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PRACA ORYGINALNA
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Cardiovascular effects of histamine H3 receptor antagonist JNJ 5207852 in haemorrhagic shock in rats

Efekty sercowo-naczyniowe działania antagonisty receptorów histaminowych H3 JNJ 5207852 we wstrząsie krwotocznym u szczurów

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ABSTRACT

INTRODUCTION: Histamine H3 receptors are widely distributed in the central and peripheral nervous system, including postganglionic adrenergic endings. They act mainly as presynaptic auto- and heteroceptors and are responsible for regulating the synthesis and release of histamine and other neurotransmitters/neuromodulators. The aim of the study was to examine the cardiovascular effects of the histamine H3 receptor blockade in the sympathoinhibitory phase of haemorrhagic shock.
MATERIAL AND METHODS: Studies were carried out on male Wistar rats anaesthetized with ketamine/xylazine (100 mg/kg + 10 mg/kg, intraperitoneally), subjected to irreversible haemorrhagic shock (0% survival at 2 h) with a mean arterial pressure (MAP) of 20–25 mmHg. At 5 min of critical hypotension, the rats were injected intravenously with H3 receptor antagonist JNJ 5207852 or saline.
RESULTS: Haemorrhage led to a decrease in pulse pressure (PP) and heart rate (HR). JNJ 5207852 (1 and 5 mg/kg) evoked long-lasting rises in MAP, PP and HR, with an improvement in survival at 2 h (5 mg/kg). Chemical sympathectomy with 6-hydroxydopamine (50 mg/kg for three consecutive days) inhibited cardiovascular changes evoked by JNJ 5207852 and decreased to 0% the survival rate at 2 h in rats treated with JNJ 5207852 (5 mg/kg).
CONCLUSIONS: Histamine H3 receptor antagonist JNJ 5207852 induces the resuscitating effect in haemorrhage-shocked rats, and the mechanism responsible is associated with the activity of postganglionic sympathetic neurons.

KEY WORDS
histamine, H3 receptor, haemorrhagic shock, rat

STRESZCZENIE

WSTĘP: Receptory histaminowe H3 występują w ośrodkowym i obwodowym układzie nerwowym, w tym na zakończeniach pozazwojowych układu współczulnego. Działają głównie jako presynaptyczne auto- i heteroreceptory, są odpowiedzialne za regulację syntezy oraz wydzielania histaminy i innych neurotransmiterów/neuromodulatorów. Celem pracy było zbadanie wpływu zablokowania receptorów H3 na czynność układu krążenia podczas fazy hamowania aktywności układu współczulnego w modelu wstrząsu krwotocznego u szczurów.

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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 2 h: 0%). W 5 min krytycznej hipotensji zwierzętom podawano dożylnie antagonistę receptorów H3 JNJ 5207852 bądź 0,9% roztwór NaCl.
WYNIKI: Krwotok prowadził do obniżenia ciśnienia tętna (PP) i częstości rytmu serca (HR). JNJ 5207852 (1 i 5 mg/kg) wywoływał długotrwałe wzrosty MAP, PP i HR, a także zwiększenie do 100% wskaźnika przeżycia 2 h (5 mg/kg). Chemiczna sympatektomia wykonana przy użyciu 6-hydroksydopaminy (50 mg/kg przez trzy kolejne dni) hamowała zmiany MAP, PP i HR wywoływane przez JNJ 5207852 (5 mg/kg) i zmniejszała do 0% wskaźnik przeżycia 2 h.
WNIOSKI: Antagonista receptorów histaminowych H3 JNJ 5207852 wywołuje efekt resuscytacyjny u szczurów we wstrząsie krwotocznym, a jego mechanizm działania związany jest z aktywnością pozazwojowych neuronów układu współczulnego.

SŁOWA KLUCZOWE
histamina, receptor H3, wstrząs krwotoczny, szczur

INTRODUCTION

Histamine, a product of L-histidine decarboxylation, belongs to the widely distributed biogenic amines in mammals. It is present both in the central nervous system, as a neurotransmitter secreted by histaminergic neurons, and in peripheral tissues, mainly in basophils and mast cells. It exerts biological effects acting via four types of histamine receptors: H1–H4 [1].
Histamine is able to influence cardiovascular system functions directly and indirectly. In normotensive animals, indirect action is mediated mainly by the sympathetic nervous system [2]. There is a pressor effect accompanied by tachycardia in anaesthetised animals, and bradycardia in conscious ones after the central administration of exogenous histamine [3]. Similarly, an increase in endogenous extracellular histamine concentration after the inhibition of histamine N-methyltransferase activity, the enzyme responsible for histamine catabolism, leads to an increase in mean arterial pressure (MAP) in rats [4]. Interestingly, in critical haemorrhagic hypotension, centrally acting histamine induces a few fold higher increases in MAP in comparison to normotensive animals [4,5]. The observed resuscitating action results from activation of the sympathetic system [6], renin-angiotensin system [7], as well as the secretion of arginine vasopressin (AVP) [8] and melanocortin peptides [9]. Both in normotension and critical hypotension, histamine-induced effects are mediated via central H1 receptors [4,5].
Direct circulatory effects of histamine – induced after H1 and H2 receptor activation – are known well and characterize anaphylactic reactions [10]. Peripherally acting histamine induces a completely different action in comparison to central effects – a decrease in vascular resistance leading to hypotension. In contrast to H1 and H2 receptors, the role of the histamine H3 receptor in peripheral cardiovascular regulation is not fully recognized.
Histamine H3 receptors were firstly identified in the rat brain by Arrang et al. [11], and later cloned by Lovenberg et al. [12]. These receptors are present on neurons, mainly presynaptically, and act as auto- and heteroceptors. They are widely distributed in the central and peripheral nervous system and are responsible for modulating the synthesis and release of histamine and other neurotransmitters/neuromodulators [13].
The H3 receptor is a G-protein coupled receptor and displays constitutive activity, i.e. it is able to signal without activation by an agonist [13]. Inhibition of histamine synthesis and release through adenylate cyclase/protein kinase A and calcium/calmodulin-dependent protein kinase type II pathways occurs after H3 receptor activation. Additionally, it can activate phospholipase A2 and phosphoinositol-3-kinase [13]. Experimental data confirm the role of H3 receptors in the pathogenesis of many diseases, including Alzheimer's disease, attention-deficit hyperactivity syndrome, narcolepsy, Tourette syndrome, schizophrenia, epilepsy, substance abuse and obesity [13].
In the cardiovascular system, H3 receptors are present on postganglionic adrenergic endings innervating the heart and vessels [14]. According to the study by Li et al. [15], in the heart the histamine H3 receptor may act as an autoreceptor, and histamine may be a novel sympathetic neurotransmitter. On the other hand, the activation of H3 receptors located on postganglionic ending innervating vessels leads to vasodilatation as in vitro studies demonstrate [16]. Furthermore, the essential in vivo studies by Malinowska and Schlicker [17] show that the neurogenic vasopressor tone can be modulated via H3 receptors.
Haemorrhagic shock is a life-threatening condition characterized by inadequate tissue perfusion as a result of blood loss. There are three phases of neurohormonal response to blood loss [18]. The first phase is characterized by an increase in sympathetic nervous system activity (sympathoexcitatory phase), the second one – by a decrease in sympathetic activity (sym-

pathoinhibitory phase), and in the third, terminal phase, there is a transient increase in sympathetic activity [19]. The aim of the present study was to examine the cardiovascular effects of histamine H3 receptor blockade in the sympathoinhibitory phase of haemorrhagic shock.

METHODS

Animals

All the procedures were performed according to European Union directives and reviewed by the Local Ethics Committee, Katowice, Poland (Notification No 36/2013). Studies were performed on male Wistar rats weighing 255–295 g (6–8 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 carotid artery and the right jugular vein. MAP and heart rate (HR) were measured using a TAM-A transducer amplifier module and ECGA amplifier (Hugo Sachs Elektronik, Germany), respectively.

Experimental protocol

Chemical sympathectomy was induced by subcutaneous (sc) injections of 6-hydroxydopamine (6-OHDA) at a dose of 50 mg/kg for three consecutive days [20], and on the fourth day the animals started haemodynamic procedures. In the control group, the animals were injected with saline.

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. Five min after the induction of critical MAP, the animals were injected intravenously (iv) with histamine H3 receptor neutral antagonist JNJ 5207852 (1 and 5 mg/kg in 0.2 ml of 0.9% NaCl solution) or saline (0.2 ml). Since all the animals survived 2 h after treatment with JNJ 5207852 at a dose of 5 mg/kg, this dose was chosen for the studies with animals subjected to chemical sympathectomy. The doses of JNJ 5207852 were taken from literature [22]. 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 recommendations of the Local Ethics Committee, to avoid duplicating studies performed at our laboratory with the same rat strain, using the same experimental protocol of haemorrhagic shock [23], we did not repeat experiments in the control saline-treated group and we cited and discussed previously published results.

Drugs

The following drugs were used: heparin (Polfa, Poland), JNJ 5207852 dihydrochloride (Tocris Bioscience, UK), 6-OHDA, ascorbic acid (Sigma-Aldrich, USA), 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. Fisher's exact test was used to examine the statistical differences in rat survival. Statistical evaluation of the other results was performed using the analysis of variance (ANOVA) and post-ANOVA of the Student-Newman-Keuls test.

RESULTS

The initial pre-bleeding MAP values (Fig. 1A), pulse pressure (PP) (Fig. 1B) and HR (Fig. 1C) did not reveal significant differences among all the groups.

The total bleeding volume necessary for inducing critical hypotension in all the saline-pre-treated animals was 2.29 ± 0.36 ml/100 g body weight. In the rats subjected to chemical sympathectomy, the bleeding volume was significantly lower (1.87 ± 0.25 ml/100 g body weight; $p < 0.05$).

In the control saline-pre-treated group, bleeding from MAP 84.3 ± 4.9 mmHg to 20–25 mmHg was associated with decreases in PP from 26.2 ± 5.1 mmHg to 10.2 ± 2.3 mmHg and in HR from 344 ± 18 beats/min to 229 ± 21 beats/min [23]. There were no differences among all the groups in post-bleeding values of MAP, PP and HR (Fig. 1A-C).

JNJ 5207852 given at 5 min of critical hypotension at a dose of 5 mg/kg induced an increase in MAP, PP and HR (Fig. 1A-C). The effects started within 5––10 min after injection, were long-lasting and associ-

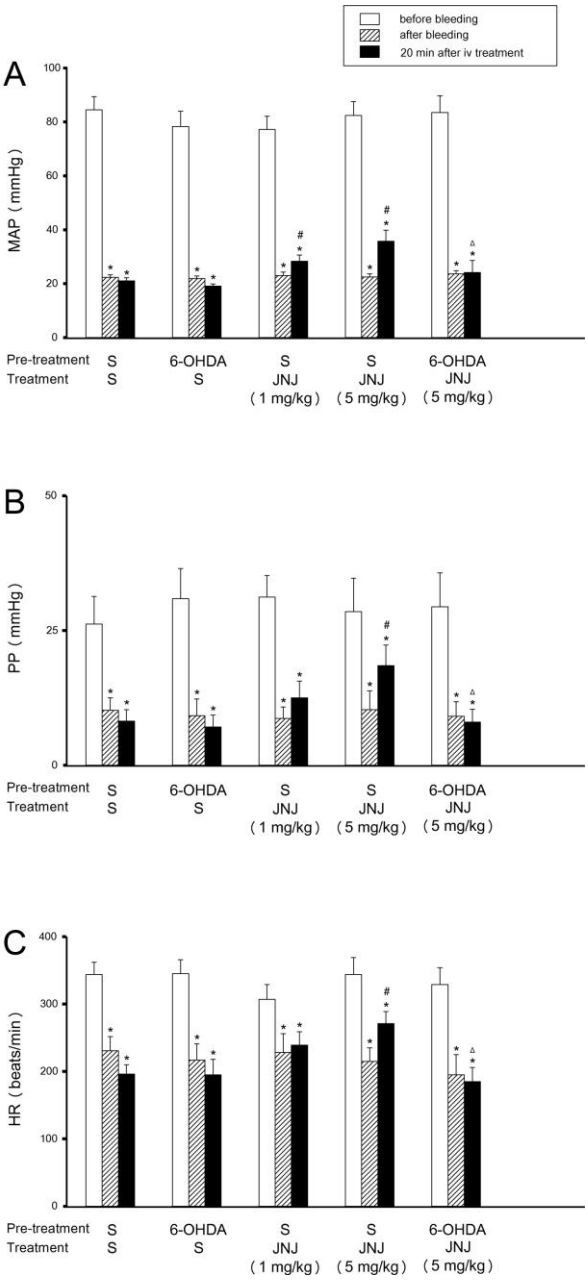

Fig. 1. Influence of chemical sympathectomy with 6-OHDA and saline (S) on MAP (A), PP (B) and HR (C) before and after bleeding and 20 min after JNJ 5207852 (JNJ, 1 and 5 mg/kg) or saline (0.2 ml) *iv* administration; means ± SD; 6 animals per group. * $p < 0.05$ vs. pre-bleeding value; # $p < 0.05$ vs. corresponding value in the saline-treated group; in animals with chemical sympathectomy, $^{\Delta}$ $p < 0.05$ vs. the saline-pre-treated JNJ 5207852-injected group; the data in the control saline-injected group are cited from [23].

Ryc. 1. Wpływ chemicznej sympatektomii przy użyciu 6-OHDA oraz 0,9% roztworu NaCl (S) na MAP (A), PP (B) i HR (C) przed i po krwotoku oraz 20 min po dożylnym podaniu JNJ 5207852 (JNJ, 1 I 5 mg/kg) oraz 0,9% roztworu NaCl (0,2 ml): średnie ± SD; 6 zwierząt w grupie. * $p < 0,05$ w porównaniu z wartością sprzed krwotoku; # 0,05 w porównaniu z odpowiednią wartością w grupie kontrolnej; u zwierząt po chemicznej sympatektomii Δ $p < 0,05$ w porównaniu z grupą, w której podawano JNJ 5207852 po premedykacji 0,09% roztworem NaCl; dane z grupy kontrolnej zacytowano na podstawie [23].

ated with a 100% survival rate at 2 h ($p < 0.05$ vs. control saline-treated animals [23]; Fisher's exact test). In contrast, JNJ 5207852 at a dose of 1 mg/kg evoked transient increases in MAP, PP and HR (Fig. 1A-C) associated with a 33.3% survival rate at 2 h (not different from control saline-treated animals [23]; Fisher's exact test).

Chemical sympathectomy almost completely blocked the cardiovascular changes evoked by JNJ 5207852 (5 mg/kg) (Fig. 1A-C) and decreased to 0% the survival rate at 2 h. Pre-treatment with 6-OHDA in the saline-treated animals did not affect the measured cardiovascular parameters (Fig. 1A-C) or the survival rate at 2 h (0%) in comparison to the control group.

DISCUSSION

The results of the present study demonstrate the pressor effect resulting from the blockage of histamine H3 receptors in haemorrhage-shocked rats. Moreover, we show – indirectly – the involvement of postganglionic sympathetic endings in this reaction.

The present studies are a continuation of our research concerning the role of histamine – acting centrally and peripherally – in the cardiovascular regulation in haemorrhagic shock [4,5,6,7,8,9]. In all our studies, we used the model of experimental haemorrhagic shock introduced by the Guarini et al. [21]. This model belongs to models of irreversible shock, with 0% survival of 2 h without treatment. Indeed, as we confirmed in earlier studies, all the control animals die within 30 min [4,5,6,7,8,9]. The used model of shock is characterised by early initiation of the sympatho-inhibitory phase of regulation, which is typical for reaction to increasing hypovolaemia in anaesthetised rodents [18]. As we demonstrated earlier, critical hypotension (MAP 20–25 mmHg) is accompanied by a reduction to 15–20% of renal, mesenteric and hindquarter blood flows [6,7,8,9] and the development of metabolic acidosis [24].

We presented earlier that centrally acting exogenous and endogenous histamine is able to reverse critical haemorrhagic hypotension [4,5,6,7,8,9]. The effect is associated not only with increases in peripheral blood flows [6,7,8,9], but also with partial normalization of blood gas and acid-base parameters [24]. The mechanism of histamine action is associated mainly with the activation of central H1 receptors [4,5].

In the present paper, we decided to present the influence of the diamine-based H3 receptor neutral antagonist JNJ 5207852 (1-[3-[4-(1-piperidinylmethyl)phenoxy]propyl]piperidine hydrochloride) given iv on the cardiovascular parameters in the second, sympatho-inhibitory phase of regulation in haemorrhagic shock.

JNJ 5207852 was earlier used to study the role of H3 receptors in sleep and wakefulness regulation [25], learning and memory [26] and anxiety [22]. We demonstrate clearly that JNJ 5207852 is also able to influence cardiovascular regulation in shock. In these conditions, it induces a long-lasting pressor effect with a significant increase in the survival rate at 2 h.

We hypothesize that the action is associated with the blockade of H3 receptors located on the postganglionic sympathetic endings in the heart and vessels and the release of noradrenalin from these endings. Noradrenalin could be responsible for the observed cardiovascular effects – the increase in blood pressure and heart rate, especially since, as we demonstrated previously in [6,7,8,9], an increase in peripheral vascular resistance is a predominant mechanism of resuscitation in the studied model of haemorrhagic shock.

To verify this hypothesis, we decided to perform experiments on animals after chemical sympathectomy with 6-OHDA. The used pharmacological method is generally accepted to study the role of the sympathetic nervous system, especially postganglionic neurons, in many physiological and pathophysiological conditions, for example in the activation of natural killer cytotoxicity [27], anaphylaxis mechanisms [28] and colon motility [29].

Our results show no differences in the measured cardiovascular parameters between the control and 6-OHDA-pre-treated groups, however, the volume of blood necessary to induce critical hypotension (20––25 mmHg) was significantly lower after administering 6-OHDA. This can be explained by the lack of noradrenalin secretion from the peripheral postganglionic endings, despite the reflex-mediated activation of the sympathetic system in the first phase of regulation in haemorrhagic shock.

Chemical sympathectomy almost completely blocked the resuscitating effects of JNJ 5207852. We demonstrated not only decreased values of MAP, PP and HR, but also the reduction of the survival rate at 2 h. Therefore, the present results may confirm the hypothesis that the mechanism of JNJ 5207852 action is associated with the function of postganglionic sympathetic endings and noradrenalin secretion.

Although we demonstrated the role of the sympathetic system in JNJ 5207852-mediated cardiovascular effects in haemorrhagic shock in rats, we can suggest the limitations of our study. Firstly, we cannot exclude the involvement of other possible mechanisms, for example activation of the renin-angiotensin system and AVP secretion in JNJ 5207852-induced effects. Moreover, since JNJ 5207852 is able to cross the blood-brain barrier, we cannot exclude a possible action of JNJ 5207852 at a level of the central nervous system [22], where H3 receptors are also involved in the regulation of the synthesis and secretion of histamine and other neuromodulators/neurotransmitters which are able to influence the cardiovascular centre functions.

In conclusion, histamine H3 receptor antagonist JNJ 5207852 induces the resuscitating effect in haemorrhage-shocked rats, and the mechanism responsible is associated with the activation of postganglionic sympathetic neurons.

Author's contribution

Study designe – J. Jochem, A. Mitera
Data collection – J. Jochem
Data interpretation – J. Jochem, A. Mitera
Statistical analysis – A. Mitera, M. Izydorczyk
Manuscript preparation – J. Jochem, D. Nowak
Literature research – M. Izydorczyk, D. Nowak, M. Waliczek

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