Histamine H₁ receptors (H₁-Rs) are found in peripheral tissues and in regions of the hypothalamus that are concerned with regulating body composition. In the present study, we investigated the detailed mechanisms of histamine H₁-Rs in the development of obesity. Histamine H₁-R knockout (H1KO) mice gradually developed mature-onset obesity, which was accompanied by hyperphagia and decreased expression of uncoupling protein-1 (UCP-1) mRNA. Both younger nonobese (12-week-old) and older obese (48-week-old) H1KO mice exhibited impairment of the responsiveness to the leptin. In addition, disruption of the diurnal rhythm of feeding occurred before the onset of obesity in H1KO mice. Correction of these abnormal feeding rhythms by means of scheduled feeding caused a reduction in obesity and associated metabolic disorders in H1KO mice. Furthermore, central administration of a histamine H₁-R agonist affected feeding behavior, body weight, and c-fos–like immunoreactivity in the hypothalamus. Taken together, these findings suggest that histamine H₁-Rs are crucial for the regulation of feeding rhythm and in mediating the effects of leptin. Early disruption of H₁-R–mediated functions in H1KO mice may lead to hyperphagia and decreased expression of UCP-1 mRNA, which may contribute to the development of obesity in these animals. In addition, centrally acting histamine H₁-R may be a novel therapeutic target for the treatment of obesity and related metabolic disorders. Diabetes 53:2250–2260, 2004

The development of obesity is regulated by genetic and environmental factors (1,2). Recent studies have revealed that the hypothalamic functions that regulate energy balance play a central role in the development of obesity (3,4). In genetically obese animal models, the disruption in the hypothalamus of leptin and melanocortin synthesis and release, as well as of their receptor systems, contributes to the development of obesity (5–7). Several orexigenic and anorexigenic neuropeptides in the hypothalamus are involved in leptin signaling, although the contribution of each peptide to the development of obesity is different (8–10).

Recently, we demonstrated that hypothalamic neuronal histamine and its H₁ receptor (H₁-R) are part of the leptin signaling pathway within the hypothalamus (11,12). Central administration of histamine can reduce body mass and adiposity in diet-induced and genetically obese mice by altering food intake and energy expenditure (12,13). In particular, histamine H₁-Rs in the ventromedial hypothalamic nucleus (VMH) and the paraventricular nucleus (PVN) have been implicated in the neuronal regulation of appetite (14). Neuronal histamine and H₁-Rs are also involved in the central regulation of energy homeostasis through sympathetic influences on uncoupling protein (UCP) expression in brown adipose tissue (BAT) (12,13). In addition, neuronal histamine accelerates lipolysis in adipose tissues by activating the sympathetic nervous system (15). Targeted disruption of histidine decarboxylase, histamine H₁-R, or H₂-R in mice results in leptin-resistant obesity (12,16–18). In addition, H1KO mice develop diet-induced and aging-related obesity (12,16). Each of the aforementioned findings indicates that neuronal histamine and its receptors are crucial to the regulation of body mass (12,16–18). However, the precise role of histamine H₁-Rs in the development of obesity in H1KO mice is not known.

To further the examination, in the present study, we studied the feeding rhythm and leptin-induced hypothalamic c-fos expression in wild-type and H1KO mice. In addition, we examined the effects of administration of histamine H₁-R agonist on obesity.

RESEARCH DESIGN AND METHODS
We used male H1KO mice (Kyushu University, Fukuoka, Japan) (19), and H1KO mice were maintained for backcrossing at Oita University. Backcrossing H₁-R homozygous mice to the C57BL/6N strain (Seac Yoshitomi, Fukuoka, Japan) for six generations resulted in the incipient congenic N5 mice of two genotypes (H₁−/−, H₁+/−) used here. All genotypes were confirmed by Southern blot according to previous report (19). All animals were treated in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Feeding behavior (specifically, the diurnal rhythm of food intake) was estimated with a feeding analyzer (Eiko, Fukuoka, Japan). Feeding rhythm impulses were integrated using a rate meter with a reset time of 15 min. The feeding rhythm was measured during both the dark and the light phases for 14 days. Scheduled feeding was performed as described previously (20). Briefly, one group received food ad libitum, and another received food each day only during the 14th dark phase. In a preliminary study, schedule-fed mice were able to maintain food intake at levels that were equivalent to those that were fed ad libitum. In addition, after

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ARC, arcuate nucleus; BAT, brown adipose tissue; DMH, dorsomedial nucleus; FFAs, free fatty acid; H₁-R, H₁ receptor; IVC, intracerebroventricular; LHA, lateral hypothalamic area; PVN, paraventricular nucleus; SCN, suprachiasmatic nucleus; UCP, uncoupling protein; VMH, ventromedial hypothalamic nucleus; WAT, white adipose tissue.

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the completion of the schedule feeding, we confirmed no changes in cumulative food intake between them. Serum samples were collected after overnight fasting and were assayed with commercially available kits (Eiken Chemical, Tokyo, Japan).  

**Lateral ventricle cannulation.** Mice were anesthetized (1 mg/kg Nembual i.p.) and placed in a stereotaxic frame for chronic implantation of a 29-gauge stainless steel cannula into the left lateral ventricle (0.5, 1.0, and 2.0 mm posterior, lateral, and ventral to the bregma, respectively) (21). After the completion of the experiments, the cannula placement was verified histologically.

**Reagents and treatments.** Recombinant leptin (Amgen) and the histamine H2-R agonist methyl (2-2-pyridyl)ethylamine dihydrochloride (Sigma, Tokyo, Japan) were infused into the lateral ventricle (0.5 and 1 μg/g per mouse, respectively) or intraperitoneally (30 and 1 μg/g per mouse, respectively) for 7 days. These doses were selected on the basis of other study (12) and a preliminary study. Control animals received injections of an equivalent volume of PBS. To avoid different rates of food consumption in leptin-treated, methyl(2-2-pyridyl)ethylamine dihydrochloride–treated mice, and controls, control animals were paired with treated mice and fed daily, according to a schedule.

**Histology.** Small pieces of white adipose tissue (WAT) and BAT were removed, rinsed with saline, fixed with 10% formalin, and embedded in paraffin. Tissue sections (5 μm) were cut and then stained with hematoxylin and eosin (HE). HE-stained sections were analyzed with an image analysis system (Olympus, Tokyo, Japan). Measurement of cell sizes and other histological quantifications were performed on a computerized microscope system (BX-50; Olympus). The picture displayed on the monitor (TX-M9755-J; Matsushita Electric Industry, Osaka, Japan) was analyzed by specialized software (Studio Lite; Apple Store, Tokyo, Japan).

**Preparation of cDNA probes and Northern blot analysis.** PCR primers were designed to amplify the coding region of UCP-1 (upstream primer, 5′-TACACGGGACCTACATGCTTGA; reverse primer, 5′-TCCGACAGCTTTGACTGGT-3′) and ob (upstream primer, 5′-AAGATCCCGGAGGAAGAAS-3′; reverse primer, 5′-CTTGGGCTCTTGTGAAACT-3′). Reverse transcription (RT) of 10 μg total RNA from C57BL/6 mice was performed using reverse transcriptase (Life Technologies, Gaithersburg, MD). PCR was carried out, and the nucleotide sequence of the amplified cDNA was confirmed by sequencing. Total cellular RNA was prepared from various mouse tissues using TRIzol (LifeTech, Tokyo, Japan). Total RNA (20 μg) was electrophoresed on a formaldehyde agarose gel, and the separated RNA was transferred to a Biodyne B membrane (Pall Canada, Mississauga, ON, Canada) in sodium saline citrate by capillary blotting. Prehybridization and hybridization were carried out according to the manufacturer’s protocol. After washing the membranes, the hybridization signals were analyzed with an image analyzer (Bio-image BAS 2000; Fuji Film, Tokyo, Japan). The membranes were rehybridized with 18S ribosomal RNA to quantify the amount of RNA on each blot.

**c-fos-like immunohistochemistry.** Two hours after the infusion of leptin, methyl(2-2-pyridyl)ethylamine dihydrochloride, or PBS, mice were anesthetized (3.3 mg/kg Nembual, i.p.) and perfused transcardially with isotonic PBS, followed by 4% paraformaldehyde, in 0.1 mol/l phosphate buffer. Brains were removed, postfixed for 24 h, and then processed for c-fos immunohistochemistry. Sections were cut at 40 μm and transferred without rinsing to a solution that contained the primary antibody (5 μg/ml polyclonal rabbit anti–c-fos; Santa Cruz Biotechnology). Sections were incubated on ice for 24 h, rinsed in PBS, and then processed with an ABC kit (Vector Laboratories, Burlingame, CA). Sections were transferred to a solution that contained biotinylated goat anti-rabbit antibody for 1 h, rinsed, transferred to avidin-biotinylated peroxidase for 1 h, rinsed, and finally developed using diaminobenzidine as a substrate. Each section was examined for c-fos immunoreactivity in the PVN, lateral hypothalamic area (LHA), arcuate nucleus (ARC), VMH, dorsomedial nucleus (DMH), and supraoptic nucleus (SCN) [on the basis of the atlas of Paxinos and Franklin (22)]. We calculated the average number of c-fos-immunoreactive cells for all sections in which the aforementioned locations could be observed. Data are presented as the mean number of c-fos-immunoreactive cells (unilateral) per section.

**Statistical analysis.** All data are expressed as the mean ± SE. Differences between treatment groups were assessed using an unpaired t test or a two-way ANOVA.

**RESULTS**

**Body mass, adiposity, triglyceride levels, and histological changes in adipose tissue in H1KO mice.** There were no differences between HIKO and wild-type mice in the rate of growth and body mass between 0 and 24 weeks of age (Fig. 1A). Body mass increased gradually after 28 weeks of age in both types of mice (P < 0.05 for wild-type and H1KO mice, respectively). HIKO mice exhibited a relatively greater increase in WAT mass (23, 48, and 40% increase in epididymal, mesenteric, and retroperitoneal fat mass, respectively), as compared with wild-type mice at 48 weeks of age (P < 0.05 or P < 0.01 for each; Fig. 1B–D). HIKO mice had 45 and 20% more triglycerides in the liver and skeletal muscle, respectively (Fig. 1E). At 12 weeks of age, body adiposity and triglyceride levels in wild-type and HIKO mice were indistinguishable (Fig. 1D and E). There were changes in the histological characteristics of adipose tissue in 48-week-old H1KO mice (Fig. 1F). Specifically, adipocytes in epididymal WAT were larger in 48-week-old HIKO mice as compared with wild-type mice of the same age, but this was not the case in 12-week-old mice (Fig. 1F). Similarly, there was a relatively greater amount of fat deposition in BAT in 48-week-old mice (Fig. 1F) but not 12-week-old HIKO mice as compared with the wild-type controls.

**Serum glucose, insulin, free fatty acid, and leptin levels; WAT ob; and BAT UCP-1 mRNA expression in H1KO mice.** Fasting serum concentrations of insulin and free fatty acids (FFAs) were greater in HIKO mice than in wild-type mice (P < 0.01 for both) at 48 but not at 12 weeks of age (Fig. 2A–C). Relative to wild-type mice, HIKO mice had a significantly greater level of expression of ob mRNA in epididymal WAT (95% increase; P < 0.01) and significantly greater concentrations of leptin (66% increase; P < 0.01) in 48-week-old but not 12-week-old mice (Fig. 2D and E). The level of expression of UCP-1 mRNA in BAT in 48-week-old H1KO mice was lower than in the wild-type controls (P < 0.05; Fig. 2F). There were no significant differences in any of the above-mentioned parameters in 12-week-old HIKO and wild-type mice (Fig. 2).

**Effects of leptin administration on food intake, body mass, expression of UCP-1 mRNA in BAT, and hypothalamic c-fos-like immunoreactivity.** Intracerebroventricular (ICV) administration of leptin (0.5 μg) decreased food intake, body mass (P < 0.01 for all; Fig. 3A and B), and BAT UCP-1 mRNA expression in 12- and 48-week-old wild-type mice. The same treatment for 12- (nonobese) and 48-week-old (obese) HIKO mice caused a relatively smaller attenuation of food intake, body mass (P < 0.05 for each; Fig. 3A and B), and BAT UCP-1 mRNA expression relative to wild-type mice. ICV administration of leptin caused a significant increase in c-fos-like immunoreactivity in the PVN, VMH, DMH, and ARC (P < 0.01 for each). The effect of leptin on c-fos-like immunoreactivity in the PVN and ARC was attenuated in both 12- and 48-week-old HIKO mice (P < 0.05 or P < 0.01 for both; Fig. 3C–E). The number of c-fos–immunoreactive cells in each of the hypothalamic nuclei that were examined in the present study, as well as representative photomicrographs of the PVN and ARC, are presented in Fig. 3D and E. The effects of intraperitoneal infusion of leptin (50 μg) were similar to those of ICV infusion (data not shown).

**Feeding behavior of H1KO mice.** The feeding behavior of HIKO mice differed remarkably from that of wild-type mice (Fig. 4A, B, E, and F). Daily food consumption was the same for wild-type and HIKO mice between 1 and 32 weeks of age (P > 0.1) but was slightly greater in HIKO

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FIG. 1. Growth curves (A); representative photomicrographs (48 weeks; B and C); epididymal fat (EPI), mesenteric fat (MES), retroperitoneal fat (RET), heart (HER), and kidney (KID) weight (D); triglyceride content in liver and muscle in younger nonobese (12 weeks; Y) and older obese (48 weeks; O) histamine H1KO (H) and wild-type (W) control mice (E); and representative photomicrographs of BAT and WAT of older obese (48 weeks) H1KO and wild-type control mice (F) (scale bar = 100 μm). Value and vertical bar, mean ± SE (n = 6–12 for each). *P < 0.05, **P < 0.01 vs. wild-type controls; +P < 0.05, ++P < 0.01 vs. the corresponding younger age.
FIG. 2. Serum glucose (A), serum insulin (B), serum FFA (C), leptin mRNA expression in WAT (D), serum leptin (E), and UCP-1 mRNA expression in BAT (F) in younger nonobese (12 weeks; Y) and older obese (48 weeks; O) histamine H1KO (H) and wild-type (W) control mice. Value and vertical bar, mean ± SE (n = 6–12 for each). *P < 0.05, **P < 0.01 vs. wild-type controls; +P < 0.05, ++P < 0.01 vs. the corresponding younger age.
FIG. 3. Effect of leptin (L) or PBS (P) infusion on cumulative food intake (A), body weight (B), and number of c-fos–positive nuclei in PVN and ARC (C–E) in histamine H1KO (H) and wild-type (W) mice in younger nonobese (12 weeks; Y) and older obese (48 weeks; O) mice. Value and vertical bar, mean ± SE (n = 6–12 for each). *P < 0.05, **P < 0.01 vs. wild-type controls; +P < 0.05, ++P < 0.01 vs. the corresponding younger age.
FIG. 4. Daily food intake and ratio of light/dark food intake in histamine H1KO (H) and wild-type (W) mice in younger nonobese (Y; A–C) and older obese (O) mice (D–F). Value and vertical bar, mean ± SE (n = 6–12 for each). *P < 0.05, **P < 0.01 vs. wild-type controls.
mice at 48 weeks of age (P < 0.05; Fig. 4C and G). At 12 weeks of age, the total amount of food that was consumed per day was the same in wild-type and H1KO mice (Fig. 4G). However, the ratio of food consumption in the light versus dark phase was smaller in 12-week-old H1KO mice compared with wild-type mice of the same age (P < 0.01; Fig. 4D); this difference was even greater at 48 weeks of age (P < 0.05; Fig. 4F). In addition, the total amount of food consumed per day was greater for 48-week-old H1KO mice (P < 0.05; Fig. 4G).

Changes in body mass and levels of serum glucose, insulin, and ob mRNA expression in WAT. Scheduled feeding for 4 weeks had no effect on the increase in body mass of wild-type mice when compared with control animals that were fed ad libitum (P > 0.1; Fig. 5A). However, in 48-week-old H1KO mice, the scheduled feeding attenuated the increase in body mass in comparison with H1KO controls of the same age that were fed ad libitum (P < 0.05; Fig. 5B), although the cumulative food consumption of each group was almost the same. Serum concentrations of glucose and insulin and ob mRNA expression in WAT were the same in wild-type mice that were fed either according to a schedule or ad libitum (P > 0.1; Fig. 5C–E). By contrast, serum concentrations of insulin and expression of ob mRNA in WAT both were significantly lower in schedule-fed H1KO mice as compared with H1KO controls that were fed ad libitum (P < 0.05 for each; Fig. 5C–E).

Effects of histamine administration on SCN c-fos–like immunoreactivity in wild-type and H1KO mice. ICV administration of histamine (10 μg) caused a significant increase in SCN c-fos–like immunoreactivity in wild-type mice (P < 0.01; Fig. 5F). The effect of histamine on c-fos–like immunoreactivity in the SCN was attenuated in 12-week-old H1KO mice.

Effects of methyl (2-[2-pyridyl]ethyl)amine dihydrochloride on food intake, body mass, UCP-1 mRNA expression, and hypothalamic c-fos expression. Intraperitoneal administration of the a histamine H1-R agonist methyl (2-[2-pyridyl]ethyl)amine dihydrochloride had no effect on cumulative food intake, body mass, and adiposity in wild-type mice compared with PBS-treated controls (data not shown). By contrast, ICV administration of the same substance (1 μg/g mice for 7 days) decreased cumulative food intake, body mass, and adiposity in wild-type mice by 39, 12, and 24%, relative to PBS-treated controls (P < 0.01 for each; Fig. 6A and B). The same treatment resulted in an increase in UCP-1 mRNA expression in the BAT of wild-type mice (P < 0.01; Fig. 6C) and an increase in c-fos–like immunoreactivity within the PVN (P < 0.01; Fig. 6D and E) but not in any of the other hypothalamic regions that were examined (ARC, VMH, and LHA). ICV infusion of methyl (2-[2-pyridyl]ethyl)amine dihydrochloride in H1KO mice had no effect on food intake, body mass, expression of UCP-1 mRNA in BAT, or c-fos–like immunoreactivity in the PVN (Fig. 6D and E).

DISCUSSION

Among the receptors that mediate histamine signaling, histamine H1-Rs are expressed ubiquitously in peripheral tissues, including lymphocytes, heart, and spleen, as well as in the central nervous system (23,24). As in our previous report (12), there were no significant differences between H1KO and control mice in the rate of growth and body mass between 0 and 28–30 weeks of age in the present study. After 28–30 weeks, H1KO mice gradually developed obesity. It is indicated that histamine is involved in the aging-related obesity, as in a previous study (16). In addition, the present study demonstrated that there is substantial hypertrophy of adipocytes and increased fat deposition in obese H1KO mice. These observations indicate that the disruption of H1-R signaling has a profound and specific effect on lipogenesis and/or lipolysis in WAT.

The functional and morphologic changes in WAT in H1KO mice raise the question of why these mice become obese. The first line of evidence relevant to this question includes the results of studies of the resistance of H1KO mice to leptin. Several studies have demonstrated that the administration of leptin decreases feeding behavior, fat accumulation, and body mass and increases energy expenditure (25,26). In the present study, H1KO mice were resistant to leptin treatment, irrespective of the age of the animals and whether the leptin was administered centrally or peripherally. Therefore, it seems that the blockade of histamine signaling at the level of the H1-R has consequences for both food intake and UCP mRNA expression. These observations suggest that leptin resistance in young H1KO mice (that are not yet obese) may contribute to the subsequent development of obesity in older mice.

The second line of evidence that is relevant to the aforementioned question includes the results of studies of the circadian rhythm of food intake. Previous reports have demonstrated that the circadian feeding rhythm is a crucial factor in the development of obesity, because abnormalities in the rhythm of feeding and locomotor activity are often associated with obesity (27–29). Conversely, correcting disturbances in circadian feeding and activity rhythms can partially reverse obesity and related metabolic disorders. Because the concentrations of neuronal histamine across the sleep-wake cycle in H1-R–null or histidine decarboxylase–null mice are significantly altered (19,30), it is possible that an altered circadian rhythm in H1KO mice affects their feeding behavior and consequently contributes to the development of obesity. Indeed, we found in the present study that H1KO mice had abnormal circadian rhythms of food intake relative to wild-type controls. We demonstrated the upregulation by histamine of c-fos expression in the SCN region of the hypothalamus, which contains histamine H1-R (31,32). The effect of histamine on c-fos expression in the SCN was attenuated in H1KO mice in the present study. SCN region is important for regulation of feeding rhythms (33,34), suggesting that H1-R–mediated histamine signaling in the SCN may be involved in feeding rhythm. Additional evidence that a disrupted circadian feeding rhythm contributes to the development of obesity in H1KO mice includes that scheduled feeding of obese H1KO mice attenuated an increase in body mass and ameliorated the development of related metabolic disorders.

The third line of evidence that is relevant to the aforementioned question is that of hyperphagia and a decrease in expression of UCP-1 mRNA expression in BAT in older H1KO mice. UCP-1, which is expressed exclusively in BAT, plays an important role in energy expenditure and metabolism, and its expression is closely linked to energy expenditure in both the fasted and fed states.
FIG. 5. Body weight change in wild-type (W) mice (A) and histamine H1KO (H) mice (B) by scheduled feeding. Serum glucose (C), serum insulin (D), and leptin mRNA expression in WAT (E) of older obese H1KO and wild-type mice. F: Effect of histamine (H) or PBS (P) infusion on number of c-fos–positive nuclei in SCN in H1KO and wild-type mice in younger nonobese mice. Value and vertical bar, mean ± SE (n = 6–12 for each). *P < 0.05, **P < 0.01 vs. wild-type controls; +P < 0.05, ++P < 0.01 vs. the corresponding younger age.
FIG. 6. Effect of methyl(2-[2-pyridyl]ethyl)amine dihydrochloride (B) infusion on cumulative food intake (A), body weight change (B), UCP-1 mRNA expression in BAT (C), and number of c-fos–positive nuclei in PVN (D and E) in older obese histamine H1KO (H) and wild-type (W) mice. Each parameter was changed in H1KO mice after methyl(2-[2-pyridyl]ethyl)amine dihydrochloride treatment compared with PBS (P). Value and vertical bar, mean ± SE (n = 6–12 for each). **P < 0.01 vs. the corresponding nontreated controls.
nonshivering thermogenesis in rodents (35,36), and BAT plays a central role in regulating body mass. It is interesting that most genetically obese animals have reduced levels of UCP-1 mRNA (37,38). Transgenic mice, in which BAT is rendered deficient by means of UCP-1 promoter-driven diphtheria toxin A, become obese; this is initially due to reduced energy expenditure and is subsequently due to an accompanying increase in food intake (39). Thus, it seems that a lower level of energy expenditure, as a result of the disruption of UCP-1 signaling in BAT, might contribute to the development of obesity in older HIKO mice. This, when combined with hyperphagia, would probably accelerate the development of obesity in these animals.

As described above, older HIKO mice have dramatically increased levels of leptin and a decreased sensitivity to leptin. In the present study, we noted that the upregulation by leptin of c-fos expression in the PVN, DMH, VMH, and ARC regions of the hypothalamus, all of which contain a large number of leptin receptors (40,41), was lower in the PVN and ARC of HIKO mice. This suggests that histamine H1-R-mediated leptin signaling occurs in the PVN and the ARC and that neurons in these regions may be acted upon directly by leptin via leptin receptors; they could also be influenced indirectly via histamine H1-R-expressing neurons. In the hypothalamus, H1-Rs, especially in the PVN, are important for feeding (11,42). Consequently, a reduction of leptin-induced c-fos expression in the PVN, as a result of H1-R-mediated signaling, as well as NOS signaling between the PVN and the ARC, may constitute important signaling pathways. Although the PVN might be an important leptin signaling pathway that is mediated by H1-Rs, other hypothalamic regions, such as the DMH and the lateral hypothalamus, may be upstream or independent of leptin-mediated H1-R signaling.

We found that the central administration of a histamine H1-R agonist altered food intake, body mass, and BAT UCP-1 mRNA expression. These results have revealed that agonism of histamine H1-Rs can inhibit food intake and decrease body mass gain, probably as a result of the stimulation of energy homeostasis at the level of the CNS. This suggests that the anti-obesity effects of histamine H1-R agonists are exerted primarily in the CNS. The same treatment induced expression of c-fos-like immunoreactivity in the PVN, in which there are many H1-Rs (11,42). This raises the possibility that the PVN constitutes a major component of the histamine H1-R-signaling pathway to peripheral tissues. Other hypothalamic regions, including the ARC, VMH, and lateral hypothalamus, which were not activated by the histamine H1-R agonist, may lie upstream of this pathway or may be independent of histamine signaling. None of the aforementioned effects of the histamine H1-R agonist were observed in HIKO mice, which supports the view that the histamine H1-R-signaling pathway is disrupted at the level of hypothalamic H1-Rs in HIKO mice. This leads us to two conclusions: first, the H1-R agonist specifically activated H1-Rs and, second, disruption of histamine H1-R signaling can completely abolish histamine H1-R signaling.

Neuronal histamine is synthesized by histidine decarboxylase (HDC) and affects on postsynaptic histamine H1-R, histamine H2-R, and presynaptic histamine H3-R in the brain. The present study demonstrated that disruption of posthistamine H1-R signaling that occurs in knockout mice results in leptin-resistant obesity. Similar to our report, others demonstrated that mutations of HDC, postsynaptic histamine H1-R, and presynaptic histamine H3-R have also been shown to induce leptin-resistant obesity (16–18). Collectively, these studies demonstrated histamine signaling involved HDC and its pre- and postsynaptic receptors and regulate body weight downstream of leptin.

In summary, histamine H1-R signaling is central to the regulation of the circadian rhythm of feeding, leptin sensitivity, and obesity. In addition, H1-Rs in the PVN seem to be important in regulating food intake and body mass. These observations raise the possibility that treatment with histamine H1-R agonists (or derivatives that have better access to the central nervous system, e.g., the PVN) might be an effective and novel means of therapy for the treatment of obesity and related metabolic disorders.

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