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Forum Minireview

Recent Advances in Molecular Pharmacology of the Histamine Systems: Physiology and Pharmacology of Histamine H_3 Receptor: Roles in Feeding Regulation and Therapeutic Potential for Metabolic Disorders

Shigeru Tokita[1], Kazuhiko Takahashi[1], and Hidehito Kotani[1,*]

[1]*Tsukuba Research Institute, Banyu Pharmaceutical Co., Ltd., Tsukuba, Ibaraki 300-2611, Japan*

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Abstract. Histamine H_3 receptors (H3Rs) are autoreceptors that negatively regulate the release of histamine and other neurotransmitters such as norepinephrine, dopamine, and acetylcholine in the central nervous system (CNS). Consistent with the wide-spread projection of histaminergic neurons from the lateral hypothalamus, H3Rs are widely distributed in the CNS and are believed to play a variety of physiological roles, including regulation of feeding, arousal, cognition, pain, and endocrine systems. To further understand the physiological roles of H3Rs in vivo, we produced H3R knockout ($H3R^{-/-}$) mice and found that $H3R^{-/-}$ mice displayed hyperphagia and late-onset obesity associated with hyperinsulinemia and leptinemia, the fundamental marks of metabolic syndromes. A series of non-imidazole H3R antagonists/inverse agonists with improved selectivity and potency have been developed and were found to regulate feeding and body weight gain in laboratory animals. Taken together, these observations suggest that H3Rs are involved in the regulation of feeding behavior and body weight. Several H3R inverse agonists targeting cognitive disorders and dementia have entered clinical trials. These trials will give critical information about the physiological functions of H3Rs in humans.

Keywords: histamine, histamine H_3 receptor, obesity, central nervous system disorder, inverse agonist

Introduction

Histaminergic neurons are exclusively found in the tuberomammillary nucleus in the posterior hypothalamus but project widely throughout the central nervous system (CNS), thus suggesting the important physiological roles of histamine in the brain (1). Several reports have suggested that histamine (HA) is involved in the regulation of arousal state (2), locomotor activity (3), cardiovascular control (4), water intake (5), food intake (6), and memory formation (7).

Histamine H_3 receptors (H3Rs) were identified pharmacologically in 1983 by Arrang et al. as autoreceptors that negatively regulate HA release in the brain, and hence modulate histaminergic tone (8). Consistent with the widespread projection of histamine neurons, H3Rs are widely distributed throughout the CNS (9, 10). Furthermore, extensive pharmacological studies with both H3 agonists, such as (*R*)-*α*-methylhistamine, and H3 inverse agonists (IAs), such as thioperamide, have demonstrated that H3Rs also work as heteroreceptors at pre-synaptic terminals and regulate the release of other neurotransmitters such as dopamine, serotonin, noradrenaline, GABA, and acetylcholine (11, 12). Taken together, these observations suggest the therapeutic potential of H3 agonists/IAs as a means to address various CNS disorders.

*Corresponding author. hidehito_kotani@merck.com
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Molecular and functional profiles of H3R

Despite tremendous effort to identify H3Rs, their molecular profiles remained unknown for a decade. In the late 1990s, several groups identified the genes

encoding H3Rs using reverse pharmacological methods and clarified their molecular profiles. H3R is a member of the G-protein-coupled receptor (GPCR) family and is functionally linked to $G_{i/o}$ proteins, hence negatively regulating intracellular cAMP levels (13 – 16). The amino acid sequences of H3Rs are highly conserved among humans, monkeys, rats, mice, and guinea pigs, thus suggesting that H3Rs play critical roles in numerous species (17). Further studies have shown that several splicing variants are present in humans, rats, mice, and guinea pigs. Drutel et al. reported that rat H3R splicing variants (H3A, B, and C) showed distinct expression patterns in the brain and were differentially coupled to $G_{i/o}$ proteins when expressed in cultured cells (18). Although, these observations suggest that the splicing variants might have distinct roles in vivo, further understanding of the physiological functions of the splicing variants remains elusive.

One of the remarkable features of H3R is its high constitutive activity both in vivo and in vitro (19). The high constitutive activity of H3R is likely endowed by the specific amino acids located in the juxtamembrane domain of the 3rd intracellular loop. In support of this notion, we reported that mutagenesis of this domain produced H3Rs with altered constitutive activities and binding affinities for several agonists and inverse agonists (20). The high constitutive activity of H3R may be critical for its regulatory function in the CNS (19, 21). Interestingly, Morisset et al. has reported that neutral antagonists and inverse agonists behave in a different manner in vivo; the former does not affect the constitutive activity and HA release, while the latter reduces constitutive activity and hence increases HA release in the brain (19). These observations have suggested that H3 neutral antagonists and inverse agonists have distinct pharmacological effects and therapeutic potential.

Phenotype of $H3R^{-/-}$ mice

As stated above, a series of pharmacological studies has demonstrated that H3Rs play a variety of physiological roles in the brain by regulating the release of HA and other neurotransmitters. To further study the physiology and pathology of H3Rs, we produced H3R-deficient mice and examined the phenotypes (22).

Northern blotting analysis and ligand binding assay using [^{3}H]N^{α}-methylhistamine, a selective H3 ligand, confirmed the complete loss of functional H3Rs in the brain. There were no significant changes in H1R and H2R mRNA expression in the brain, thus suggesting no compensatory up-regulation of post-synaptic HA receptors by the loss of functional H3Rs. Because H3Rs negatively regulate HA release from synaptic endings, the loss of H3R function was thought to increase HA release in the brain. As expected, $H3R^{-/-}$ mice displayed enhanced HA release when compared with wild-type (WT) littermates, as demonstrated by increased *tele*-methylhistamine (*tele*-MHA) levels. Increased HA release was observed in all tested areas; forebrain, hypothalamus/thalamus, hippocampus, cerebellum, and brain stem.

$H3R^{-/-}$ mice are viable and fertile, and body size did not differ significantly between $H3R^{-/-}$ mice and WT littermates. Gross examination of the brain and other tissues revealed no overt abnormalities in $H3R^{-/-}$ mice. Interestingly, $H3R^{-/-}$ mice displayed mild hyperphagia and late-onset obesity (Fig. 1). Furthermore, enhanced body weight gain was observed in both male and female $H3R^{-/-}$ mice. The increased adiposity and decreased energy expenditure of $H3R^{-/-}$ mice suggest that the obese phenotype of $H3R^{-/-}$ mice may be caused by the combination of excessive feeding and reduced energy efficiency.

Blood chemistry confirmed hyperinsulinemia and hyperleptinemia, which are fundamental pathologies of obesity and metabolic syndrome, in $H3R^{-/-}$ mice. Although $H3R^{-/-}$ mice retained normal plasma glucose levels, they displayed both impaired IPITT and IPGTT, indicating that $H3R^{-/-}$ mice developed insulin resistance.

The obese phenotype of $H3R^{-/-}$ mice is a paradoxical finding based on what was expected from HA physiology; increased HA release reduces feeding behavior by activating post-synaptic H1Rs and increases energy expenditure by activating lipolysis in white adipose tissue via activation of sympathetic tone. The etiology of the obese $H3R^{-/-}$ phenotype remains to be elucidated. At present, we can not exclude the possibility that a lack of H3Rs alters neural circuitry during the development stage. Another possibility is that sustained increases in HA release may desensitize and/or down-regulate post-synaptic histamine receptors (H1R, H2R) and hence attenuate net histaminergic tone. Our preliminary data confirmed that mRNA levels of H1R and H2R in the brain are comparable in $H3R^{-/-}$ and WT mice, while H1R binding activity trends to be lower in $H3R^{-/-}$ mice than in WT mice, which supports the notion that reduced H1R activity explains, at least partially, the obese phenotype of $H3R^{-/-}$ mice. With regard to energy expenditure, $H3R^{-/-}$ mice exhibited reduced expression of UCP-1 and UCP-3, critical regulators of energy expenditure, in adipose tissues. The decreased levels of these UCPs could be explained by leptin resistance, as demonstrated by hyperleptinemia.

$H3R^{-/-}$ mice displayed the obese phenotype reminiscent of those of $H1R^{-/-}$ mice and histidine decarboxylase $(HDC)^{-/-}$ mice. Clinical evidence that drugs with H1R-

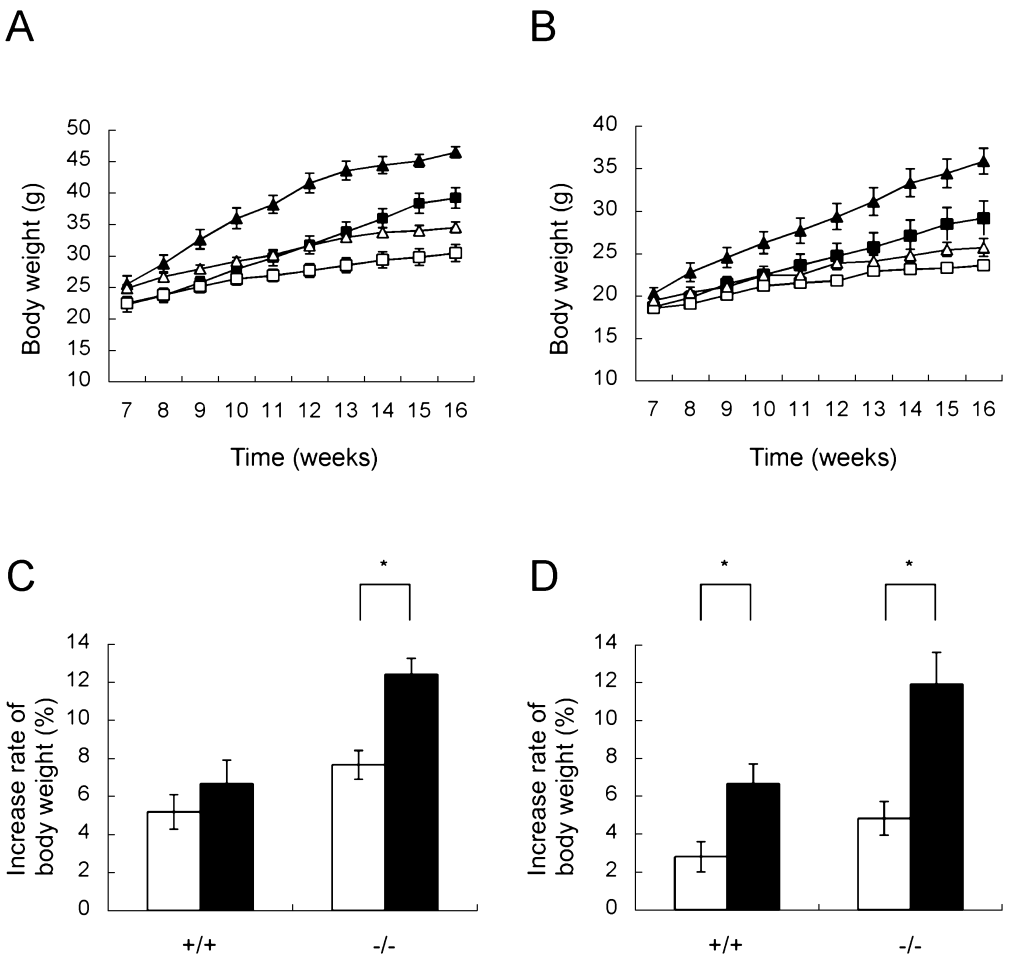


Fig. 1. Effects of high-fat diet loading. Body weight growth in male (n = 7) (A) and female (n = 10) (B) $H_3^{-/-}$ and $H_3^{+/+}$ mice are shown. $H_3^{+/+}$ mice are indicated by open squares (regular diet) and filled squares (high-fat diet) and $H3^{-/-}$ mice, by open triangles (regular diet) and filled triangles (high-fat diet). Increase rate of body weight from 7 to 8 weeks in male (n = 7, **P*<0.05) (C) and female (n = 10, **P*<0.05) (D) mice. White bars indicate regular diet and black bars high-fat diet.

blocking properties increase the appetite and body weight gain strongly suggest that H1Rs are involved in the regulation of feeding and energy expenditure (22, 23). Consistent with these observations, Masaki et al. showed that $H1R^{-/-}$ mice displayed late-onset obesity and decreased energy expenditure (24). Interestingly, the anorectic activity of ICV leptin was significantly attenuated in $H1R^{-/-}$ mice (25), suggesting that the obese phenotype of $H1R^{-/-}$ mice could be, at least partially, explained by reduced sensitivity to leptin. $HDC^{-/-}$ also displayed the late-onset obese phenotype accompanied by severe hyperleptinemia and insulin resistance, which suggests critical roles for the histaminergic pathway in integrating leptin signals in the brain (26). Morimoto et al. reported that intraperitoneal but not central administration of leptin enhances hypothalamic HA release possibly through the chorda tympani nerve (27, 28). Although the mode of action of leptin on central HA release needs to be further examined, these observations suggest that HA is a critical messenger of the anorectic activity of leptin and that disruption of leptin-HA pathway by loss of HDC may cause the leptin resistance.

Pharmacology of H3R: H3R IAs as anti-obesity drugs

Extensive pharmacological experiments have demonstrated that the brain HA system plays critical roles in the regulation of feeding and energy expenditure (29, 30). The fact that drugs with H1R-blocking properties stimulate food consumption in humans as well as in animals clearly indicates the critical role of H1R in the regulation of feeding behavior (23, 31). Because H3Rs negatively regulate the release of HA in the brain, H3R IAs are believed to suppress appetite through the

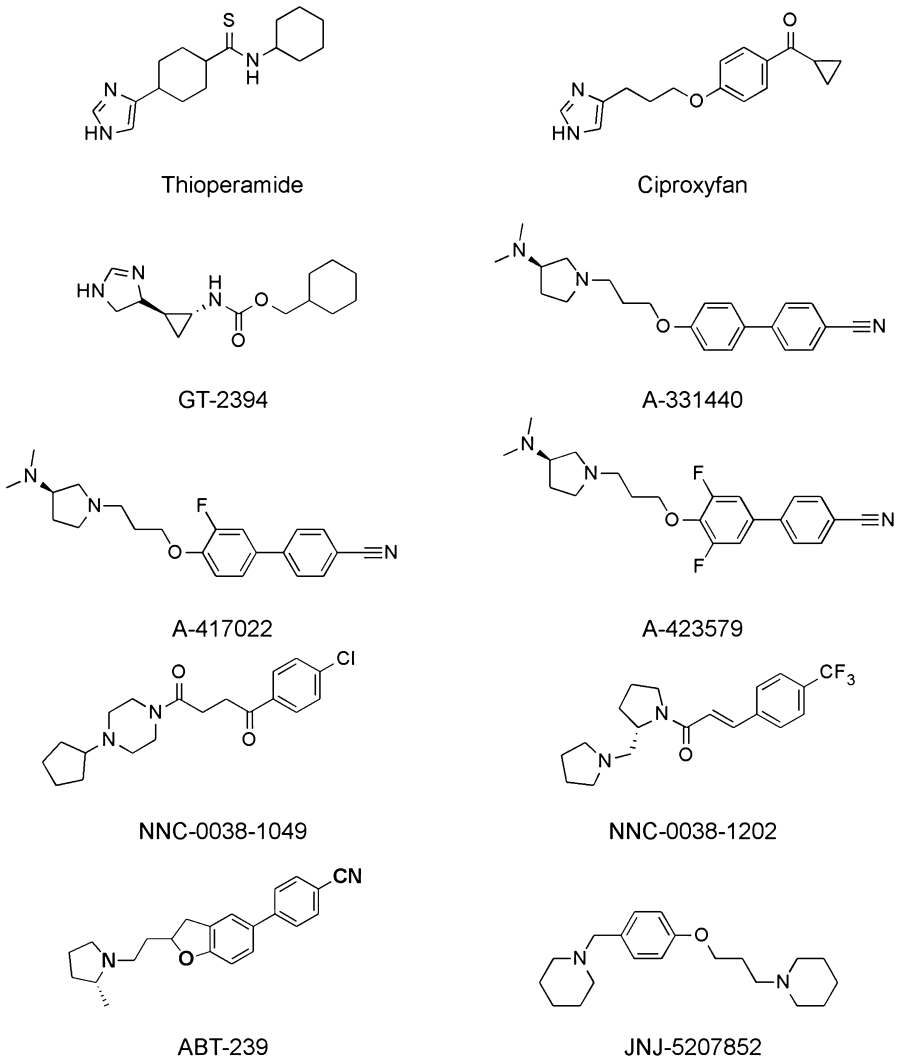


Fig. 2. Structure of histamine H3R inverse agonists. Structurally diverse H3R inverse agonists have been developed so far. Classical compounds contain the imidazole-moiety that may interact with P450 proteins. Recently identified compounds are a non-imidazole type and posses improved potency and selectivity. ABT-239 recently has entered clinical trial targeting cognitive dysfunction.

Table 1. Anti-obese effects of histamine H3R inverse agonists

	Mice		Rats	
Lean	Thioperamide: NPY-induced feeding	↓	Thioperamide: spontaneous feeding	↓
			Ciproxyfan: scheduled feeding	↓
H_3R KO	A-331440	→		
DIO	A-331440, A-417022, A-423579	↓	NNC-0038-1049	↓
	ABT-239	→	NNC-0038-1202	↓
			GT-2393	↓
ObR deficit (*db*/*db*, *ob*/*ob* Zucker)	JNJ-5207852	→	GT-2394	↓
	A-331440	↓		

Diverse effects of histamine H3R inverse agonists on feeding and body weight have been reported. Several compounds (thioperamide, A-331440, A-417022, A-423579) reduced feeding and/or body weight gain in mouse obese models while the other structurally diverse compounds (ABT-239, JNJ-5207852) had no effects. Various compounds showed anorectic or anti-obese effects in rats, suggesting the species-related differences may exist in H_3 ligand pharmacology. Upward arrow, BW increase; downward arrow, BW decrease.

activation of H1Rs in the post-synaptic areas. To address the therapeutic potential of H3R ligands as an anti-obesity drug, several groups have reported the pharmacological profiles of H3R IAs in animal studies (Fig. 2, Table 1). Thioperamide, an imidazole-containing H3 inverse agonist, has been shown to suppress food consumption in spontaneous, fasted-induced, scheduled- and NPY-induced feeding paradigms in rats and mice (32 – 35). Although these reports have suggested the therapeutic potential of H3R IAs, their anti-obesity effects remain controversial. Recently, Sindelar et al. reported the in-depth analysis of the effects of thioperamide in rats (36). They showed that both intraperitoneal (IP) and oral (PO) administration of thioperamide enhanced HA release (increase in *tele*-MHA) in the brain, while only IP administration caused significant reductions in food intake. Moreover, the decrease in RQ with IP administration also decreased energy expenditure, thus resulting in unchanged energy balance. In addition, several reports have demonstrated the possibility that the imidazole moiety of thioperamide is responsible for toxicity through its interaction with P450 proteins (37, 38), thus suggesting the possibility that imidazole-containing H3 drugs may exert adverse effects.

In order to address these concerns, several pharmaceutical companies have developed non-imidazole H3R inverse agonists (39 – 41). Among these, Hancock et al. reported that A-331440 potently suppresses feeding and body weight gain in diet-induced obese mice when dosed b.i.d. (42, 43). They also reported that the anti-obesity effects were not observed in $H3R^{-/-}$ mice, thus suggesting that A-331440 exhibits its anti-obesity activity in a mechanism-based manner. However, ABT-239, another structurally distinct H3R IA, did not show any anti-obesity activity in the same obesity model, while ABT-239 showed marked pharmacological activity in cognition studies such as five-trial inhibitory avoidance and social memory (44, 45). In addition, Barbier et al. reported that JNJ-5207852 showed significant wakefulness-promoting effects in rats, but showed no anti-obesity effects in *ob/ob* mice (46). Hancock et al. reported that anorectic H3R IA (e.g., A-331440) and non-anorectic H3R IA (e.g., ABT-239) were able to activate distinct brain regions, as demonstrated by different c-Fos expression patterns, in drug-treated animals (47). Although, these observations may explain why some classes of H3R IA exert anti-obesity activity, potentially unknown off-target activity of specific compounds might contribute to their anorectic effects and thus further investigation is required.

Rimvall et al. recently reported that NNC-0038-1049 and NNC-0038-1202, structurally distinct H3R antagonists (IA activity unknown), reduced body weight in diet-induced obese rats (48). Furthermore, NCC-0038-1202 reduced food consumption and body weight gain in pigs and obese rhesus monkeys. Although, detailed profiles of these compounds have not been reported, these observations demonstrate that H3R antagonists/IAs may possess anti-obese activity and their efficacy may differ among species. Although the brain HA system is a highly conserved system among species, it is possible that the system plays slightly different physiological roles. Oishi et al. reported that HA content and turnover in several brain areas differ between mice and rats (49), thus supporting the notion of species-related differences in H3R ligand functions. Splicing variants would play different roles in CNS, interacting differently with the pharmacological reagents described above, and resulting in distinct outcomes in each species. This may also explain the fact that different H3R IAs showed distinct outputs in mouse obesity models.

Summary

Identification of the H3R genes has triggered drug discovery efforts by pharmaceutical companies for a range of CNS disorders, and pre-clinical studies in animal models have demonstrated that H3R IAs may have therapeutic effects in the treatment of central disorders, including obesity. The fact that $H3R^{-/-}$ mice displayed an obese phenotype and the pharmacological effects of H3R IAs strongly suggest that H3Rs play critical roles in the regulation of feeding and body weight.

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