0022-3565/11/3361-24–29$20.00
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
JPET 336:24–29, 2011

Vol. 336, No. 1
171306/3645339
Printed in U.S.A.

JPET Miniseries: H_3 Receptors

The Histamine H_3 Receptor and Eating Behavior

Maria Beatrice Passani, Patrizio Blandina, and Fernando Torrealba

Dipartimento di Farmacologia Preclinica e Clinica, Universitá di Firenze, Firenze, Italy (M.B.P., P.B.); and Departamento de Fisiología, Facultad de Ciencias Biológicas, Pontificia Universidad Católica de Chile, Santiago, Chile (F.T.)

Received June 9, 2010; accepted July 20, 2010

ABSTRACT

Interest in the histaminergic system as a potential target for the treatment of feeding disorders is driven by the unsatisfactory history of the pharmacotherapy of obesity. Eating behavior is regulated by a complex interplay of central neurotransmitter systems, peripheral endocrine stimuli, the circadian rhythm, and environmental cues, all factors that change the behavioral state and alter homeostatic aspects of appetite and energy expenditure. Key factors driving eating behavior are appetite and satiety that are regulated through different mechanisms. Brain histamine has long been considered a satiety signal in the nervous system. Recent observations, however, indicate that histamine does not meet the criteria for being a satiety signal, because augmented histamine release accompanies the appetitive phase of feeding behavior rather than food consumption and satiety. The appetitive phase requires a high and yet optimal arousal state, and the histaminergic system is crucial for sustaining a high degree of arousal during motivated behavior. Histamine H_1 receptors in the brain are crucial for the regulation of the diurnal rhythm of food intake and the regulation of obesity; however, from a therapeutic standpoint, no brain-penetrating H_1 receptor agonists have been identified that would have antiobesity effects. Despite conflicting preclinical data, insights are emerging into the potential role of histamine H_3 receptors as a target of antiobesity therapeutics. The aim of this review is to outline the relevance of the histaminergic system in controlling feeding behavior and evaluate the potential therapeutic use of histaminergic ligands for the treatment of eating disorders.

Central Control of Eating Behavior

Controlling food intake and body weight is an issue of ever-growing importance because of the significant health consequences brought about by obesity. Obesity is associated with an increased risk of metabolic and cardiovascular conditions such as hypertension, dyslipidemia, diabetes mellitus, and obstructive sleep apnea. According to the World Health Organization, between 30 and 80% of adults and up to one-third of children in the World Health Organization's European region are overweight. Obesity's prevalence has tripled in many European countries since the 1980s, and the number of those affected continues to rise at an alarming rate. Obesity is already responsible for 2 to 8% of health costs and 10 to 13% of deaths in parts of Europe. Efficacious treatments of this condition are certainly among the greatest public health challenges of the 21st century. Pharmacotherapy for obesity should be considered in combination with lifestyle changes in obese or overweight patients with other conditions that put them at risk for developing heart disease. Medications currently available for long-term treatment of obesity belong essentially to two categories, those acting on the gastrointestinal system, such as orlistat (a pancreatic lipase inhibitors that decreases ingested triglyceride hydrolysis), and those that act on the central nervous system (CNS) to primarily suppress appetite, such as sibutramine, a monoamine reuptake inhibitor. Diethylpropion and phenter-

This study was supported by the Ministero Universitá e Ricerca (I) [Grant 519MIUR068], the Universitá di Firenze (I) [Grant 519ATEN276], Cooperation in Science and Technology Action [Grant BM0806], Fondo Nacional de Desarrollo Científico y Tecnológico (Chile) [Grant 91100465], and Millenium Nucleus (Chile) [Grant P06/008-F].
Article, publication date, and citation information can be found at http://jpet.aspetjournals.org.
doi:10.1124/jpet.110.171306.

ABBREVIATIONS: CNS, central nervous system; AAPD, atypical antipsychotic drug; TMN, tuberomammillary nucleus; α-FMH, α-fluoromethylhistidine; VMH, ventromedial hypothalamus; PVN, paraventricular hypothalamus; Ucp1, uncoupling protein 1; GLP-1, glucagon-like peptide 1; TRH, thyrotropin-releasing hormone; NTS, nucleus of the solitary tract; SR141716A, *N*-(piperidine-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide hydrochloride; PF-03654746, (1*R*,3*R*)-*N*-ethyl-3-fluoro-3-[3-fluoro-4-(pyrrolidin-1-ylmethyl)phenyl]cyclobutane-1-carboxamide.

mine of the amphetamine class were recently reinstated in Europe. Moreover, rimonabant (a cannabinoid receptor 1 antagonist), the first of a series of potent and selective antagonists of the endocannabinoid receptor [*N*-(piperidine-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide hydrochloride (SR141716A); Rinaldi-Carmona et al., 1994], was approved by the Committee for Medicinal Products for Human Use of the European Medicines Agency as an adjunct to diet and exercise in treating obesity in 2006. However, despite extensive clinical trial data, European Medicines Agency officials announced in 2008 that the agency has recommended suspension of rimonabant because of its psychiatric side effects (Li and Cheung, 2009). The fact that these compounds work by different mechanisms reflects the complex etiology of the disease. Often these medications achieve a rather modest degree of weight loss, and psychiatric and cardiovascular disorders are reported as adverse drug reactions. As a consequence, new molecular targets are being probed by academic and industrial research teams in the pursuit of novel treatments that may provide advantages over the currently available ones. In this respect, understanding the brain circuitry that regulates appetite and food consumption is of paramount importance.

Eating behavior is driven by a very complex interplay of hierarchically organized brain structures, central neurotransmitter systems, and peripheral endocrine stimuli modulated by circadian rhythms and environmental cues, all factors that change the behavioral state and combine to alter homeostatic and hedonic aspects of appetite and energy expenditure (Saper et al., 2002). The key factors driving eating behavior are hunger (appetite) and satiety after food consumption; they are regulated through different mechanisms not yet well understood. Satiety is triggered by peripheral signals, such as gastric or duodenal distension, by gastrointestinal peptide hormones, such as incretins, cholecystokinin, and by lipid-derived messengers, such as oleoylethanolamide. These satiety signals influence individual meals, reducing meal size; also, they affect central neurotransmission either directly or indirectly by stimulating primary vagal afferents that in turn send information to the nucleus of the solitary tract (NTS). The NTS processes and distributes information to central interoceptive regions in a manner not completely understood. Long-term signals, such as insulin and the adipose cell-derived peptide leptin, decrease food intake by modulating satiety mechanisms (Morton et al., 2006) and altering the hedonic value of food (Fulton, 2010). Much less is known about the mechanisms at the onset of feeding behavior or those that control meal initiation when food is freely available. It is, however, clear that decreases in either glucose or triglyceride availability are signals that converge on medial hypothalamic neurons to increase food intake. The same hypothalamic regions contain the neurons that respond to long-term signals from energy deposits, leptin, and insulin to promote food intake. Such medial hypothalamic regions then are thought to be a key site of convergence of short- and long-term signals of fuel availability and energy balance.

Brain Histamine and Eating Behavior

The association of histamine with eating disorders became evident when it was observed that atypical antipsychotic drugs (AAPDs) stimulate appetite and induce weight gain through selective and potent stimulation of hypothalamic AMP kinase, which has been linked to the regulation of food intake (Minokoshi et al., 2004), and reverse the actions of the anorexigenic hormone leptin. This action involves the histamine H_1 receptor, because AAPD augmentation of AMP kinase is abolished in mice with deletion of histamine H_1 receptors (Kim et al., 2007). Moreover, the relative potencies of AAPDs in blocking H_1 receptor have been reported to correlate with their orexigenic potencies (Kroeze et al., 2003; Kim et al., 2007). However, relatively few studies have been carried out to unequivocally establish a relationship between food consumption and H_1 receptors blockade in humans (Deng et al., 2010). Histamine neurons are crucial for sustaining a high level of arousal during motivated behavior, because histaminergic activity shows a clear circadian rhythm with high levels during the active period and low levels during sleep (reviewed in Haas et al., 2008). Histamine neurons are localized exclusively in the tuberomammillary nucleus (TMN) in the posterior hypothalamus and send projections throughout the CNS that are organized in functionally distinct circuits impinging on different brain regions (Giannoni et al., 2009). Brain histamine affects both sides of energy balance: by decreasing intake and increasing expenditure (Fig. 1). Brain histamine induces a loss of appetite that we will argue is an adaptive anorexia. Early studies showed that treatments increasing brain histamine availability or activating H_1 receptors in the CNS of rats and mice suppressed food intake (Clineschmidt and Lotti, 1973; Machidori et al., 1992; Lecklin et al., 1998; Masaki et al., 2004), whereas administration of H_1 receptor antagonists or α-fluoromethylhistidine (α-FMH), a suicide inhibitor of histidine decarboxylase that decreases central histamine (Garbarg et al., 1980), increased food consumption and body weight (Sheiner et al., 1985; Ookuma et al., 1993). The site of brain histamine-mediated suppression of food intake is probably the ventromedial hypothalamus (VMH), because H_1 receptors blockade within the VMH, but not in other hypothalamic nuclei such as the paraventricular hypothalamus (PVN) or lateral hypothalamus, increases both meal size and duration, and suppresses the activity of glucose-responding neurons (Fukagawa, 1989). The VMH contains glucose-responding neurons, has descending axonal projections to hindbrain regions that contain premotor sympathetic neurons, and was considered a satiety center. At present, this idea, however, is no longer sustained (King, 2006), because the

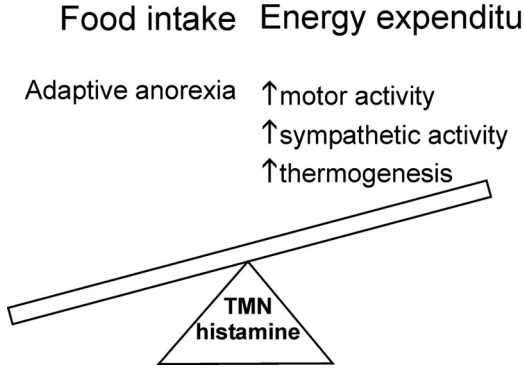

Fig. 1. Summary of the known effects of brain histamine on energy balance that results from decreased intake and increased spending.

VMH is seen as a somatomotor center for motivated behavior-related activity (Simerly, 2004). Intracerebral infusion of histamine inhibits the development of obesity in both diet-induced and *db*/*db* obese mice (Masaki and Yoshimatsu, 2006). These mice are hyperleptinemic and develop obesity and severe type 2 diabetes partly because of a functional defect in a leptin receptor. Brain histamine apparently also regulates body weight and adiposity by modulating peripheral energy expenditure. One of the markers of energy expenditure is the uncoupling protein 1 (Ucp1) present in brown adipose tissue. The expression of Ucp1 is regulated by humoral and neuronal factors. Central administration of histamine or H_1 receptor agonists increases the expression levels of Ucp1 mRNA in rodents' brown adipose tissue, whereas the central administration of histamine or the H_3 receptor antagonist thioperamide increases the lipolytic response in rodents' white adipose tissue. Pretreatment with a H_1 receptor antagonist blocks the thioperamide-induced response, suggesting that the effect is mediated by sympathetic nerves that innervate white adipose tissue (reviewed in Masaki and Yoshimatsu, 2006). TMN neurons are also essential for the increase in temperature during a motivated behavior, in part by acting on premotor sympathetic neurons in the raphe pallidus nucleus (Valdés et al., 2010) that promotes brown adipose tissue thermogenesis, and in part by increasing arousal, leading to increased motor activity and, altogether, to enhanced energy spending (Fig. 2). The appetitive and consummatory phases of feeding behavior that have been profitably distinguished involve very different brain and behavioral mechanisms. Behavioral or physiological challenges typically engage catabolic mechanisms with a predominance of sympathetic activation and energy-mobilizing functions. The appetitive phase of feeding is an example of a behavioral challenge, and it requires a high, yet optimal, arousal state, but the brain circuits that generate and orchestrate such a motivated behavior are not quite clear. The appetitive phase is characterized by increased arousal, which entails increased sensory, motor, emotional, and sympathetic responses that are normally initiated and controlled by hierarchically organized forebrain mechanisms. During the ingestive phase, in contrast, the parasympathetic system predominates, and its predominance usually goes with relative quiescence. Ingestion may be expressed in decerebrated adult rats (Grill and Kaplan, 2002), indicating that the basic mechanisms of consummatory behavior, such as low-level food acceptance/rejection, mastication, swallowing, and low-level satiety lie in the hindbrain. Histamine from the TMN influences the activity of other ascending activating nuclei, regulating the release of neurotransmitters such as dopamine, acetylcholine, and serotonin (Threlfell et al., 2004; Fox et al., 2005; Medhurst et al., 2007; Giannoni et al., 2010) and presumably it acts in concert with and complementary to reward systems and learning circuits to influence appetitive behaviors (Fig. 2).

Histamine-Induced Loss of Appetite Is an Adaptive Anorexia: A Working Hypothesis

The above-mentioned observations have suggested two different explanations for the anorectic effect of central histamine. One is that central histamine neurons may be part of a danger response system (Brown et al., 2001) that inhibits appetite to allow the animal to better concentrate on a more pressing situation. The other explanation is that histamine is a satiety signal that is released during eating (Sakata et al., 1997). To meet the criteria for a satiety signal, histamine should be released transiently after the onset of a meal. We used a behavioral protocol to clearly separate the appetitive from the consummatory phases of feeding, and we have shown that histamine is transiently released when rats are trying to obtain food, either by attempting to open a mesh container filled with food (Valdés et al., 2010) or pressing a lever in an operant conditioning box under a progressive ratio protocol (M.E. Riveros et al., personal communication). In contrast, eating easily available food was not accompanied by histamine release. These observations are making it clear that histamine release during feeding is better interpreted in the context of the appetitive phase of feeding behavior rather than in food consumption and satiety (Valdés et al., 2010). We proposed an expanded version of Brown et al.'s danger hypothesis (Brown et al., 2001). In this view, brain histamine

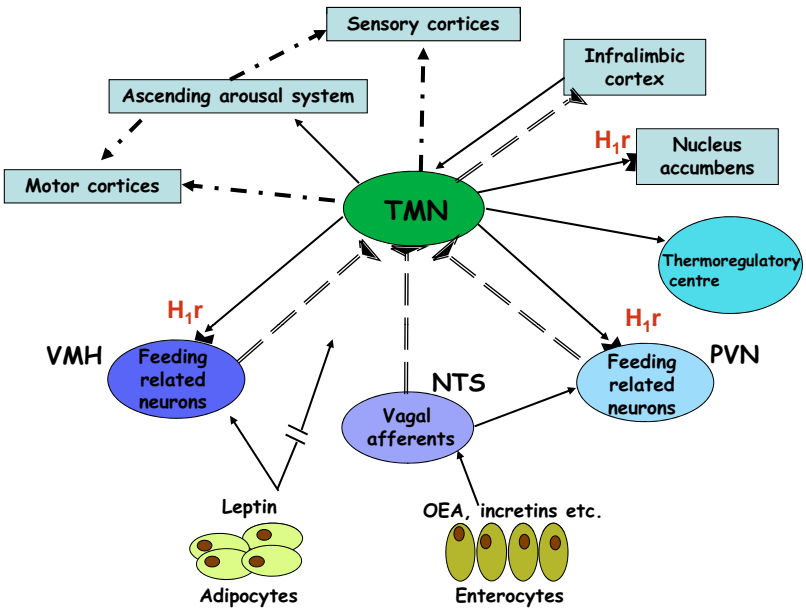

Fig. 2. Schematic drawing of some hypothesized actions of hypothalamic histamine neurons in feeding behavior. Histamine supposedly suppresses food intake via H_1 receptors expressed on feeding-related neurones in the VMH. According to Valdés et al. (2010), the infralimbic cortex manages the arousal and vegetative responses necessary for the correct unfolding of the appetitive behavior. The TMN provides the cortical arousal, characterized by increased sensory, motor, and emotional responsiveness and supposedly contributes to inducing thermal responses. H_1r, histamine H_1 receptor. Double lines indicate presumed connections between feeding-related centers and the TMN. Dot/dash lines indicate presumed connections between TMN and cortical areas probably involved in appetitive behavior.

is released during the appetitive phase of motivated behaviors, such as feeding (or eventually escaping from danger), resulting in increased arousal and sympathetic activity and decreased drive to consume food. In such a way, TMN activation under the control of the infralimbic cortical area (Valdés et al., 2006) and histamine release allow the optimal unfolding of a motivated behavior. This short-lived, adaptive anorexia is probably an important feature of motivated behaviors (Fig. 2).

Anorexia may also be a normal response to a variety of physiological or pathological conditions. An extensively studied physiological condition is the reliable and phasic decrease in food intake that follows the cyclic increase in estrogens in rodents and primates, including humans (Geary, 2004). Although several hypothalamic nuclei express estrogen receptors, it seems accepted that the ones expressed by the PVN mediate the anorectic effects of estradiol. Microinjections of estradiol induce anorexia only when administered into the PVN. No such effect was observed after microinjections into the VMH or the medial preoptic area. Furthermore, estradiol-induced suppression of feeding is partially attenuated in rats treated with α-FMH or mice with a genetic deletion of histamine H_1 receptors (Gotoh et al., 2009).

Interactions between Brain Histamine and Some Peptides that Control Feeding Behavior

Several peptides, such as orexin, leptin, glucagon-like peptide 1 (GLP-1), and thyrotropin-releasing hormone (TRH), or hormones, such as estradiol, function as satiety or hunger signaling molecules activating or silencing hypothalamic nuclei through, at least in part, the histaminergic system. Orexin-containing neurones intermingle partially with histaminergic neurons in the posterior hypothalamus. Histamine and orexin neurons exert different, but complementary, control on wakefulness, the former being more important for aspects of consciousness and cognitive functions, whereas the peptidergic neurons are involved primarily in behavioral arousal including muscle tone, locomotion, and emotional reactions (Anaclet et al., 2009). Perfusion of orexin A into rat TMN increases wakefulness (Huang et al., 2001) and stimulates food intake (Jorgensen et al., 2005), effects that depend on an intact histaminergic neuronal system that seems to involve a mechanism mediated by the H_1 receptor. Leptin provides a hormonal long-term adiposity signal, linking peripheral adiposity levels to the regulation of energy homeostasis in the brain. Leptin affects feeding behavior partially by activating histamine-containing neurons. Indeed, the administration of α-FMH to rats and mice decreases the leptin-induced suppression of food intake, and leptin-induced hypophagia is diminished in H_1 receptor-deficient mice (Yoshimatsu et al., 1999). PVN neurons release the anorexigenic TRH, directly activate the majority of TMN neurones (Parmentier et al., 2009), and increase histamine turnover (Gotoh et al., 2007). In food-deprived H_1-receptor knockout mice and histamine-depleted rats, TRH-induced suppression of feeding is significantly attenuated (Gotoh et al., 2007). GLP-1 is produced by and released from intestinal L cells in response to dietary fat and carbohydrates and is also expressed by neurons in the nucleus of solitary tract and ventrolateral medulla of the brainstem. GLP-1 reduces food intake by inhibiting gastric emptying, increasing satiety through central actions, and suppressing glucagon release. Hypothalamic neuronal histamine partially mediates the GLP-1-induced suppression of feeding behavior, because its anorexigenic effects are blunted by the pharmacological or genetic loss of H_1 receptor function (Gotoh et al., 2007). Using a more direct experimental approach, microdialysis in freely moving rats, it was found that the anorexiant oleoylethanolamide decreases both spontaneous and stimulated histamine release in the TMN and brain regions that receive histamine innervation and control appetitive behavior (Passani et al., 2009). On the other hand, orexigenic cannabinoid CB_1 receptor agonists augment histamine release in the TMN (Cenni et al., 2006) (Fig. 2). These observations further strengthen the argument that histamine is not a satiety signal. All together, these results further prove the intricacy of the histaminergic system as a regulator of food intake and energy metabolism, because both orexigenic and anorexigenic effects of endogenous molecules seem to necessitate the integrity of the histaminergic system.

H_3 Receptors and Feeding Behavior: Controversial Findings

Whereas there is no indication that H_2 receptor ligands affect eating behavior, it is unarguable that exogenous pharmacological manipulation of H_1 receptors affects food consumption in experimental animals. Translation to the clinic, however, is unattainable, because no brain-penetrating H_1 receptor agonists have been identified that would have anti-obesity effects. Hence, the growing interest in the histaminergic H_3 receptor as a potential target for developing anti-obesity drugs stems from the unavailability of selective H_1 receptor agonists devoid of peripheral action. The use of compounds that enhance histamine release from nerve terminals, such as H_3 receptor antagonists, may afford an effective therapeutic alternative. The role of H_3 receptor ligands in the treatment of metabolic diseases, however, is still unclear, because results from different studies are inconsistent, which is understandable in light of the above-mentioned complexity of the histaminergic system as a regulator of food intake and energy balance.

Several experimental observations in rodents seem to agree that blockade of hypothalamic H_3 receptors is beneficial in decreasing energy intake, body weight, and plasma triglycerides (Hancock and Brune, 2005; Malmlöf et al., 2005), whereas H_3 receptor agonists enhance feeding in rats (Chiba et al., 2009). Indeed, several studies have shown that H_3 receptor antagonists increase histamine release from the hypothalamus and reduce energy intake in normal and leptin-resistant mice with diet-induced obesity (Ishizuka et al., 2008). In addition, administration of H_1 receptor antagonists attenuates the feeding suppression induced by H_3 antagonists (Hancock and Brune, 2005). H_3 receptor takes part in the appetite signaling pathways; agonists reduce satiety induced by amylin (Lutz et al., 1996) or bombesin (Kent et al., 1997); whereas H_3 receptor antagonists attenuate the orexigenic effect of neuropeptide Y (Itoh et al., 1999) and enhance cholecystokinin-induced satiety. To our knowledge, there is no direct evidence that histamine or H_3 receptor ligands affect the hedonic value of food. Nonetheless, TMN neuronal activity increases in direct relation to the internal drive to obtain food as shown by rats enticed to obtain regular versus

stronger-tasting food (Valdés et al., 2010). Not all data, however, support an appetite-suppressant effect of H_3 receptor blockade. A report showed that in diet-induced obese mice an H_3 receptor agonist suppresses food intake and decreases body weight, presumably with a mechanism independent of histamine release modulation (Yoshimoto et al., 2006). In addition, H_3 receptor-deficient mice manifest disrupted regulation of body weight, energy expenditure, and food intake. H_3 receptor deletion produced obese hyperphagic mice with reduced energy expenditure, which resembles the phenotype of H_1 receptor-deficient mice (Takahashi et al., 2002). Why then does deletion of the H_3 receptor induce hyperphagia with reduced energy expenditure in mice? One possible explanation hypothesized by Takahashi et al. is that a concomitant down-regulation of the H_1 receptor in the hypothalamus of H_3 receptor-deficient mice leads to hyperphagia and obesity. It is clear that the effects of H_3 receptor modulators on food consumption and metabolism are more complex and not only mediated by histamine release, but they are regulated through a variety of receptors and neurotransmitters and may be responsible for the discrepancies described above. The role of the H_3 receptor activity in AAPD-induced weight gain remains speculative so far (Deng et al., 2010). In fact, coadministration of olanzapine with betahistine (an H_3 receptor antagonist and weak H_1 receptor agonist) to schizophrenic patients for 6 weeks produced a weight gain during the initial 2 weeks of the trial with no additional increase in weight or a minor reduction of body weight up to the sixth week of treatment (Poyurovsky et al., 2005). On the other hand, clozapine possesses moderately low H_3 receptor antagonistic properties (Schlicker and Marr, 1996), which is counterintuitive to its weight gain liability. It is important to remember, however, that H_3 heteroreceptor antagonism disinhibits the release of several neurotransmitters that may participate in the control of food consumption and energy balance in different manners. In addition, patients enrolled in clinical trials aimed at testing the efficacy of new H_3 receptor antagonists [e.g., pitolisant, (1*R*,3*R*)-*N*-ethyl-3-fluoro-3-[3-fluoro-4-(pyrrolidin-1-ylmethyl)phenyl]cyclobutane-1-carboxamide (PF-03654746), or MK-0249] in narcolepsy or attention-deficit hyperactivity syndrome did not report significant weight change (http://www.clinicaltrials.gov). Nonetheless, these compounds may turn out to be effective in treating eating disorders. In this regard, phase II clinical trials with SCH-497079 were recently completed to evaluate its effect on weight in obese and overweight subjects (http://www.clinicaltrial.gov). Given the substantial differences of the preclinical outcome and the discrepancies in clinical trials, considerable experimental effort remains necessary to prove the so far unclear concept of H_3 receptor antagonists in the treatment of obesity and weight gain. Certainly, the general profile of the more recently synthesized H_3 receptor ligands suggest that they may offer clinical advantages over currently used drugs or those used in the past for treating obesity. Considering the abuse and addiction of amphetamines, for instance, H_3 receptor antagonists lack stimulant and sensitization properties (Fox et al., 2003) and tend to show a gradual and prolonged decrease in body weight in contrast to the rapid and often quickly waning effect of other antiobesity drugs.

Concluding Remarks

Hypothalamic histamine neurons are involved in basic brain and body functions and link behavioral state and biological rhythms with vegetative and endocrine control of body weight and temperature. For as much as it may seem that the role of the histaminergic system is redundant in modulating the sleep-wake cycle, it is becoming clear that histamine in the brain finely orchestrates diverse aspects of behavioral responses that require an aroused state. Histamine plays a major role in many homoeostatic mechanisms, among them the regulation of energy expenditure, and also in higher integrative brain functions (Passani and Blandina, 2004). Novelty-induced attention and arousal are of major importance for adaptation to changing environments by comparing new information with the recollection of past events. This has a major impact on feeding behavior, because histamine supposedly drives food intake by increasing the arousal state of the animal, and secondary to arousing the animal, it coordinates satiety and the consolidation of temporal information associated with food consumption. The histamine H_3 receptor seems to have a role in food intake and body weight control because it is an autoregulator of histamine synthesis and release, as well as a heteroreceptor for neurotransmitter signaling pathways implicated in the regulation of feeding behavior. Histamine H_1 and H_3 receptor ligands have proven so far to be excellent pharmacological tools to learn how satiety signals affect brain circuits and histamine neurotransmission. Understanding the role of the histaminergic system in driving or modulating feeding behavior is of therapeutic relevance and may contribute to the development of more effective strategies for treating obesity and ameliorating the profile and side effects of centrally acting drugs.

Authorship Contributions

Participated in research design: Blandina and Torrealba.
Conducted experiments: Blandina and Torrealba.
Performed data analysis: Blandina and Torrealba.
Wrote or contributed to the writing of the manuscript: Passani, Bandina, and Torrealba.

References

Anaclet C, Parmentier R, Ouk K, Guidon G, Buda C, Sastre JP, Akaoka H, Sergeeva OA, Yanagisawa M, Ohtsu H, et al. (2009) Orexin/hypocretin and histamine: distinct roles in the control of wakefulness demonstrated using knock-out mouse models. *J Neurosci* **29:**14423–14438.

Brown RE, Stevens DR, and Haas HL (2001) The physiology of brain histamine. *Prog Neurobiol* **63:**637–672.

Cenni G, Blandina P, Mackie K, Nosi D, Formigli L, Giannoni P, Ballini C, Della Corte L, Mannaioni PF, and Passani MB (2006) Differential effect of cannabinoid agonists and endocannabinoids on histamine release from distinct regions of the rat brain. *Eur J Neurosci* **24:**1633–1644.

Chiba S, Itateyama E, Sakata T, and Yoshimatsu H (2009) Acute central administration of immepip, a histamine H_3 receptor agonist, suppresses hypothalamic histamine release and elicits feeding behavior in rats. *Brain Res Bull* **79:**37–40.

Clineschmidt BV and Lotti VJ (1973) Histamine: intraventricular injection suppresses ingestive behavior of the cat. *Arch Int Pharmacodyn Ther* **206:**288–298.

Deng C, Weston-Green K, and Huang XF (2010) The role of histaminergic H_1 and H_3 receptors in food intake: a mechanism for atypical antipsychotic-induced weight gain? *Prog Neuropsychopharmacol Biol Psychiatry* **34:**1–4.

Fox GB, Esbenshade TA, Pan JB, Radek RJ, Krueger KM, Yao BB, Browman KE, Buckley MJ, Ballard ME, Komater VA, et al. (2005) Pharmacological properties of ABT-239 [4-(2-[2-[(2*R*)-2-methylpyrrolidinyl]ethyl]-benzofuran-5-yl)benzonitrile]: II. Neurophysiological characterization and broad preclinical efficacy in cognition and schizophrenia of a potent and selective histamine H_3 receptor antagonist. *J Pharmacol Exp Ther* **313:**176–190.

Fox GB, Pan JB, Radek RJ, Lewis AM, Bitner RS, Esbenshade TA, Faghih R, Bennani YL, Williams M, Yao BB, et al. (2003) Two novel and selective nonimidazole H_3 receptor antagonists A-304121 and A-317920: II. In vivo behavioral and neurophysiological characterization. *J Pharmacol Exp Ther* **305:**897–908.

Fukagawa K, Sakata T, Shiraishi T, Yoshimatsu H, Fujimoto K, Ookuma K, and Wada H (1989) Neuronal histamine modulates feeding behavior through H_1-

receptor in rat hypothalamus. *Am J Physiol Regul Integr Comp Physiol* **256:**R605–R611.
Fulton S (2010) Appetite and reward. *Front Neuroendocrinol* **31:**85–103.
Garbarg M, Barbin G, Rodergas E, and Schwartz JC (1980) Inhibition of histamine synthesis in brain by α-fluoromethylhistidine, a new irreversible inhibitor: in vitro and in vivo studies. *J Neurochem* **35:**1045–1052.
Geary N (2004) The estrogenic inhibition of eating, in *Neurobiology of Food and Fluid Intake* (Stricker E and Woods S eds) pp 307–345, Kluwer Academic/Plenum Publishers, New York.
Giannoni P, Medhurst AD, Passani MB, Giovannini MG, Ballini C, Corte LD, and Blandina P (2010) Regional differential effects of the novel histamine H_3 receptor antagonist 6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)oxy]-*N*-methyl-3-pyridinecarboxamide hydrochloride (GSK189254) on histamine release in the central nervous system of freely moving rats. *J Pharmacol Exp Ther* **332:**164–172.
Giannoni P, Passani MB, Nosi D, Chazot PL, Shenton FC, Medhurst AD, Munari L, and Blandina P (2009) Heterogeneity of histaminergic neurons in the tuberomammillary nucleus of the rat. *Eur J Neurosci* **29:**2363–2374.
Gotoh K, Fukagawa K, Fukagawa T, Noguchi H, Kakuma T, Sakata T, and Yoshimatsu H (2007) Hypothalamic neuronal histamine mediates the thyrotropin-releasing hormone-induced suppression of food intake. *J Neurochem* **103:**1102–1110.
Gotoh K, Masaki T, Chiba S, Higuchi K, Kakuma T, Shimizu H, Mori M, Sakata T, and Yoshimatsu H (2009) Hypothalamic neuronal histamine signaling in the estrogen deficiency-induced obesity. *J Neurochem* **110:**1796–1805.
Grill HJ and Kaplan JM (2002) The neuroanatomical axis for control of energy balance. *Front Neuroendocrinol*. **23:**2–40.
Haas HL, Sergeeva OA, and Selbach O (2008) Histamine in the nervous system. *Physiol Rev* **88:**1183–1241.
Hancock AA and Brune ME (2005) Assessment of pharmacology and potential anti-obesity properties of H_3 receptor antagonists/inverse agonists. *Expert Opin Investig Drugs* **14:**223–241.
Huang ZL, Qu WM, Li WD, Mochizuki T, Eguchi N, Watanabe T, Urade Y, and Hayaishi O (2001) Arousal effect of orexin A depends on activation of the histaminergic system. *Proc Natl Acad Sci USA* **98:**9965–9970.
Ishizuka T, Hatano K, Murotani T, and Yamatodani A (2008) Comparison of the effect of an H(3)-inverse agonist on energy intake and hypothalamic histamine release in normal mice and leptin resistant mice with high fat diet-induced obesity. *Behav Brain Res* **188:**250–254.
Itoh E, Fujimiya M, and Inui A (1999) Thioperamide, a histamine H_3 receptor antagonist, powerfully suppresses peptide YY-induced food intake in rats. *Biol Psychiatry* **45:**475–481.
Jørgensen EA, Knigge U, Watanabe T, Warberg J, and Kjaer A (2005) Histaminergic neurons are involved in the orexigenic effect of orexin-A. *Neuroendocrinology* **82:**70–77.
Kent P, Plamondon H, and Merali Z (1997) Pharmaco-ontogeny of bombesin's suppression of food intake and its attenuation by histamine H_3 receptor agonists. *Brain Res Dev Brain Res* **102:**87–95.
Kim SF, Huang AS, Snowman AM, Teuscher C, and Snyder SH (2007) From the cover: Antipsychotic drug-induced weight gain mediated by histamine H_1 receptor-linked activation of hypothalamic AMP-kinase. *Proc Natl Acad Sci USA* **104:**3456–3459.
King BM (2006) The rise, fall, and resurrection of the ventromedial hypothalamus in the regulation of feeding behavior and body weight. *Physiol Behav* **87:**221–244.
Kroeze WK, Hufeisen SJ, Popadak BA, Renock SM, Steinberg S, Ernsberger P, Jayathilake K, Meltzer HY, and Roth BL (2003) H_1-histamine receptor affinity predicts short-term weight gain for typical and atypical antipsychotic drugs. *Neuropsychopharmacology* **28:**519–526.
Lecklin A, Etu-Seppälä P, Stark H, and Tuomisto L (1998) Effects of intracerebroventricularly infused histamine and selective H_1, H_2 and H_3 agonists on food and water intake and urine flow in Wistar rats. *Brain Res* **793:**279–288.
Li M and Cheung BM (2009) Pharmacotherapy for obesity. *Br J Clin Pharmacol* **68:**804–810.
Lutz TA, Del Prete E, Walzer B, and Scharrer E (1996) The histaminergic, but not the serotoninergic, system mediates amylin's anorectic effect. *Peptides* **17:**1317–1322.
Machidori H, Sakata T, Yoshimatsu H, Ookuma K, Fujimoto K, Kurokawa M, Yamatodani A, and Wada H (1992) Zucker obese rats: defect in brain histamine control of feeding. *Brain Res* **590:**180–186.
Malmlöf K, Zaragoza F, Golozoubova V, Refsgaard HH, Cremers T, Raun K, Wulff BS, Johansen PB, Westerink B, and Rimvall K (2005) Influence of a selective histamine H_3 receptor antagonist on hypothalamic neural activity, food intake and body weight. *Int J Obes (Lond)* **29:**1402–1412.
Masaki T and Yoshimatsu H (2006) The hypothalamic H_1 receptor: a novel therapeutic target for disrupting diurnal feeding rhythm and obesity. *Trends Pharmacol Sci* **27:**279–284.
Masaki T, Chiba S, Yasuda T, Noguchi H, Kakuma T, Watanabe T, Sakata T, and Yoshimatsu H (2004) Involvement of hypothalamic histamine H_1 receptor in the regulation of feeding rhythm and obesity. *Diabetes* **53:**2250–2260.
Medhurst AD, Atkins AR, Beresford IJ, Brackenborough K, Briggs MA, Calver AR, Cilia J, Cluderay JE, Crook B, Davis JB, et al. (2007) GSK189254, a novel H_3 receptor antagonist that binds to histamine H_3 receptors in Alzheimer's disease brain and improves cognitive performance in preclinical models. *J Pharmacol Exp Ther* **321:**1032–1045.
Minokoshi Y, Alquier T, Furukawa N, Kim YB, Lee A, Xue B, Mu J, Foufelle F, Ferré P, Birnbaum MJ, et al. (2004) AMP-kinase regulates food intake by responding to hormonal and nutrient signals in the hypothalamus. *Nature* **428:**569–574.
Morton GJ, Cummings DE, Baskin DG, Barsh GS, and Schwartz MW (2006) Central nervous system control of food intake and body weight. *Nature* **443:**289–295.
Ookuma K, Sakata T, Fukagawa K, Yoshimatsu H, Kurokawa M, Machidori H, and Fujimoto K (1993) Neuronal histamine in the hypothalamus suppresses food intake in rats. *Brain Res* **628:**235–242.
Parmentier R, Kolbaev S, Klyuch BP, Vandael D, Lin JS, Selbach O, Haas HL, and Sergeeva OA (2009) Excitation of histaminergic tuberomamillary neurons by thyrotropin-releasing hormone. *J Neurosci* **29:**4471–4483.
Passani M and Blandina P (2004) The neuronal histaminergic system in cognition. *Curr Med Chem* **4:**17–26.
Passani MB, Munari L, Benetti F, and Blandina P (2009) Oleoylethanolamide modulates histamine release in selected rat brain regions, in *Society for Neuroscience Meeting*; 2009 Oct 17–21; Chicago, IL. Society for Neuroscience, Washington, DC.
Poyurovsky M, Pashinian A, Levi A, Weizman R, and Weizman A (2005) The effect of betahistine, a histamine H_1 receptor agonist/H_3 antagonist, on olanzapine-induced weight gain in first-episode schizophrenia patients. *Int Clin Psychopharmacol* **20:**101–103.
Rinaldi-Carmona M, Barth F, Héaulme M, Shire D, Calandra B, Congy C, Martinez S, Maruani J, Néliat G, Caput D, et al. (1994) SR141716A, a potent and selective antagonist of the brain cannabinoid receptor. *FEBS Lett* **350:**240–244.
Sakata T, Yoshimatsu H, and Kurokawa M (1997) Hypothalamic neuronal histamine: implications of its homeostatic control of energy metabolism. *Nutrition* **13:**403–411.
Saper CB, Chou TC, and Elmquist JK (2002) The need to feed: homeostatic and hedonic control of eating. *Neuron* **36:**199–211.
Schlicker E and Marr I (1996) The moderate affinity of clozapine at H_3 receptors is not shared by its two major metabolites and by structurally related and unrelated atypical neuroleptics. *Naunyn Schmiedebergs Arch Pharmacol* **353:**290–294.
Sheiner JB, Morris P, and Anderson GH (1985) Food intake suppression by histidine. *Pharmacol Biochem Behav* **23:**721–726.
Simerly RB (2004) Anatomical substrates of hypothalamic integration, in *The Rat Nervous System* (Paxinos G ed), pp 335–368, Elsevier Academic Press, San Diego, CA.
Takahashi K, Suwa H, Ishikawa T, and Kotani H (2002) Targeted disruption of H_3 receptors results in changes in brain histamine tone leading to an obese phenotype. *J Clin Invest* **110:**1791–1799.
Threlfell S, Cragg SJ, Kalló I, Turi GF, Coen CW, and Greenfield SA (2004) Histamine H_3 receptors inhibit serotonin release in substantia nigra pars reticulata. *J Neurosci* **24:**8704–8710.
Valdés JL, Maldonado P, Recabarren M, Fuentes R, and Torrealba F (2006) The infralimbic cortical area commands the behavioral and vegetative arousal during appetitive behavior in the rat. *Eur J Neurosci* **23:**1352–1364.
Valdés JL, Sánchez C, Riveros ME, Blandina P, Contreras M, Farías P, and Torrealba F (2010) The histaminergic tuberomammillary nucleus is critical for motivated arousal. *Eur J Neurosci* **31:**2073–2085.
Yoshimatsu H, Itateyama E, Kondou S, Tajima D, Himeno K, Hidaka S, Kurokawa M, and Sakata T (1999) Hypothalamic neuronal histamine as a target of leptin action on feeding behavior. *Diabetes* **48:**2286–2291.
Yoshimoto R, Miyamoto Y, Shimamura K, Ishihara A, Takahashi K, Kotani H, Chen AS, Chen HY, Macneil DJ, Kanatani A, et al. (2006) Therapeutic potential of histamine H_3 receptor agonist for the treatment of obesity and diabetes mellitus. *Proc Natl Acad Sci USA* **103:**13866–13871.

Address correspondence to: Maria Beatrice Passani, Dip. Farmacologia Preclinica e Clinica, V.le G. Pieraccini 6, 50139 Firenze, Italy. E-mail: beatrice.passani@unifi.it