

Involvement of the histaminergic system in renal sympathetic and cardiovascular responses to leptin and ghrelin

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Abstract

Previous studies have demonstrated that histamine affects blood pressure (BP) in anesthetized rats. Here, we examined the effects of lateral cerebral ventricular (LCV) injection of various doses of histamine on renal sympathetic nerve activity (RSNA) and BP in anesthetized rats. LCV injection of a low dose of histamine (0.0001 nmol) suppressed RSNA and BP. Conversely, a high dose of histamine (100 nmol) elevated both RSNA and BP. Moreover, inhibiting effects of a low dose of histamine were eliminated by LCV pre-injection of thioperamide, an antagonist of histaminergic H3-receptor, and accelerating effects of a high dose of histamine were abolished by LCV pre-injection of diphenhydramine, an antagonist of histaminergic H1-receptor. Thus, these evidences suggest that central histamine affects RSNA and BP via histaminergic receptors. In addition, we examined a role for histaminergic system in cardiovascular modulators such as leptin and ghrelin. The LCV pre-injection of thioperamide clearly blocked suppressing effects of ghrelin on RSNA and BP. The LCV pre-injection of diphenhydramine also blocked elevating effects of leptin. Therefore, these results suggest that leptin and ghrelin might affect RSNA and BP by mediating central histaminergic H1- and H3-receptors, respectively.

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Histaminergic neurons are located in the tuberomammillary nucleus (TMN) of the hypothalamus and project to the various regions in the brain widely [16]. Histamine released from histaminergic neurons, functions as modulator of feeding behavior, sleep-wake cycle, and blood pressure (BP) [2]. Previous study observed that lateral cerebral ventricular (LCV) injection of high dose histamine (0.1–100 nmol) elevated BP in anesthetized rats [7]. With respect to histaminergic neurotransmission, presynaptic histaminergic H3-receptor has higher affinity and inhibits histamine production automatically when low dose histamine is released from presynapse [1]. However, it is unknown whether low dose histamine change BP and renal sympathetic nerve activity (RSNA) playing an important role in BP regulation [5].

Leptin and ghrelin are peptide hormones and they were known to influence autonomic and cardiovascular systems. Lep-

tin is peptide hormone produced in white adipose tissue, and acts on the brain and increases RSNA and BP [3]. On the other hand, ghrelin is peptide hormone produced in stomach, acts on brain and lowers RSNA and BP [9]. Recent study showed that elevating effect of leptin on BP is mediated by central histaminergic H1-receptors [14]. However, it is unclear possible role of histaminergic system in sympathetic and cardiovascular responses to leptin and ghrelin. Therefore, in the present study, we firstly examined effects of LCV injections of various doses of histamine on RSNA and BP in urethane-anesthetized rats. Next, we examined effects of antagonists of histaminergic receptors on leptin- and ghrelin-mediated RSNA and BP changes.

Male Wistar rats, weighing 300–350 g, were used. Rats were housed in a room maintained at $24 \pm 1^\circ\text{C}$ and illuminated for 12 h (07:00 to 19:00) everyday. Food and water were freely available. Rats were adapted to the environment for at least 1 week prior to the experiment. All animal care and handling procedures were approved by the Institutional Animal Care and Use Committee of the Institute for Protein Research, Osaka University.

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General preparations were performed as described previously [15]. Briefly, under anesthesia [1 g/kg urethane, intraperitoneal (IP)], a polyethylene catheter was inserted into the left femoral vein for intravenous (IV)-injection, and another catheter was inserted into the left femoral artery for BP determination. The depth of anesthesia was coordinated by the paw pinch method as described previously [11]. The rats were then cannulated intratracheally, and fixed in a stereotaxic apparatus, and the body temperature was maintained at 37.0–37.5 °C. For recording RSNA, the left renal nerve was exposed retroperitoneally through a left flank incision. The distal end of the respective nerve was ligated, and then hooked up with a pair of silver wire electrodes for recording efferent nerve activity. The recording electrodes were immersed in a pool of liquid paraffin oil to prevent dehydration and for electrical insulation, respectively. The rat was allowed to stabilize for 30–60 min after being placed on the recording electrodes. Electrical change in RSNA was amplified, filtered, monitored by an oscilloscope and converted to standard pulses by a window discriminator. A catheter in the left femoral artery was connected to a BP transducer, and its output signal was amplified in a BP amplifier and monitored with an oscilloscope. Both the counted discharge rate and BP were sampled with a Power-Lab analog-to-digital converter, and stored on hard disk for off-line analysis. Mean arterial pressure (MAP) was calculated from the BP data sampled in off-line analysis.

Baseline measurements of RSNA and MAP were made for 5 min prior to LCV injections of artificial cerebrospinal fluid (aCSF), histamine (0.0001, 0.001, 0.01, 0.1, 1, 10, and 100 nmol/10 μ l aCSF), leptin (100 μ g/10 μ l aCSF), ghrelin (1 nmol/10 μ l aCSF) or aCSF (10 μ l). After the injection, these parameters were recorded for 60 min. To examine the effect of thioperamide or diphenhydramine on changes in RSNA and BP due to histamine, leptin or ghrelin, a brain cannula made of polyethylene tubing was inserted into the left LCV under pentobarbital anesthesia 1 week before the experiment [12]. An LCV injection of thioperamide maleate (2 μ g/10 μ l aCSF, Sigma–Aldrich) or diphenhydramine hydrochloride (5 μ g/10 μ l aCSF, WAKO) was administered 15 min prior to injection of histamine, leptin or ghrelin. At the end of the experiment, hexamethonium chloride (10 mg/kg, IV) was administered to block evoked potentials in order to determine the noise level of the recording. RSNA and MAP were measured during each 5 min period after injection and analyzed by digital signal processing and appropriate statistical analyses. All data were expressed as mean $\pm$ S.E.M. Because of the inter-individual variability in the pre-injection state, percent changes from baseline values were calculated for RSNA and MAP. For statistical analyses, two-way analysis of variance (ANOVA) was performed.

Typical recordings of RSNA and BP before and after LCV injection of aCSF or histamine are presented in Fig. 1A. The aCSF injection did not affect either RSNA or MAP. However, both were suppressed by LCV injection of 0.0001 nmol of histamine, and both were elevated by LCV injection of 100 nmol of histamine. Following injection of 0.0001 nmol of histamine, both RSNA and MAP decreased gradually (Fig. 1B), with the greatest level of suppression occurring at 30 and 60 min, respectively. The lowest levels attained were with

52.2 $\pm$ 17.4% (RSNA) and 86.2 $\pm$ 7.2% (MAP). Following injection of 100 nmol of histamine, both RSNA and MAP increased gradually (Fig. 1B and D), with maxima occurring at 60 and 25 min, respectively. The highest levels attained were 252.7 $\pm$ 32.7% (RSNA) and 123.2 $\pm$ 1.0% (MAP). In contrast, injection of aCSF did not cause a significant alteration in the levels of either RSNA or MAP. 60 min following LCV injection of lower doses of histamine (0.0001 and 0.001 nmol), the levels of both RSNA and MAP decreased (Fig. 1E). The maximum suppressive responses occurred following injection of 0.0001 nmol of histamine. In contrast, at 60 min, the higher doses of histamine (10 and 100 nmol) had significantly increased both RSNA and MAP (Fig. 1E). The maximum enhancing responses occurred following injection of 100 nmol of histamine. On the other hand, pretreatment with thioperamide or diphenhydramine eliminated the effects of LCV injection of both either lower (0.0001 nmol) or higher (100 nmol) doses of histamine, respectively (Fig. 1C and E). Furthermore, diphenhydramine or thioperamide did not block the effects of lower or higher doses of histamine, respectively (Fig. 1C and E). The significance of the differences between values from 5 to 60 min was analyzed as a group by ANOVA. The following comparisons were made: (1) RSNA: aCSF versus histamine (0.0001 nmol), $P < 0.0005$ ($F = 61.9$); saline versus histamine (100 nmol), $P < 0.0005$ ($F = 205.6$); (2) MAP: aCSF versus histamine (0.0001 nmol), $P < 0.0005$ ($F = 31.8$); saline versus histamine (100 nmol), $P < 0.0005$ ($F = 378.5$). Absolute basal (0 min) RSNA and MAP values for the experiments shown in Fig. 1 are summarized in Table 1. Differences in respective basal values were not statistically significant (Mann–Whitney U -test).

Fig. 2 shows the effect of LCV pre-injection of diphenhydramine on the changes in RSNA and MAP caused by

Table 1
Basal levels (0 min) of RSNA and MAP in experimental groups

Groups	RSNA (spikes/5 s)	MAP (mmHg)
Experiment (1)		
aCSF	73.3 $\pm$ 12.0 (4)	76.7 $\pm$ 7.1 (4)
Histamine 0.0001 nmol	130.5 $\pm$ 22.7 (4)	76.3 $\pm$ 15.5 (4)
Histamine 0.001 nmol	142.4 $\pm$ 16.8 (4)	70.8 $\pm$ 8.2 (4)
Histamine 0.01 nmol	104.2 $\pm$ 11.9 (4)	83.3 $\pm$ 6.9 (4)
Histamine 0.1 nmol	133.0 $\pm$ 16.0 (4)	81.8 $\pm$ 9.3 (4)
Histamine 1 nmol	175.9 $\pm$ 54.8 (4)	81.0 $\pm$ 12.9 (4)
Histamine 10 nmol	90.8 $\pm$ 5.8 (4)	75.4 $\pm$ 4.9 (4)
Histamine 100 nmol	98.0 $\pm$ 12.5 (4)	83.5 $\pm$ 7.8 (4)
Thiop + histamine 0.0001 nmol	97.7 $\pm$ 29.4 (4)	73.7 $\pm$ 7.3 (4)
Diphen + histamine 100 nmol	126.7 $\pm$ 35.8 (4)	78.5 $\pm$ 4.3 (4)
Diphen + histamine 0.0001 nmol	103.3 $\pm$ 12.1 (4)	79.8 $\pm$ 12.4 (4)
Thiop + histamine 100 nmol	128.3 $\pm$ 24.8 (4)	84.9 $\pm$ 7.3 (4)
Experiment (2)		
aCSF + aCSF	96.9 $\pm$ 10.9 (4)	84.5 $\pm$ 8.7 (4)
aCSF + leptin	94.1 $\pm$ 9.2 (4)	86.5 $\pm$ 3.5 (4)
Diphen + leptin	121.1 $\pm$ 29.3 (4)	90.7 $\pm$ 2.8 (4)
Experiment (3)		
aCSF + aCSF	96.1 $\pm$ 32.3 (4)	87.1 $\pm$ 7.2 (4)
aCSF + ghrelin	87.0 $\pm$ 15.0 (4)	90.3 $\pm$ 6.0 (4)
Thiop + ghrelin	95.9 $\pm$ 7.0 (4)	92.4 $\pm$ 15.7 (4)

Data are presented as mean $\pm$ S.E.M. (number of rats).

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