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Involvement of the histamine H1 receptor in the regulation of sympathetic nerve activity

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ABSTRACT

The histamine system is involved in the regulation of the autonomic nervous system. We used gene-targeted mice to investigate the role of histamine receptors in the regulation of the sympathetic nervous system. Reverse transcription-polymerase chain reaction (RT-PCR) analysis revealed histamine H1, H2, and H3 receptor expression in the superior cervical ganglion, which contains sympathetic nerve cell bodies. We measured the heart rate variability (HRV), the changes in the beat-to-beat heart rate, which is widely used to assess autonomic activity in the heart. H1 blockade attenuated the baroreflex-mediated changes in heart rate in wild-type (WT) mice, whereas the heart rate response to H2- and H3-specific blockers was unaffected. L-Histidine decarboxylase (HDC) expression in the superior cervical ganglion of H1R-null mice was higher than that in WT controls, whereas the enzyme levels in H2R- and H3R-null mice were not significantly different from those in the WT. All mutant mice (H1R-, H2R-, and H3R-null mice) showed normal electrocardiogram (ECG) patterns with little modification in ECG parameters and the expected response to the β-adrenergic blocker propranolol. Similar to our findings in WT mice, H1 blockade attenuated the baroreflex-mediated heart rate change in H1R-null mice, whereas the heart rate response was unaffected in H2R- and H3R-null mice. The HRV analysis revealed relatively unstable RR intervals, an increased standard deviation of the interbeat interval (SDNN), and low-frequency (LF) component in H1R-null mice compared with the other groups, suggesting that sympathetic nerve activity was altered in H1R-null mice. Taken together, our findings indicate that H1 receptors play a major role in the regulation of sympathetic nerve activity.

1. Introduction

The histaminergic system plays important roles in the regulation of circadian rhythm, including maintaining wakefulness, and in bioprotection against noxious and adverse stimuli such as nociception and drug sensitization [1]. The endogenous histaminergic system plays a major role in cardiovascular diseases, such as hypertension [2], atherosclerosis [3], and chronic heart failure [4]. Norepinephrine and histamine have been shown to coexist in the superior cervical ganglion and cardiac sympathetic axons [5]. Several studies have investigated the relationship between histamine and cardiac arrhythmia [6,7]. Furthermore, the involvement of H2 and H3 receptors in the modulation of ventricular arrhythmogenesis during ischemia and reperfusion is under investigation [8,9]. Based on the findings of previous experimental and clinical studies, histamine receptors have been suggested as novel therapeutic targets for cardiovascular disease [4,10]. Previous studies have shown that cardiac sympathetic neurons express histamine

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and L-histidine decarboxylase (HDC), the rate-limiting enzyme for histamine synthesis [11,12], and that sympathetic nerve terminals release histamine following appropriate stimulation [12,13]. Based on these findings, histamine is thought to be a newly recognized sympathetic neurotransmitter. Furthermore, the postsynaptic effects of sympathetic histamine are positively associated with the firing activity of sympathetic nerves [13]. Over-activation of cardiac sympathetic nerves in ischemic hearts, as reported previously, further correlates with ischemia-induced ventricular arrhythmias [9,10]. Furthermore, He et al. [14] reported that the histaminergic system, and the H2 receptor in particular, was involved in the regulation of sympathetic nerve activity.

Thus, one can reasonably postulate that sympathetic histamine, like norepinephrine, is involved in physiological function. Although a relationship between histamine and the autonomic cardiovascular system has been supposed, several factors, such as the effect of histamine on heart rate variability (HRV), have not been well characterized. We investigated the relationship between histamine and the cardiovascular autonomic system using histamine H1-, H2-, and H3-receptor-null mice to assess the effect of the neurotransmitter on HRV and to clarify the pathophysiological role of cardiac sympathetic histamine.

2. Materials and methods

2.1. Histamine receptor-deficient mice

Mouse lines were maintained in the hemizygous state (H1R-null, H2R-null, H3R-null mice) [15–17]. Throughout the study, animals were housed under a constant 12 h light/dark cycle with free access to food and water. All experimental procedures were approved by the Institutional Animal Care and Research Advisory Committee of the Tohoku University School of Medicine.

2.2. Reverse transcription-polymerase chain reaction (RT-PCR)

Poly(A)+ RNA was isolated from cells using TRIzol reagent (Invitrogen, Carlsbad, CA, USA) and Oligotex-dT30 (TaKaRa, Shiga, Japan). The RT reaction was performed using a first-strand cDNA synthesis kit (SuperScript II Reverse Transcriptase; Invitrogen). PCR amplification was performed using GoTaq Green Master Mix (Promega, Madison, WI, USA).

Specific sequences of H1, H2, H3, and H4 receptors and HDC were amplified by PCR (34 cycles) [18]. (Detailed information is provided in the Supplementary information.)

2.3. General anesthesia

The mice (12–16 weeks of age) were anesthetized in an induction chamber (25 × 25 × 14 cm) containing 4% isoflurane (Forane; Abbott Japan Co., Ltd., Tokyo, Japan) and room air. Anesthesia was maintained for 45 min (anesthetic maintenance state) using 2% isoflurane inhalation anesthesia at an airflow rate of 0.5 L/min. Ten minutes after the induction of anesthesia, the baseline electrocardiogram (ECG) was recorded for 5 min, and then the pharmacological tests were performed. All experiments were conducted between 10:00 and 16:00 h.

2.4. ECG evaluation

ECG, heart rate, and RR interval were measured simultaneously (ML846 Power Lab system; AD Instruments, Dunedin, New Zealand) [19,20]. An M-button connector was used to connect the electrode [19]. We used HRV as a measure of cardiac autonomic nerve control [19–21]. (Detailed information is provided in the Supplementary information.)

2.5. Statistical analysis

The results are expressed as the mean ± standard error (SE). Statistical significance was tested using an analysis of variance (ANOVA) with a Dunnett's *post hoc* test. p-Values <0.05 were deemed to indicate statistical significance.

3. Results

3.1. Expression profile

We used gene-targeted mice to investigate the role of histamine receptors in the sympathetic nervous system regulation. RT-PCR analysis was used to detect the expression of histamine receptors and HDC in the superior cervical ganglion of the genetically modified and wild-type (WT) mice. The analysis confirmed that the H1, H2, and H3 receptors were expressed in WT mice, but not in H1R-, H2R-, and H3R-null mice, respectively (Fig. 1Ai). PCR amplification of the H4 receptor in the superior cervical ganglion was negligible (data not shown). HDC expression was confirmed in all animals; however, expression of the enzyme was higher in H1R-null (156 ± 8%) than in WT mice (100 ± 8%), whereas HDC expression in H2R- (103 ± 7%) and H3R (111 ± 10%) -null mice was not significantly different from that of the WT controls ($n = 6$ for each gene; Fig. 1Aii), suggesting a compensatory increase in histamine synthesis in the superior cervical ganglion of the H1R-null mice. β-actin expression was used as a control. We found no difference in mRNA expression in the H1 and H2 receptors of the heart (Supplementary Fig. 1).

3.2. ECG analysis

We first investigated the ECG response to histamine antagonists in WT mice. We observed no changes in heart rate following the administration of fexofenadine hydrochloride (H1 antagonist, 10 mg/kg, i.p.), famotidine (H2 antagonist, 10 mg/kg, i.p.), and JNJ-5207852 (H3 antagonist, 10 mg/kg, i.p.). We used the carotid baroreflex to assess sympathetic nerve function. Fig. 1B shows representative heart rate changes in response to baroreflex activation following the serial administration H3, H2, and H1 blockers. JNJ-5207852 (H3 antagonist) and famotidine (H2 antagonist) did not affect the baroreflex response (second and third traces) significantly. In contrast, the H1 blocker significantly attenuated the baroreflex-induced changes in heart rate (Fig. 1B, arrow).

We then investigated heart rate responses in the gene-targeted mice without histamine receptors. Fig. 2A shows representative ECG traces of WT, H1R-, H2R-, and H3R-null mice. We did not assess H4 receptor function because H4-deficient mice were not available, and thus PCR amplification revealed minimal expression of the receptor in the superior cervical ganglion. Furthermore, the H4 receptor is primarily involved in the inflammatory response and allergic reactions.

The ECG of WT and histamine receptor (H1, H2, and H3)-null mice revealed a regular pattern indicative of pacemaking activity and excitation propagation, suggesting that unlike the β-adrenergic system, histamine does not play an important pacemaker role. Intraperitoneal injection of propranolol (0.4 mg/kg) significantly extended the RR intervals in all groups (Fig. 2A, right panel). The ECG Averaging View (Power Lab System; AD Instruments) revealed that the P, Q, R, S, and T waves were conserved (Supplementary Fig. 2A), and that the ECG waveform was normal with no significant differences in PQ, QT, and QTc intervals or QRS duration among

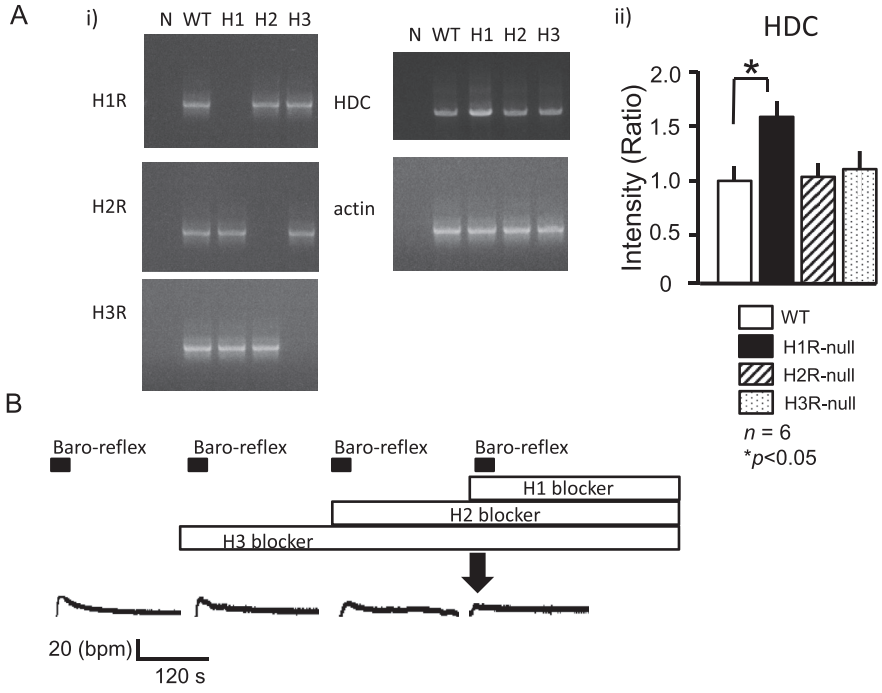

Fig. 1. (A) Expression of histamine receptors and L-histidine decarboxylase (HDC) in the superior cervical ganglion. (i) RT-PCR analysis of the superior cervical ganglion in wild-type (WT), H1R-, H2R-, and H3R-null mice. Histamine (H1, H2, and H3) receptor-specific transcripts (left panel) and HDC- and β-actin-specific transcripts (right panel) in the mouse superior cervical ganglion (N, negative control without cDNA; H1, H1R-null mice; H2, H2R-null mice; H3, H3R-null mice. β-Actin expression was used as a control. Each PCR amplification cycle is shown. (ii) Upregulation of HDC expression in the superior cervical ganglion of H1R-null mice. WT (open bar), H1R-null (H1KO, closed bar), H2R-null (H2KO, hatched bar), and H3R-null mice (H3KO, stippled bar). $^{*}p < 0.05$, difference between WT and other mice. Each group contained at least six samples. (B) H1 blocker-induced attenuation of the sympathetic baroreflex response in WT mice. Representative heart rate changes following the serial application of H3 (JNJ-5207852, 10 mg/kg), H2 (famotidine, 10 mg/kg), and H1 (fexofenadine 10 mg/kg) blockers. Scale bar = 120 s. Closed boxes show baroreflex activation. The arrow indicates attenuated responsiveness following administration of the H1 blocker.

genotypes (data not shown). These findings suggest that histamine does not play a pivotal role in the electrical conduction system of the mouse heart.

Fig. 2B shows representative baroreflex-mediated heart rate changes in the WT, H1R-, H2R-, and H3R-null mice (left panel). The WT, H2R-, and H3R-null mice showed a significant increase in heart rate in response to baroreflex activation, but the baroreflex response was attenuated in H1R-null mice (arrow). The adrenergic β-blocker propranolol (0.4 mg/kg, i.p.) served as a negative control. We observed no baroreflex-induced changes in heart rate following the administration of propranolol, confirming that the response was mediated by the sympathetic nervous system. Furthermore, all genotypes showed dose-dependent heart rate changes in response to propranolol (Supplementary Fig. 2B), with no significant differences in responsiveness among groups.

Fig. 3 shows basal heart and heart rate changes in response to baroreflex activation and atropine administration in the WT, H1R-, H2R-, and H3R-null mice. Baseline heart rate did not differ among groups (Fig. 3A). WT, H2R-, and H3R-null mice showed a significant increase in heart rate in response to baroreflex activation, whereas the heart rate response was attenuated in H1R-null mice (Fig. 3B, $p < 0.05$ vs. WT mice).

Parasympathetic blockade using the muscarinic receptor antagonist atropine (0.5 mg/kg, i.p.) increased the heart rate in all groups (Fig. 3C).

3.3. Changes in heart rate variability

We constructed Poincaré plots of the beat-to-beat heart rate dynamics (RRn vs. RRn + 1) to assess HRV in the WT, H1R-, H2R-, and H3R-null mice (Fig. 4A). The Poincaré plot of the H1R-null mice revealed significant fluctuations in the beat-to-beat dynamics (Fig. 4Aii).

In the frequency domain analysis, low-frequency (LF; 0.15–1.5 Hz) and high-frequency (HF; 1.5–5.0 Hz) components were determined in the power spectral density (Fig. 4Bi–iv). The power spectral density analysis revealed that the LF component was significantly higher in H1R-null mice than in other groups (Fig. 4Bii, arrow, and Fig. 4Ci, asterisk), suggesting that the sympathetic tone changed in these mice. Although the HF component tended to be higher in H1R-null mice than in other groups, the difference did not reach statistical significance (Fig. 4Cii). Although the LF/HF ratio was lower in H2R-null mice compared with the other groups, the differences among groups were not significant (Fig. 4Ciii).

The standard deviation of the interbeat interval (SDNN) was significantly higher in H1R-null mice than in the other groups, although no significant difference was observed between the other gene-targeted mice (Fig. 4Civ).

Because our pharmacological findings in the WT (Fig. 1B) and gene-targeted (Figs. 2–4) mice suggested a role for the H1 receptor in the regulation of sympathetic nerve activity, we assessed the effect of pharmacological blockade of the H1 and H2 receptors in H1R- and H2R-null mice (Supplementary Fig. 3). Baroreflex activation produced a slight increase in heart rate in H1R-null mice (Supplementary Fig. 3A, upper panel). Intraperitoneal administration of an H2 blocker attenuated the heart rate response to baroreflex activation in H1R-null mice, but did not alter the response in H2R-null mice, suggesting that H2 receptors play a compensatory role in H1R-null mice (Supplementary Fig. 3A, lower panel).

Furthermore, administration of an H1 blocker did not significantly alter the baroreflex response in H1R-null mice

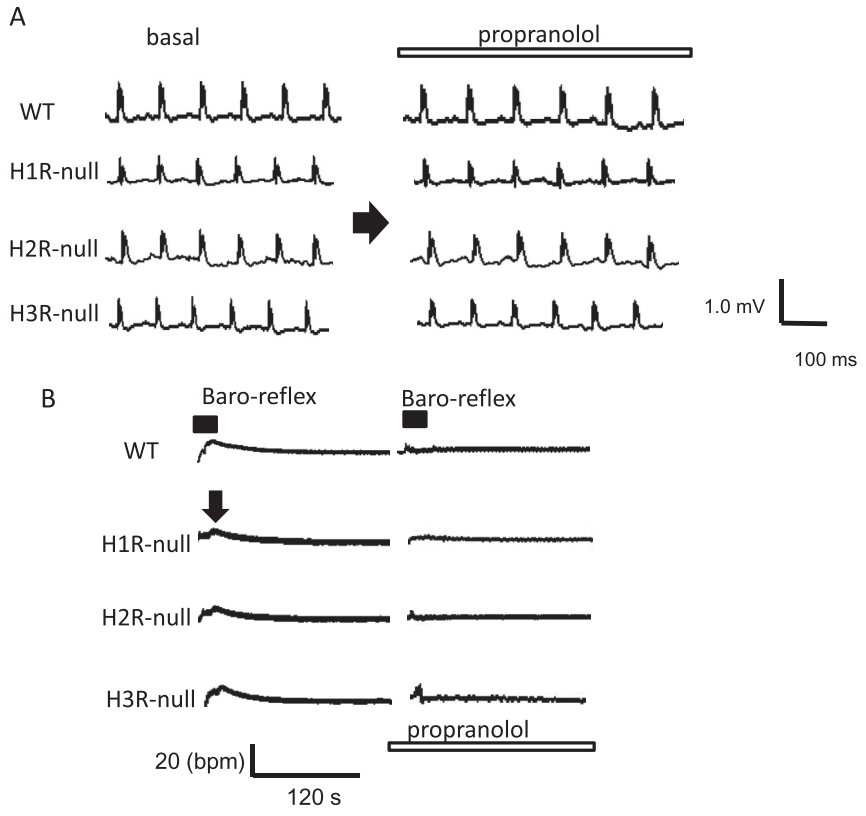

Fig. 2. (A) ECG data in the gene-targeted and wild-type (WT) mice. Representative ECG tracings at baseline (left panel) and 10 min after intraperitoneal administration of propranolol (right panel). Scale bar is 100 ms. (B) Attenuated baroreflex response in H1R-null mice. (B) Representative heart rate changes induced by baroreflex activation alone (left panel) and baroreflex activation plus the β-blocker propranolol (0.4 mg/kg, i.p.; right panel). The baroreflex response was attenuated in H1R-null mice (arrow). Propranolol administration attenuated the baroreflex response in all groups. Scale bar is 120 s.

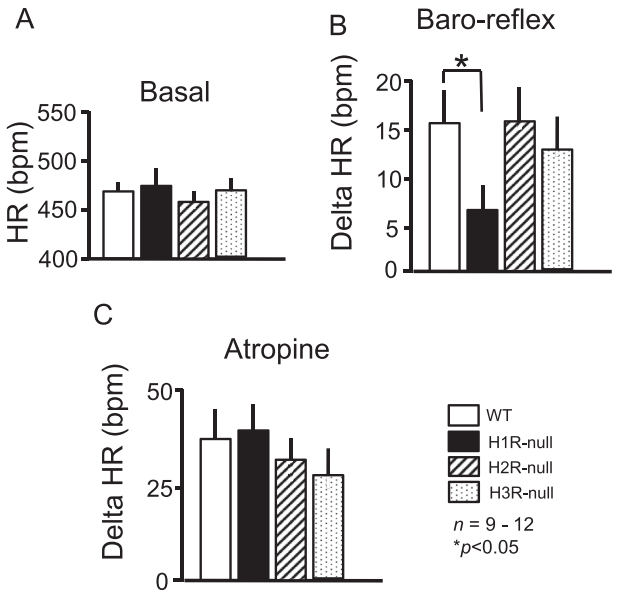

Fig. 3. Basal heart and heart rate changes in response to baroreflex activation and atropine. (A) Basal heart rate did not differ significantly among groups. (B) The baroreflex-induced change in heart rate was significantly attenuated in H1R-null mice compared with the wild-type (WT) controls. However, the delta heart rate did not differ among the WT, H2R-, and H3R-null mice. (C) Atropine-induced change in heart rate. Atropine (0.5 mg/kg, i.p.) increased the heart rate in all animals with no statistical differences among groups. Open bar, WT; closed bar, H1R-null (H1KO); hatched bar, H2R-null (H2KO); dotted bar, H3R-null mice (H3KO). *$p < 0.05$, difference between WT and other mice. Each group contained at least nine samples.

(Supplementary Fig. 3B, upper panel); however, the drug significantly decreased the baroreflex response in H2R-null mice (Supplementary Fig. 3B, lower panel). Taken together, our findings suggest that the H1 receptor modulates sympathetic nerve activity.

4. Discussion

We investigated histamine system involvement in regulation of the autonomic nervous system. In WT mice, an H1 blocker attenuated the baroreflex heart rate response, whereas H2- and H3-specific blockers had no effect on the baroreflex response.

Furthermore, the expression of HDC in the superior cervical ganglion was significantly higher in H1R-null mice than in the WT controls, whereas HDC levels in H2R- and H3R-null groups were not significantly different from those of WT mice.

The ECG patterns were normal in all mutant mice (H1R-, H2R-, or H3R-null mice) with no modification in parameters. Propranolol, the β-adrenergic blocker, decreased heart rate in all mice with similar responsiveness. The baroreflex heart rate response was attenuated in H1R-null mice, whereas it increased heart rates in the H2R-null and H3R-null mice like wild-type mice. The analysis of HRV revealed relatively unstable RR intervals and a higher LF and SDNN in H1R-null mice compared with the other groups, suggesting that sympathetic nerve activity changed in H1R-null mice.

The RT-PCR analysis revealed expression of the H1, H2, and H3 histamine receptors in the superior cervical ganglion, which contains sympathetic nerve cell bodies. However, we were unable to confirm the expression of the H4 receptor in the superior cervical ganglion. The histamine H4 receptor was originally cloned from cells of immunological origin such as human leukocytes [22], and

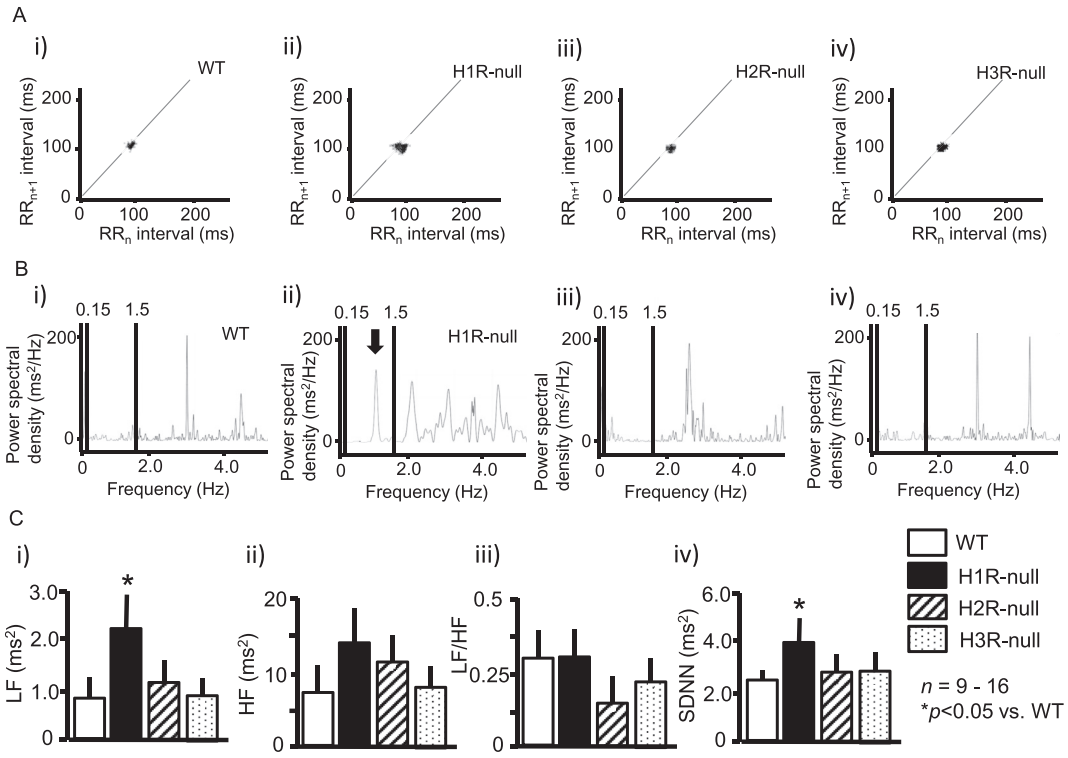

Fig. 4. Modified heart rate variability in H1R-null mice. (A) Representative heart rate variability (HRV) analysis of wild-type (WT; i), H1R-null (ii), H2R-null (iii), and H3R-null (iv) mice. Poincaré plots (RRn vs. RRn + 1) in which consecutive pairs of RR intervals during the control period were plotted with the nth + 1 RR interval plotted against the nth RR period. The H1R-null mice showed marked fluctuations in the beat-to-beat dynamics (Aii). (B) Representative power spectral densities of the WT (i), H1R-null (ii), H2R-null (iii), and H3R-null (iv) mice. The low-frequency (LF) component was significantly higher in H1R-null mice than in the other groups (Bii, arrow). (C) Comparisons of the LF (i), HF (ii), LF/high-frequency (HF) ratio (iii), and standard deviation of the interbeat interval (SDNN). Open bar, WT; closed bar, H1R-null; hatched bar, H2R-null; dotted bar, H3R-null mice. $^{*}p < 0.05$, difference between WT and other mice. Each group contained at least nine mice.

Strakhova et al. [23] reported widespread expression of the H4 receptor in the central nervous system in humans and rats. Because H4 receptor expression is relatively unstable, confirming a lack of H4 receptor expression using RT-PCR analysis was difficult; thus, involvement of the H4 receptor and its physiological role should be investigated in future studies.

Whyment et al. [24] investigated the electrophysiological excitability of histamine in the sympathetic preganglionic neurons of neonatal rats and used single-cell PCR to detect the expression of histamine receptors. They found that histamine regulated the excitability of sympathetic preganglionic neurons via activation of H1 receptors. Furthermore, the authors reported that an H1 receptor agonist (histamine trifluoromethyl toluidide dimaleate) induced membrane depolarization associated with a decrease in membrane conductance in the majority (70%) of sympathetic preganglionic neurons, whereas H2- and H3-antagonists had only a marginal effect. Our results are consistent with the findings of Whyment et al. [24].

He et al. [14] reported that acute ischemia-related responses in the cardiac sympathetic nerve were mediated via the H2 receptor. Our finding that the H1, but not H2 or H3, receptor mediates cardiac sympathetic nerve activity is not consistent with that of He et al. [14], suggesting that the H2 receptor mediates cardiac sympathetic nerve activity. However, this disparity may be explained by methodological differences. Our investigation was conducted under physiological conditions, whereas the ischemia model used by He et al. [14] is a highly pathogenic condition that often causes ventricular arrhythmia.

We used HRV to evaluate cardiovascular parameters. The calculation of HRV from ECG recordings is not as precise a measure as electrophysiological techniques, which directly record the excitability of neurons. However, HRV can be affected by other factors and may not always provide an accurate assessment of autonomic nerve status Thus, HRV may not be dependent on the autonomic nervous system alone: the sympathetic and parasympathetic nervous systems are likely to have an effect on LF and HF components in a nonlinear fashion [21,25]. Furthermore, RR intervals are influenced by factors such as the respiratory cycle. Accordingly, HRV parameters produce complex LF, HF, and LF/HF data. Thus, we suggest that LF/HF calculations may not be an accurate measure of cardiac “sympathovagal balance” [21,25]. However, an advantage of HRV analysis is that it assesses the effect of various manipulations using simple ECG recordings.

Christian and Weinreich [26] reported that the histamine H1 receptor triggered, and the H3 receptor depressed, activation of ganglionic neurotransmission. These opposing effects of histamine have been attributed to the activation of different histamine receptor subtypes [27]. Histamine-induced facilitation of synaptic transmission in the sympathetic ganglia has been shown to be mediated by histamine H1 receptors in several species [27], and histamine-induced synaptic depression has been linked to H2 histamine receptor activation [28]. In contrast, histamine in the presence of the H1 antagonist pyrilamine or the H3 agonist (R)-α-methylhistamine has been shown to depress the mean excitatory postsynaptic potential (EPSP) amplitude significantly [29]. The effects of histamine receptor antagonists on the histamine-mediated modulation of EPSPs support the conclusion that histamine-induced potentiation of synaptic transmission at the single synapse level is mediated via H1 and depressed via H3 receptors.

Note that several H2 agonists and antagonists have been shown to act as antagonists at the H3 receptor [30]. If one were to accept the seemingly unlikely assumption that no histamine H3 component is present in tissues in which H2-mediated depression has been reported previously (see above), the results would suggest that substantial phylogenetic diversity exists among histamine receptor subtypes mediating a similar effect (i.e., synaptic inhibition) within analogous tissues of different species. If this were the case, conclusions about histamine receptor-mediated functions based on pharmacological findings in a single species may lead to unwarranted conclusions.

We did not address the question of whether histamine can mediate potentiation and depression at a single synapse; however, our findings in H2R- and H3R-null mice suggested minor involvement of the H2 and H3 receptors in the regulation of sympathetic nerve activity.

In conclusion, sympathetic nerve tone was altered in H1R-null mice. Moreover, HDC expression in the superior cervical ganglion was higher in H1R-null mice than in WT or H2R- and H3R-null mice, suggesting a compensatory increase in histamine synthesis in H1R-null mice. Our findings suggest that the histamine system, the H1 receptor in particular, is involved in the regulation of sympathetic nerve activity.

Conflict of interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.bbrc.2015.02.009.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.bbrc.2015.02.009.

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