Chapter 15
Histamine and Appetite

Gustavo Provensi, Patrizio Blandina, and Maria Beatrice Passani

Abstract Our survival relies on the ability to search for food to attend immediate metabolic needs and to store excess energy in the form of fat to meet metabolic demands during fasting. Hunger and satiety are key factors driving eating behavior and are under control of a complex interplay of several central and peripheral neuroendocrine systems. Interest in the control of feeding has increased as a result of the obesity epidemic and rising incidence of metabolic diseases. The first evidence of the involvement of brain histaminergic system in the regulation of feeding dates back to the 1970s. Since then, many studies ensued, and up-to-date evidence suggests an inverse relationship between neuronal histamine and food intake. Preclinical studies demonstrated that brain histamine is released during both the appetitive and consummatory phases of feeding behavior and is also involved in the control of peripheral mechanisms regulating energy expenditure. Hypothalamic H_1 and H_3 receptors are crucial for the regulation of the diurnal rhythm of food consumption; furthermore, these receptors have been specifically recognized as mediators of energy intake and expenditure. All these features point for the histaminergic system as an attractive target for the development of new anti-obesity drugs. Unfortunately, so far, no selective brain-penetrating H_1 receptor agonists have been identified, and clinical trials of the potential H_3 receptor antagonists-induced weight loss did not meet up to the expectations or were interrupted. Not all is lost tough, recent clinical trials demonstrated the potential of betahistine (an H_1 agonist/H_3 antagonist) in opposing metabolic side effects associated with chronic antipsychotic treatment.

Keywords Histamine • Food consumption • Energy homeostasis • Body weight • Neuropeptides • H1 receptor • H3 receptor • Betahistine • Antipsychotics • Clinical trials

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15.1 Introduction

Body weight is tightly regulated by complex homeostatic mechanisms controlling the balance between food intake and energy expenditure; even subtle mismatches (less than 0.5 %) in this balance are sufficient to cause weight gain [1]. Thus, obesity can be defined as a state in which energy intake chronically exceeds energy expenditure and is widely recognized as a pervasive and fast-growing public health problem in many countries. In 2010, the World Health Organization estimated more than 700 million people worldwide are obese and nearly 2 billion people are overweight; thus, the neologism "globesity" was created to define the growing global epidemic of overweight and obesity [2]. The impact of morbidity and mortality associated with obesity on healthcare cost is also expected to rise with the increased incidence of obesity. Although prevention through education and changes in the lifestyle associated with psychological therapies are the first-line choices, this is not effective in all patients. A complementary strategy is the pharmacological therapy, but unfortunately, available anti-obesity drugs are scarce, and some were hastily withdrawn from market owing to their unacceptable side-effect burden [3].

Brain histamine plays a fundamental role in eating behavior. Animal studies have shown that brain histamine is released during the appetitive phase to provide a high level of arousal preparatory to feeding, but it also mediates satiety. Moreover, histamine regulates energy expenditure and regulates peripheral metabolic processes (Fig. 15.1). This chapter will provide an overview of the role of histamine and histaminergic receptors in feeding behavior and maintenance of body weight summarizing preclinical and clinical research and discuss the emerging clinical trials evaluating the potential utility of histaminergic compounds for the treatment of metabolic side effects associated with chronic antipsychotic treatment.

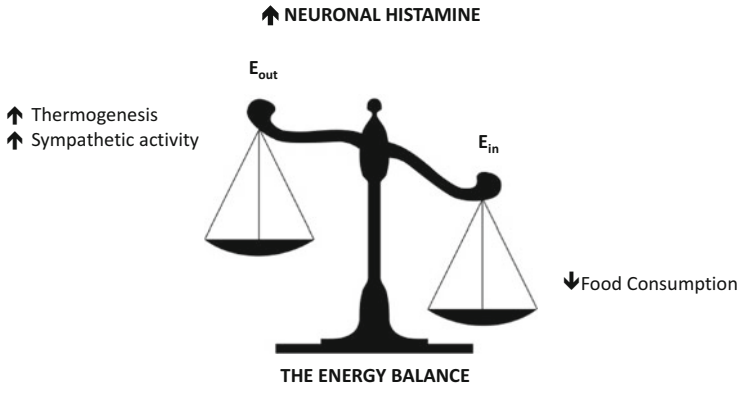

Fig. 15.1 Brain histamine affects both sides of the energy balance, by reducing energy intake (E_{in}) and increasing energy expenditure (E_{out})

15.2 Role of Histamine in Feeding and Weight Regulation

The first evidence of the inverse relationship between brain histaminergic activity and appetite dates back to 1973 when Clineschmidt and Lotti administered histamine into the lateral ventricle of cats and observed a long-term suppression of food intake [4]. Years later, a reduction on food intake was also observed when histamine was continuously infused into the suprachiasmatic nucleus of the hypothalamus [5] or acutely injected into the lateral ventricles [6] of rats. In analogy, systemic administration of the histamine precursor, L-histidine, [7–11] or the inhibitor of histamine catabolism, metoprine [12], also inhibited food consumption.

Conversely, restriction of neuronal histamine synthesis due to injections of the histidine decarboxylase (HDC) inhibitor alpha-fluoromethylhistidine (α-FMH) into the rat lateral ventricle increased significantly food consumption [13–15]. Bilateral microinfusion of α-FMH into the ventromedial hypothalamus (VMH) and the paraventricular nuclei (PVN) mimicked this effect, while injections into the lateral hypothalamus (LH), the dorsomedial hypothalamic (DMH), or the preoptic anterior hypothalamus (POAH) nuclei had no effect on food intake [14]. Histamine plays also an important role in regulating aspects of meal size and duration: depletion of histamine in the mesencephalic trigeminal sensory nucleus decreased the speed of meal consumption, whereas histamine depletion of VMH increased the amount of food they eat and the duration of feeding [16].

The generation of histidine decarboxylase gene knock-out (HDC-KO) mice, lacking functional HDC enzyme, and therefore unable to synthesize histamine [17] represented a very interesting tool to investigate the functions of endogenous histamine in the brain, including feeding behavior. Based on previous results, one could expect an obese phenotype for these animals, but surprisingly, no differences in caloric intake and body weight were observed between normal and histamine-deficient mice up to 11 weeks of age. Increases of 13 and 20 % in body weight were found in HDC-KO mice with respect to wild-type controls just at 16 and 30 weeks of age, respectively [18]. HDC-KO mice showed also an increased tendency to develop high-fat diet-induced obesity (DIO) when compared with wild-type littermates [19].

Neuronal histamine affects not only food intake but also regulates feeding circadian rhythms. Sustained infusion of α-FMH into the lateral ventricle disrupted light–dark cycles of feeding, drinking, and ambulatory activity in rats fed ad libitum [20]. It is known that food availability is a powerful circadian signal; thus, when food availability is restricted to a predictable time of the day, animals show increased motor activity and food searching behaviors before the anticipated daily meal, reflecting a state of increased arousal, related to an enhanced feeding motivation [21]. The involvement of the histaminergic system in feeding-induced arousal was demonstrated by a cluster-specific activation of neurons in the E3 subdivision of the histaminergic tuberomammillary nucleus (TMN) immediately before meal time in food-restricted rats under a scheduled feeding [22–24]. Furthermore, hypothalamic histamine increased when hungry rats were challenged to open a mesh container filled with palatable food [25]. On the contrary, rats fed ad libitum were not inter-

ested in the food, remained in quiet wake or sleeping during enticing, and showed no changes in histamine concentration [25]. Hence, in these experimental settings, increased activity of histaminergic neurons parallels a situation of arousal induced either by the expectation of food or the attempt to open the box with the food during enticing; thus, it is linked to the appetitive phase of feeding behavior.

There is also consistent evidence indicating that histamine regulates the consummatory phase of feeding behavior, as demonstrated by the transient but significant increase of histamine release in the hypothalamus when 24-h fasted rats were fed [26, 27]. When an animal eats, the oral cavity receives a variety of sensory information from food, such as taste and texture. Elegant studies demonstrated that the gustatory information can modulate the histaminergic activity by two mechanisms: the physiological excitation of the chorda tympani nerve, one of the taste nerves [28] and emotions elicited by taste perception, i.e., taste palatability [29]. Treesukosol and coworkers showed that adverse and hazardous taste stimuli like NaCl, HCl, or quinine caused significant increases in histamine release in the hypothalamus. On the other hand, histamine release was decreased by sucrose and saccharin solutions [29]. In rodents, chemicals that are described by humans as "bitter" or "nauseous" are rejected, while those described as "sweet" or "pleasurable" by humans are avidly accepted [30]. Therefore, it was postulated that histamine increase is related to aversive taste stimuli, but not to palatable tastes. Moreover, these findings suggest the possibility that palatable food blunts histamine release which results in overeating it [27]. Not only taste perception but also sensory information related to food texture can influence histaminergic activity. As an example, Ishizuka and colleagues [31] observed increased histamine release from the amygdala when rats were fed hard pellets, while no significant differences were observed when the animals ate soft pellets.

15.3 Role of Histaminergic Receptors in Feeding and Weight Regulation

Histamine exerts its actions through the activation of distinct subtypes of G-protein-coupled receptors. To date, four histamine receptor subtypes were identified, namely: H_1R, H_2R, H_3R, and H_4R [32]. The involvement of the different histaminergic receptors on feeding regulation was extensively studied and, so far, a major role for H_1 and H_3 receptors acting at hypothalamic nuclei was identified.

In an interesting study, Haq and coworkers investigated the effects of dietary composition (quantity and quality of proteins and energetic level) on voluntary food intake and H_1 receptor expression in the whole rat brain [33]. High concentration of H_1 receptors, as assessed with binding assays on tissue homogenates, was associated with decreased food intake of rats fed with a low-protein diet. On the other hand, rats that received a low-energy diet displayed reduced H_1 receptor concentration that was associated with increased food intake [33]. Subsequent pharmacological studies demonstrated that centrally administered H_1 receptor agonists suppressed, whereas injection of H_1 receptor antagonist elicited food intake in rats [20, 34–41]. The effects

of H_1 receptor antagonists seem to be site-specific, since microinfusions of these compounds locally into the VMH or PVN, but not into the LH or DMH, elicited feeding responses and increased both meal size and duration [40–42]. In keeping with the pharmacological manipulations of the H_1 receptor, genetically modified H_1R-KO mice exhibit an increase in daily food consumption and visceral adiposity [43], increased hepatic steatosis, hyperglycemia, and insulin resistance when fed with a high-fat diet [44].

Most experimental observations in rodents seem to agree that blockade of brain H_3 receptor is beneficial in decreasing energy intake, body weight, and plasma triglycerides [45–47]. Indeed, there are evidences demonstrating 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 (reviewed in [45, 46]). In addition, administration of H_1 receptor antagonists attenuates the feeding suppression induced by H_3 antagonists [48]. Moreover, H_3 antagonists attenuate the orexigenic effect of neuropeptide Y (NPY) [49, 50] and enhance cholecystokinin (CCK)-induced satiety [51]. On the other hand, experiments with H_3 receptor agonists have provided mixed results. Activation of H_3 receptors increased food intake when administered intraperitoneally to mice [19], but failed to induce such an effect when centrally infused in rats [52]. However, despite the lack of effects per se, H_3 receptor agonists *R*-α-methylhistamine and imetit reduced satiety induced by amylin [53], bombesin [54] or CCK [51].

Not all data support an appetite-suppressant effect induced by H_3 receptor blockade. In diet-induced obese mice, Yoshimoto and colleagues reported that H_3 receptor activation reduced, whereas H_3 receptor antagonism increased food intake and body weight but presumably with a mechanism independent of histamine release [55]. In another study, Sindelar and coworkers observed that in spite of the administration route (oral or intraperitoneal) that produces similar pharmacokinetic profile, H_3 receptor occupancy and histamine turnover, thioperamide reduced food intake and conditioned place aversion in i.p.-treated animals only. The authors claim that blockade of central H_3 receptors does not play a direct role in decreasing food intake or altering energy homeostasis [56]. However, these data are hard to reconcile with studies in which i.c.v. administration was effective in reducing food consumption in a pathway clearly dependent on an intact histaminergic system [35].

Findings with H_3R-KO mice are also controversial. Toyota and colleagues described parallel growth curves for H_3R-KO and wild-type littermates, with the H_3R-KO animals displaying a slightly lower, but not significantly different, average body weight [57]. Conversely, Takahashi and coworkers demonstrated that H_3R-KO mice have a disrupted regulation of body weight, energy expenditure, and food intake resulting in obese hyperphagic mice with reduced energy expenditure that resembles the phenotype of H_1R-KO [58]. Such phenotype appears a paradox because one could expect that without presynaptic histamine receptors, inhibition of histamine synthesis and release would escape tonic control resulting in overstimulation of postsynaptic H_1 receptor and concomitant reduction of food intake. However, the authors found increased histamine concentration in the hypothalamus of H_3R-KO mice and proposed that elevated histamine content could desensitize H_1R resulting in hyperphagia [58]. Considering these data, it is clear that the effects of H_3R 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.

Nonhibernating seasonal mammals have adapted to temporal changes in food availability through behavioral and physiological mechanisms to store food and energy during times of predictable plenty and conserve energy during predicted shortage. Siberian hamsters (*Phodopus sungorus*) are seasonal animals that survive a winter climate by making adaptations in physiology and behavior, like reduced food intake and increased catabolism of fat reserves resulting in a natural loss of body weight [59]. Barrett and colleagues showed that H_3 receptor mRNA expression in the posterior hypothalamus is significantly decreased when animals are in a lean state during the short-day photoperiod of winter. After switching from an inhibitory short-day photoperiod to a stimulatory long-day photoperiod, increased expression of H_3 receptor occurs relatively rapidly along with body weight recovery [60]. Further studies demonstrated that administration of the H_3 receptor agonist imetit increased, whereas treatment with the H_3 receptor antagonists clobenpropit and thioperamide decreased food intake in hamsters in the lean state [61]. Differences in H_3 receptor mRNA expression were also described in golden hamster (*Mesocricetus auratus*) with a strong expression in the cortex and hippocampus of pubertals and in amygdalar areas of hibernating adult hamsters. Interestingly, thioperamide induced significant reduction of food intake in adults, but not in pubertals [62].

In contrast with H_1 receptor and H_3 receptor, there are few works using H_2 receptor ligands. Most studies demonstrate that treatment with either H_2 receptor agonist or antagonists had no effects in food consumption [38–41, 52]; therefore, H_2 receptor seems not to be involved in the regulation of feeding behavior.

15.4 Role of Histamine in Energy Homeostasis

Brain histamine affects both sides of the energy balance: by decreasing food intake and increasing expenditure [63] (Fig. 15.1). Maintenance of core temperature represents a major energy expenditure of a homeothermic organism and uncoupling proteins like UCP1 plays a central role in regulating energy expenditure and thermogenesis in rodents and neonates of larger mammalian species, including humans [64]. Infusion of histamine in the lateral ventricle or in the preoptic area, but not in the lateral hypothalamus or the ventromedial hypothalamic nucleus, caused upregulation of UCP1 mRNA expression in brown adipose tissue (BAT) and increased electrophysiological activity of sympathetic nerves that innervate it [43, 65] suggesting that the preoptic area is the principal locus of histaminergic modulation of thermogenesis. Interestingly, histamine-deficient animals have an impaired ability to express UCP1 in BAT [18], further suggesting a role of histamine signaling in the control of energy expenditure. Central administration of histamine or the H_3 receptor antagonist thioperamide increased the lipolytic response in white adipose tissue, whereas pretreatment, with a propranolol, beta-receptor antagonist, blocked the thioperamide-induced response, suggesting that the effect is mediated by

sympathetic nerves that innervate white adipose tissue [66]. Furthermore, Kimura and coworkers recently proposed that central histamine downregulates hepatic gluconeogenic gene expression by activating H_1 receptors [67].

Histamine released in peripheral organs presumably is involved in metabolic and homeostatic processes related to food intake, but evidence is circumstantial. Intestinal mucosal mast cells are activated and degranulated to release histamine and other mediators to the circulation during fat absorption [68]. H_1 receptor signaling in the central nervous system (CNS), as well as in the pancreatic tissue regulates glucose metabolism, whereas H_2 receptor activation appears to be related to a peripheral action in the liver and skeletal muscles via the adiponectin system that regulates both lipid and glucose metabolisms [44].

15.5 Interactions Between Brain Histamine and Hormones that Control Feeding Behavior

The gastrointestinal tract and adipose tissue release more than 20 different hormones that regulate diverse physiological processes. In addition to local paracrine actions and peripheral endocrine effects, these hormones play a pivotal role relaying information on nutritional status to important appetite controlling centers within the CNS, such as hypothalamus and the brain stem, which integrates this peripheral information with brain signals (e.g., reward and mood) and contribute to regulate feelings of hunger and satiety [69, 70]. Thus, a very complex network of central and peripheral stimuli interacts to regulate feeding behavior, and brain histamine seems to act as a relay station integrating peripheral signals and central functions.

Leptin is predominantly secreted by adipocytes with circulating levels proportional to fat mass [71]. Both central and systemic administrations of leptin significantly increase central histamine availability [72], and serum leptin levels are highly elevated in HDC-KO mice [73]. Conversely, levels of hypothalamic histamine are reduced in high-fat diet-induced obesity (DIO) and diabetic mice due to leptin receptor point mutation (*db/db*) [74]. Accordingly, leptin-induced suppression of food intake was significantly attenuated in α-FMH-treated [75, 76] and H_1R-KO mice [72, 77]. Leptin-induced increase in UCP1 and UCP3 expressions of brown (BAT) and white (WAT) adipose tissues, respectively, were attenuated in H_1R-KO mice [66]. Increase in food intake and body weight observed in DIO and *db/db* mice was reversed by chronic i.c.v. infusion of histamine [77]. Histamine effect was attenuated when H_1 receptor expression was additionally disrupted in DIO and *db/db* mice [77].

Leptin also stimulates pro-opiomelanocortin (POMC) neurons, and POMC activates melanocortin-4 receptors (MC4Rs). Agouti yellow (A^y/a) mice develop obesity because they overexpress agouti-related protein, a physiological MC4R antagonist. Interestingly, administration of histamine (i.c.v.) to obese (A^y/a) mice reduced food intake and body weight and increased UCP1 expression in BAT. All these effects were attenuated in H_1R-deficient (A^y/a) obese mice [78].

The hypophagic effect of Glucagon-like peptide-1 (GLP-1) seems to be mediated, at least in part, by the neuronal histaminergic system. Central infusions with GLP-1 augmented the histamine turnover in the hypothalamus and induced hypophagic effect, which was partially attenuated in histamine-deprived rats [79].

Thyrotropin-releasing hormone (TRH) is secreted by neurons in the hypothalamic PVN. It suppresses food intake, activates the TMN neurons [80], and increases histamine turnover in the hypothalamus [81]. In food-deprived H_1R-KO mice and acute histamine-depleted rats, TRH-induced suppression of feeding is significantly attenuated [81]. Similar observations were reported for the anorectic effect of i.c.v. neurotensin [82] and nesfatin-1 [83]. The anorexic effect of the neuropeptide nesfatin-1 was partially attenuated in rats administered with α-FMH and in H_1R-KO mice. Nesfatin-1 central injection increased histamine turnover, vice versa histamine centrally injected increased nesfatin-1 expression in the hypothalamus. Moreover, immunohistochemical analysis revealed H_1R expression on nesfatin-1 neurons in the PVN, and nesfatin-1 expression was significantly reduced in the hypothalamus of H_1R-KO mice as compared to wild-type littermates [83].

Estrogen inhibits food intake in mice, and consequently, ovariectomy results in hyperphagia and weight gain. This mechanism is also involved in the increased incidence of obesity in postmenopausal women. Interestingly, estrogen receptor α (Esα) is expressed on histaminergic neurons, and the anorexic effect of estrogen is attenuated in H_1R-KO mice. Moreover, estrogen supplementation completely reversed the effect of ovariectomy on weight gain and food intake in the wild type, but this response was attenuated in H_1R-KO mice [84].

Histamine and orexin neurons exert different, but complementary, controls on wakefulness: the former being more important for aspects of consciousness and cognitive functions, whereas the latter is involved primarily in behavioral arousal, including muscle tone, locomotion, and emotional reactions [85]. There is a close and reciprocal anatomical connection between histaminergic and orexinergic neurons. In vitro, orexin strongly excites TMN neurons [86]. Perfusion of orexin A into TMN increased histamine release from both the medial preoptic area and the frontal cortex and promoted wakefulness [87] in rats. When injected into the lateral ventricles, orexin A produces a significant increase in wakefulness [87], stimulates food intake, and upregulates mRNA expression of the orexigenic neuropeptide Y (NPY) in the wild type, but not in H_1R-KO mice [19]. Indeed, NPY mRNA expression was fourfold upregulated in H_1R-KO mice as compared with wild-type controls [19]. A delayed and short-lasting histamine release in rats and increased food intake to a much greater extent in H_1R-KO mice than in wild-type controls were observed after NPY i.c.v. injection suggesting that histamine may act on NPY system in a negative feedback loop downregulating NPY-stimulated food intake [88].

We recently reported a functional interaction between brain histamine and the endogenous lipid messenger oleoylethanolamide (OEA) [89]. OEA mediates fat-induced satiety by engaging sensory fibers of the vagus nerve that project centrally to the nucleus tractus solitarius (NTS). It was recently shown that noradrenergic NTS–PVN projections are involved in the activation of the hypothalamic oxytocin system [90, 91], and pharmacological blockade of oxytocin receptors in the brain prevents OEA anorexic effects [92]. We observed that in histamine-deficient mice,

OEA-induced hypophagia was significantly attenuated; thus, our hypothesis is that OEA induces anorexia indirectly stimulating also histamine neurons. We speculated that the nucleus of the solitary tract (NTS) adrenergic fibers projecting to the TMN disinhibit histaminergic neurons through α_2A adrenoceptor-mediated mechanism (Fig. 15.2). OEA also increased c-Fos expression in a subgroup of TMN neurons and increased histamine release from the cortex of hungry mice [89]. As histamine neurons send broad projections within the CNS that are organized in functionally distinct circuits impinging on different brain regions, it is conceivable that OEA indirectly increases histamine release in the PVN where activation of H_1 receptors stimulate oxytocin release [93]. Accordingly, we observed that OEA-induced activation of oxytocic neurons in the PVN was blunted in histamine-deficient mice, an observation that could account for the inefficacy of OEA in these animals.

All together, these observations further prove the complexity of the histaminergic system as a regulator of food intake and energy metabolism, as both orexigenic and anorexigenic effects of endogenous molecules appear to require the integrity of the central histaminergic system.

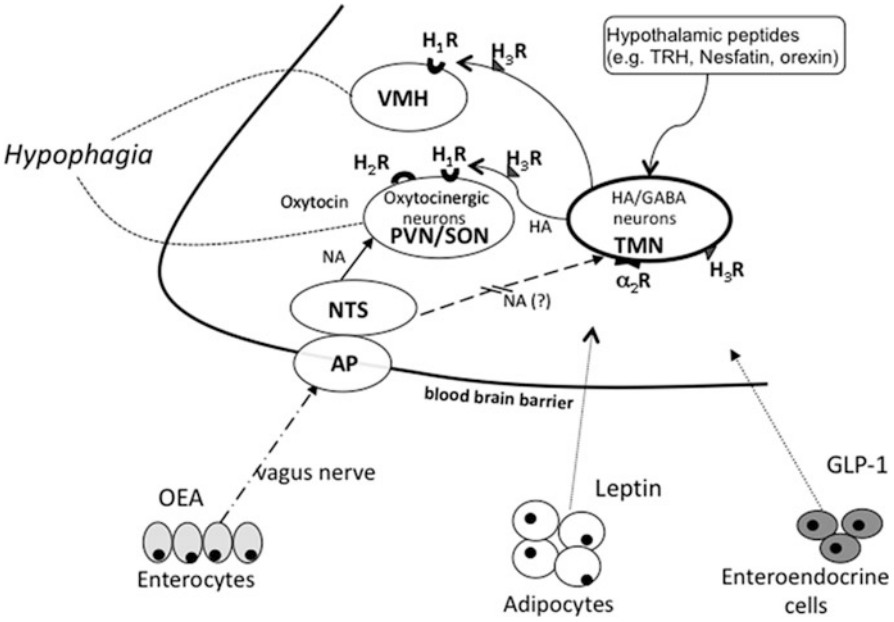

Fig. 15.2 Schematic drawing illustrating the putative interactions between hypophagic hormones and the central histaminergic system. Histaminergic neurons are exclusively localized in the tuberomammillary nucleus (TMN) of the posterior hypothalamus. The *broken lines* designate presumed noradrenergic excitatory projections from the nucleus of the solitary tract (NTS) to the TMN. Several hormones directly or indirectly activate TMN histaminergic neurons and result in increase of histamine release in the TMN itself and also in the hypothalamic projection areas, where histamine by activating H1 and H2 receptors on feeding-related neurons mediates suppression of food intake

15.6 Brain Histamine and Eating Disorders: Clinical Studies

Recently, human studies are beginning to provide evidence that the pharmacological manipulation of the histaminergic system affects weight gain and body mass index. Ratliff and colleagues, using data available from the 2005 to 2006 National Health Examination Survey, described a relationship between the use of H_1 antihistamines (cetirizine, fexofenadine, and desloratadine) and an increased risk of obesity in US adults as compared with age- and gender-matched, healthy controls. Furthermore, H_1 antihistamine use was associated with higher plasma insulin concentrations [94]. In this regard, it was recently demonstrated that chronic administration of cetirizine or fexofenadine worsened progression of hepatosteatosis in mice that had been fed a high-fat diet; this effect was associated with significantly increased levels of glucose and hepatic bile acids [95]. These drugs have low affinity for muscarinic receptors that contribute to glucose metabolism via activation of vagal efferents. Hence, the homeostatic and metabolic effects of H_1 antihistamines are presumably due to their affinity for H_1 receptors both in the brain, despite poor brain penetration of these drugs, and in the periphery.

Results from preclinical studies suggest the H_1 receptor as a useful target for the development of new anti-obesity drugs, but from a therapeutic standpoint, though, no brain-penetrating H_1 receptor agonists have been identified devoid of intolerable peripheral side effects involving the cardiovascular, respiratory, or gastrointestinal systems. Therefore, the use of compounds that enhance histamine release from nerve terminals, such as H_3 receptor antagonists/inverse agonists, afforded an alternative strategy. Despite the encouraging preclinical results, though, clinical trials with H_3 receptor antagonists were disappointing. Patients enrolled in clinical trials to test the efficacy of other H_3R antagonists (pitolisant or MK-0249) in narcolepsy [96], attention-deficit/hyperactivity disorder [97], schizophrenia [98], or epilepsy [99] did not report significant weight changes. Nonetheless, these compounds may turn out to be effective in tests evaluating specifically eating disorders. For instance, a multicenter, randomized, placebo-controlled phase II clinical trial that evaluated the efficacy of the H_3 receptor antagonist SCH 497079 on weight loss in obese and overweight subjects was recently completed, but the results were not disclosed (www.clinicatrials.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 [46].

Not only in obesity, alterations in the central histaminergic system were found also in other eating disorders. Positron emission tomography revealed in female anorexia nervosa patients an increase of [^{11}C]doxepin binding potential in the amygdala and lentiform nucleus when compared to healthy female controls [100]. This is a very interesting result because the amygdala certainly plays an important role in emotional responses [101], and histamine facilitates anxiety via H_1R in the rat amygdala [102], but further studies, particularly in patients who have recovered from anorexia nervosa, are needed to clarify if and how higher binding potential of [^{11}C]doxepin are involved in anorexia nervosa.

15.7 Betahistine: A New Strategy to Prevent Antipsychotic-Induced Weight Gain

The inconsistent results obtained with H_3R antagonists prompted researchers to change strategy and evaluate the effect of betahistine, a structural analog of histamine that combines H_1 receptor agonist and H_3 receptor antagonist properties [103] in weight control. An early study showed that acute treatment of pigmy goats with betahistine inhibited food intake and increased satiety [104]. In humans, betahistine is used in the symptomatic treatment of vestibular disorders with a remarkable safety profile that indicates that it does not cause cardiovascular, respiratory, or gastrointestinal side effects. Betahistine is orally available and readily penetrates the central nervous system [105]. These properties encouraged clinicians to examine the effects of acute and chronic regime in obese patients.

The acute effects of various doses of betahistine (48, 96, or 144 mg) on food intake and appetite were examined in a proof-of-concept, randomized, placebo-controlled study in obese, otherwise healthy women (BMI of 30–39.99 kg/m^2). Contrary to preclinical results, no significant effects of betahistine were observed in this cohort of obese women [106]. Another study evaluated weight loss and other parameters (e.g., blood pressure) during a 12-week treatment period, in an obese multiethnic population. The study reported no significant weight loss with betahistine; however, a post hoc subgroup analysis revealed a significant effect on body weight with minimal adverse effects only in women below 50 years of age [107].

Within the last 20 years, there has been a striking increase in the incidence of obesity and metabolic disorder in schizophrenic patients [108] associated with some first- and second-generation antipsychotic agents [109] that account for patients' non-compliance with these medications and increase the risk of obesity-related complications [110]. The pathophysiological mechanisms underlying antipsychotic-induced weight gain are yet to be elucidated, but the histaminergic neurotransmitter system has certainly a key role [111, 112]. For instance, olanzapine and clozapine that exhibit the highest binding affinities for the histamine H_1 and muscarinic receptors (reviewed in [113]) are associated with the greatest weight gain and metabolic impairments, including increased fasting glucose, insulin, and triglycerides. Thus, despite the disappointing results in obese patients, clinical research in schizophrenics treated with atypical antipsychotics with propensity to induce weight gain is continuing [114]. Poyurovsky and colleagues were the first to report the beneficial effects of betahistine treatment in three patients hospitalized for a first episode of schizophrenic disorder. Betahistine at the dosage used to treat vertigo was coadministered with olanzapine for 6 weeks. Although the lack of placebo controls precludes definitive conclusions, all patients after an initial weight gain during the first 2 weeks had no additional increments, suggesting a stabilizing effect of betahistine [115]. More recently, the same authors used a combination treatment with reboxetine, a selective norepinephrine reuptake inhibitor and betahistine to evaluate the olanzapine-induced weight gain in a small cohort of schizophrenic patients [116]. Compared to olanzapine/placebo-treated controls, patients in the combination therapy gained significantly less

weight. It remains to be established if the combination reboxetine/betahistine offers a therapeutic advantage over betahistine alone. In this regard, the administration of betahistine in an animal model of olanzapine-induced weight gain was associated with decreased food intake and curbed weight gain [117]. These results open the possibility that betahistine might exert weight-mitigating effects also in patients affected by other pathologies associated with obesity (e.g., diabetes mellitus) and reduce metabolic parameters relevant to weight gain.

The promising effect of betahistine in preventing the metabolic side effects induced by atypical antipsychotic, but not in healthy obese patients may have to do with changes of the histaminergic system in the brain of people affected by schizophrenia, or plausibly obesity. The level of tele-methylhistamine, the histamine metabolite that mirrors histamine release, is increased in the cerebrospinal fluid of individuals with schizophrenia [118], although the relevance of this observation needs to be determined.

A significant association between genetic variants of H_1 receptors (rs346074–rs346070) and BMI/obesity has been identified in non-affective, psychotic disorder patients treated with high H_1 receptor affinity antipsychotic olanzapine, clozapine, and quetiapine [119]. Postmortem studies found reduced H_1 receptor binding in the frontal and prefrontal cortex and in the cingulate gyrus of individuals with schizophrenia [120], whereas H_3 receptor binding, as measured by receptor radioligand binding autoradiography, was increased in the dorsolateral prefrontal cortex but unchanged in the temporal cortex of patients with schizophrenia compared with the same brain regions in healthy control subjects [121]. These differences, though, may reflect structural abnormalities of the cortical network and change in cellular composition that underlies the functional impairments in this disorder. However, they may merely represent cytological adaptations in response to pharmacological treatment. It remains to be established if the morphological features of the histaminergic system in the brain of schizophrenic patients are responsible for the suggested beneficial effects of betahistine. Regarding obese patients, though, to our knowledge, there are no published data that correlate modifications of the histaminergic system with weight gain or dysmetabolic pathologies.

In light of these observations, several parameters were studied to understand the effect of betahistine in antipsychotic-induced metabolic disorders. Recently, it was shown in rats that both subchronic (2 weeks [122]) and chronic (up to 4 weeks [123]) betahistine co-treatment prevented olanzapine-induced weight gain and fat mass and regulated feeding efficiency. In addition, co-treatment with betahistine reverted or prevented olanzapine-induced cellular changes, such as increased expression of hypothalamic H_1 receptor, of pAMPK that senses cellular energy status [124]. Betahistine also prevented chronic olanzapine-induced decreased in the expression of UCP1 and PGC-1a [125], two biomarkers of thermogenesis in the BAT. These last observations suggest that betahistine may reduce olanzapine-induced weight gain and metabolic changes by modulating the hypothalamic H_1R-AMPK/BAT-UCP1-PGC-1a pathway. One possible mechanism of action is that histaminergic neurons stimulate the PVN or other hypothalamic nuclei to release peptides that in turn signal to the BAT by activating sympathetic nerves [126].

Therefore, during treatment with second-generation antipsychotics, hypothalamic H_1 receptor antagonism not only increases appetite but also reduces thermogenesis, presumably by inhibiting sympathetic outflow to the brainstem rostral raphe pallidus and rostral ventrolateral medulla. In addition to central effects, blocking peripheral H_1 receptors may contribute to fat accumulation by decreasing lipolysis and increasing lipogenesis in white adipose tissue. Also, H_1 receptor blockade in the liver and pancreatic tissue will contribute to the onset of metabolic disorders (see [111] for a review). We may attempt to provide a mechanistic explanation for the effects of betahistine. It is a weak H_1 agonist and a more potent H_3 antagonist that enhance histamine neuron activity [127] and histamine synthesis within the TMN [128]. Antagonists of the H_3 receptor decrease food intake in several mammalian species. Therefore, the pharmacodynamic profile of betahistine may be responsible for preventing antipsychotic-induced metabolic side effects. As a weak H_1 receptor agonist, betahistine would compete with antipsychotics for binding to this same receptor, both in the CNS and in peripheral organs, whereas antagonism at the H_3 receptor would increase brain histamine release to curb appetite.

Concluding Remarks

More than 30 years have elapsed from the major discoveries that convinced the scientific community of the role of histamine as a neurotransmitter. Since then, many studies ensued, and it is now clear that brain histamine affects a variety brain functions: wakefulness, arousal, circadian rhythms, motor behavior, emotionality, and cognition [129, 130]. Brain histamine plays a central role in body weight maintenance by modulating both sides of the energy balance: decreasing food intake and increasing energy expenditure [63]. The paraventricular and ventromedial hypothalamic nuclei seem to be the brain sites where histamine, through mechanism involving H_1 and H_3 receptors, regulates food consumption. Moreover, histamine plays a major role in higher integrative brain functions, as arousal and cognition [130, 131]. 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 [46]. Encouraging results are emerging from clinical trials using betahistine, a mixed H_1 receptor agonist and H_3R antagonist, in the prevention of antipsychotic-induced weight gain. Therefore, we believe that understanding the actions of neuronal histamine especially at the hypothalamic circuits that control food intake and energy spending may be an important step toward the development of new pharmacotherapeutic approaches to the treatment of eating-related disorders.

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