muscarinic cholinergic blocker methylatropine inhibited only the pressor effect of histamine [23]. Metoprine-induced MAP and regional haemodynamic effects were also reduced by α_1 - and α_2 -adrenoceptor antagonists prazosin and yohimbine, respectively,

whereas β -adrenoceptor blocker propranolol diminished only HR changes [23]. All these results clearly demonstrate the involvement of the sympathetic nervous system in central histamine-induced cardiovascular effect in haemorrhagic shock.

We showed that [β -mercapto- β , β -cyclopentamethylenepropionyl¹,O-me-Tyr²,Arg⁸] AVP — V_{1a} receptor antagonist, but not V_{1b} and V_2 receptor blockers, inhibited metoprine-induced haemodynamic effects, with no influence on survival at 2 hrs [37]. Thus, we confirmed that AVP, acting *via* V_{1a} receptors, is involved in endogenous central histamine-induced reversal of critical haemorrhagic hypotension in rats [37].

In our further study we have shown that AT_1 receptor antagonist ZD 7155 decreased regional vascular resistance and inhibited metoprine-induced increase in MAP, whereas AT_2 receptor blocker PD 123319 had no effect [38]. In addition, captopril inhibited an increase in plasma angiotensin II level and the haemodynamic effects of metoprine [38], which together confirmed the involvement of the renin-angiotensin system in central histamine-induced cardiovascular effects in haemorrhagic shock.

Finally, we have found that centrally acting melanocortin type 4 (MC_4) receptor antagonists HS014 inhibited metoprine-induced increase in MAP due to a decrease in regional vascular resistance, however, it did not affect HR and the survival at 2 hrs [39]. We concluded that POMC-derived peptides, acting centrally *via* MC_4 receptors, participate in endogenous central histamine-induced resuscitating effect in rats and the effect is not related to the activation of glucocorticoid receptors, since glucocorticoid type II receptor blocker mifepristone did not evoke any change [39].

Summing up, all these haemodynamic studies confirm the involvement of the sympathetic nervous system, the renin-angiotensin system as well as AVP and POMC-derived peptides in central histamine-induced resuscitating action — Fig. 2.

In our recent works we demonstrated that in cardiovascular regulation in haemorrhagic hypotension there are interactions between the histaminergic and other neuronal systems, such as serotonergic [15], orexinergic [40] and cholinergic [41]. We disclosed a bi-directional interactions between the histaminergic and serotonergic systems since a selective 5-HT_{1A} receptor antagonist WAY 100635 inhibited histamine-induced action and, on the other hand, 5-HT_{1A} receptor agonist 8-OH-DPAT evoked the pressor and tachycardic effects in haemorrhage-shocked rats which were inhibited by chlorpheniramine [15]. Additionally, we demonstrated an inhibitory effect of orexin type 1 receptor antagonist SB 334867 on the central histamine-induced resuscitating effect in haemorrhage-shocked rats [40], which conforms functional interactions between the two neuronal systems in cardiovascular regulation in hypotension.

To study interactions between the histaminergic and cholinergic systems we used cytidine 5'-diphosphocholine (CDP-choline), an endogenously synthesized mononucleotide which exerts a variety of physiological effects by altering central cholinergic transmission. CDP-choline administered *icv* reverses haemorrhagic hypo-

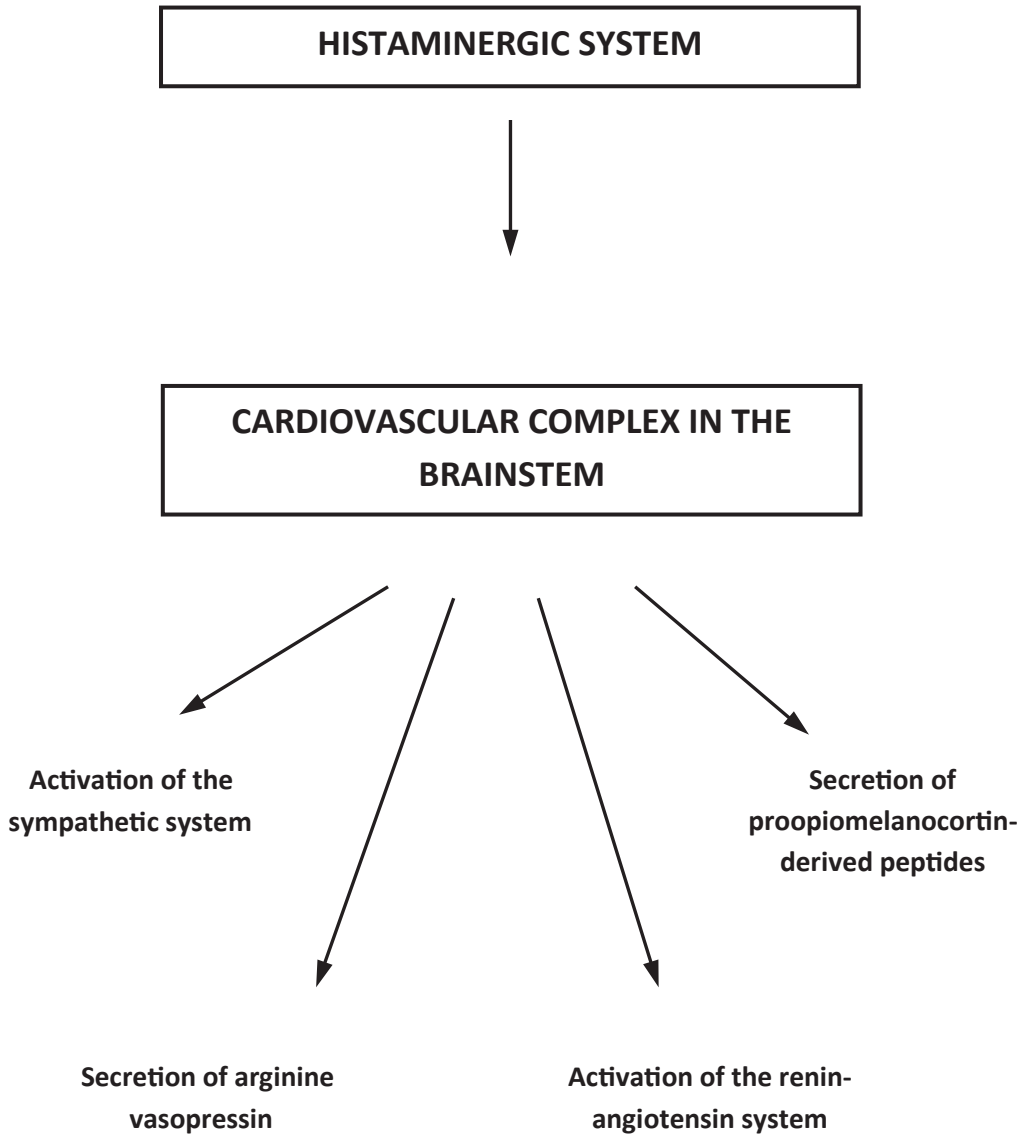


Fig. 2. Compensatory mechanisms activated by centrally acting histamine in critical haemorrhagic hypotension

tension in rats, apparently by the activation of central cholinergic receptors [41]. The action was accompanied by an increase in extracellular histamine concentration at the posterior hypothalamus, as measured by microdialysis [41]. The cardiovascular effects of CDP-choline were almost completely blocked by pretreatment with chlorpheniramine, but not with ranitidine and thioperamide [41]. Therefore

we showed that the central histaminergic system, through the activation of H₁ histaminergic receptors, is involved in CDP-choline-induced resuscitating effect in haemorrhage-shocked rats.

In conclusion, many lines of evidence support the hypothesis that in haemorrhagic shock, the histaminergic system is able to activate neural and humoral compensatory mechanisms involving the sympathetic nervous and renin-angiotensin systems, arginine vasopressin and proopiomelanocortin-derived peptides. These effects can be mediated directly or indirectly, since the histaminergic system interacts with other neuronal systems, including the serotonergic and cholinergic systems.

We suggest that the histaminergic system could be a new target for the treatment of hemorrhagic hypotension.

ACKNOWLEDGEMENT

The authors thank very much Prof. dr W. Agnieszka Fogel for a critical review of the manuscript.

REFERENCES

1. *Kauwar D.S., Lafaring R., Wade C.E.*: Impact of hemorrhage on trauma outcome: an overview of epidemiology, clinical presentations, and therapeutic considerations. *J Trauma*. 2006, 60: S3–11.
- 2. *Peden M., Scurfield R., Sleet D., et al.*: World report on road traffic injury prevention. World Health Organization, 2004.
- 3. *Schadt J.C., Ludbrook J.*: Hemodynamic and neurohumoral responses to acute hypovolemia in conscious mammals. *Am J Physiol*. 1991, 260: H305–318.
- 4. *Schadt J.C., Gaddis R.R.*: Cardiovascular responses to hemorrhage and naloxone in conscious barodenervated rabbits. *Am J Physiol*. 1986, 251: R909–R915.
- 5. *Hasser E.M., Schadt J.C.*: Sympathoinhibition and its reversal by naloxone during hemorrhage. *Am J Physiol*. 1992, 262: R444–R451.
- 6. *Evans R.G., Hayes I.P., Ludbrook J.*: Effects of α -adrenoceptor antagonists and clonidine on the haemodynamic response to acute hypovolaemia in conscious rabbits. *Eur J Pharmacol*. 1992, 216: 265–272.
- 7. *Korner P.I., Oliver J.R., Zhu J.L., Gipps J., Hanneman F.*: Autonomic, hormonal, and local circulatory effects of haemorrhage in conscious rabbits. *Am J Physiol*. 1990, 258: H229–H239.
- 8. *Ludbrook J., Potocnik S.J., Woods R.L.*: Simulation of acute haemorrhage in unanesthetized rabbits. *Clin Exp Pharmacol Physiol*. 1988, 15: 575–581.
- 9. *Victor R.G., Thorén P., Morgan D.A., Mark A.L.*: Differential control of adrenal and renal sympathetic nerve activity during hemorrhagic hypotension in rats. *Circ Res*. 1989, 64: 686–694.
- 10. *Edwards J.D., Dougan P.S., Rowley J.M., Agrawal D.K., Thorpe P.E., Adrian T.E.*: Endothelin-1 levels in ischaemia, reperfusion, and haemorrhagic shock in the canine infrarenal aortic revascularisation model. *Eur J Vasc Surg*. 1994, 8: 729–734.
11. *Zhou R., Chen F., Li Q., Hu D.Y., Liu L.M.*: Stimulation of the adenosine A3 receptor reverses vascular hyporeactivity after hemorrhagic shock in rats. *Acta Pharmacol Sin*. 2010, 31: 413–420.
- 12. *Bertolini A.*: The opioid/anti-opioid balance in shock: a new target for therapy in resuscitation. *Resuscitation*. 1995, 30: 29–42.
- 13. *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.
- 14. *Jochem J., Zwirska-Korcza K., Zabielski R., Kato I., Kuwahara A.*: Cardiovascular effects of centrally acting orexin A in haemorrhage-shocked rats. *J Physiol Pharmacol*. 2006, 57

(Suppl 11): 115–124. — **15.** 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-HT_{1A} receptors. *Inflamm Res.* 2009, 58(Suppl 1): 38–40. — **16.** Jochem J.: Cardiovascular effects of histamine administered intracerebroventricularly in critical haemorrhagic hypotension in rats. *J Physiol Pharmacol.* 2000, 51: 229–239. — **17.** Inagaki N., Yamatodani A., Ando-Yamamoto M., Tohyama M., Watanabe T., Wada H.: Organization of histaminergic fibers in the rat brain. *J Comp Neurol.* 1988, 273: 283–300. — **18.** Wada H., Inagaki N., Yamatodani A., Watanabe T.: Is the histaminergic neuron system a regulatory center for whole-brain activity? *Trends Neurosci.* 1991, 14: 415–418. — **19.** Brown R.E., Stevens D.R., Haas H.L.: The physiology of brain histamine. *Progr Neurobiol.* 2001, 63: 637–672. — **20.** Finch L., Hicks P.E.: The cardiovascular effects of intraventricularly administered histamine in the anaesthetised rat. *Naunyn-Schmiedeberg's Arch Pharmacol.* 1976, 293: 151–157.

21. Poulakos J.J., Gertner S.B.: Studies on the cardiovascular actions of central histamine H₁ and H₂ receptors. *J Pharmacol Exp Ther.* 1989, 250: 500–507. — **22.** Jochem J.: Endogenous central histamine-induced reversal of critical haemorrhagic hypotension in rats — studies with histamine N-methyltransferase inhibitor SKF 91488. *Inflamm Res.* 2002, 51: 551–556. — **23.** Jochem J.: Involvement of the sympathetic nervous system in the reversal of critical haemorrhagic hypotension by endogenous central histamine in rats. *Naunyn-Schmiedeberg's Arch Pharmacol.* 2004, 369: 418–427. — **24.** Connelly W.M., Shenton F.C., Lethbridge N., et al.: The histamine H₄ receptor is functionally expressed on neurons in the mammalian CNS. *Br J Pharmacol.* 2009, 157: 55–63. — **25.** Jochem J., Żwirska-Korczała K.: Involvement of central noradrenergic system in the pressor effect of histamine administered intracerebroventricularly in rats — haemodynamic studies. *Inflamm Res.* 2002, 51(Suppl. 1): S59–S60. — **26.** Jochem J., Żwirska-Korczała K.: Interactions between the histaminergic and opioidergic systems in the central cardiovascular regulation — haemodynamic studies. *Inflamm Res.* 2004, 53(Suppl. 1): S63–S64. — **27.** Jochem J., Żwirska-Korczała K., Sowa P., Berdowska A.: Interactions between the histaminergic and angiotensinergic systems in the central cardiovascular regulation in rats. *Inflamm Res.* 2006, 55(Suppl.1): S69–S70. — **28.** Jochem J., Rybczyk R., Irman-Florjanc T., Żwirska-Korczała K., Niwecka A.: Central serotonin-induced pressor effect in rats is mediated in part via the histaminergic system. *Inflamm Res.* 2008, 57(Suppl 1): S35–36. — **29.** Philippu A., Hagen R., Hanesch U., Waldmann U.: Changes in the arterial blood pressure increase the release of endogenous histamine in the hypothalamus of anaesthetized cats. *Naunyn-Schmiedeberg's Arch Pharmacol.* 1983, 323: 162–167. — **30.** Miklós I.H., Kovács K.J.: Functional heterogeneity of the responses of histaminergic neuron subpopulations to various stress challenges. *Eur J Neurosci.* 2003, 18: 3069–3079.

31. Jochem J.: Central histamine-induced reversal of critical haemorrhagic hypotension in rats — haemodynamic studies. *J Physiol Pharmacol.* 2002, 53: 75–84. — **32.** 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: 447–458. — **33.** Jochem J.: Central histamine-induced reversal of haemorrhagic shock versus volume resuscitation in rats. *Inflamm Res.* 2002, 51(Suppl. 1): S57–S58. — **34.** Jochem J.: Central histamine-induced reversal of critical haemorrhagic hypotension in rats: a comparison with the pressor effect of arginine vasopressin. *Inflamm Res.* 2004, 53(Suppl. 1): S61–S62. — **35.** Jochem J.: Central histamine-induced reversal of haemorrhagic shock in rats — a comparison with the pressor effect of peripheral adrenergic receptor stimulation. *Inflamm Res.* 2003, 52(Suppl. 1): S41–S42. — **36.** Jochem J.: Endogenous central histamine-induced reversal of critical hemorrhagic hypotension in rats — studies with L-histidine. *Shock.* 2003, 20: 332–337. — **37.** Jochem J.: Involvement of arginine vasopressin in endogenous central histamine-induced reversal of critical haemorrhagic hypotension in rats. *Inflamm Res.* 2004, 53: 269–276. — **38.** Jochem J.: Involvement of the renin-angiotensin system in central histamine-induced reversal of critical haemorrhagic hypotension in rats. *J Physiol Pharmacol.* 2004, 55: 39–55. — **39.** Jochem J.: Involvement of proopiomelanocortin-derived peptides in endogenous central

histamine-induced reversal of critical haemorrhagic hypotension in rats. *J Physiol Pharmacol.* 2004, 55: 57–71. — **40.** *Jochem J.*: Orexin type 1 receptor antagonist SB 334867 inhibits the central histamine-induced resuscitating effect in rats subjected to haemorrhagic shock. *Inflamm Res.* 2009, 58(Suppl. 1): 36–37.

41. *Yalcin M., Savci V., Jochem J.*: Involvement of the cholinergic system in the central histamine-induced reversal of critical haemorrhagic hypotension in rats. *J Physiol Pharmacol.* 2009, 60: 133–137.

¹Department of Basic Medical Sciences

²Chair and Clinical Department of Internal Diseases,
Allergology and Clinical Immunology
Medical University of Silesia, Katowice, Poland

Corresponding author:

Prof. dr Jerzy Jochem

Department of Basic Medical Sciences

Faculty of Public Health

Medical University of Silesia, Katowice

ul. Piekarska 18, 41-902 Bytom, Poland

Tel.: +48 32 397 65 42; Fax +48 32 397 65 37

e-mail: jjochem@poczta.onet.pl

