Targeting Histamine and Histamine Receptors for the Precise Regulation of Feeding

Yanrong Zheng and Zhong Chen

Contents

Abstract Histamine has long been accepted as an anorexigenic agent. However, lines of evidence have suggested that the roles of histamine in feeding behaviors are much more complex than previously thought, being involved in satiety, satiation, feeding motivation, feeding circadian rhythm, and taste perception and memory. The functional diversity of histamine makes it a viable target for clinical management of obesity and other feeding-related disorders. Here, we update the current knowledge about the functions of histamine in feeding and summarize the underlying molecular and neural circuit mechanisms. Finally, we review the main clinical studies about the impacts of histamine-related compounds on weight control and discuss insights into future research on the roles of histamine in feeding. Despite the recent progress in

Y. Zheng and Z. Chen (✉)
Key Laboratory of Neuropharmacology and Translational Medicine of Zhejiang Province, School of Pharmaceutical Sciences, Zhejiang Chinese Medical University, Hangzhou, China
e-mail: chenzhong@zju.edu.cn

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histamine research, the histaminergic feeding circuits are poorly understood, and it is also worth verifying the functions of histamine receptors in a more spatiotemporally specific manner.

Keywords Feeding behaviors · Feeding circadian rhythm · Feeding motivation · Histamine · Histamine receptors · Satiety · Taste perception

Eating a reasonable diet provides sufficient energy and balanced nutrients for maintaining a healthy body. However, thousands of people are troubled or even tortured by uncontrollable eating. Obsessive eating leads to obesity, which has become a global health concern, while psychiatric eating disorders including anorexia nervosa, bulimia nervosa, and binge eating disorder can even be life threatening. Deciphering the neural and molecular mechanisms behind eating behaviors would profoundly facilitate our understanding of these pathologies and help guide a healthy life.

Eating is a highly dynamic and complicated process, which can be briefly divided into three phases based on both the peripheral and central responses to food over time (Craig 1917; Kringelbach et al. 2012; Sternson and Eiselt 2017). The primary stage of an episode of eating is termed the appetitive phase since eating is primarily driven by the desire for food, motivated by either physical energy demand or pleasure after food rewards (Saper et al. 2002). In addition, the circadian rhythm is another contributor to appetite, setting the schedule for feeding (Asher and Sassone-Corsi 2015; Koch et al. 2020; Segers and Depoortere 2021). Once food is obtained, the appetitive phase ceases and there is a shift to a state of satisfaction (consumption phase), which is mainly maintained by positive reinforcement from food palatability (Sternson and Eiselt 2017). When satisfaction peaks, further ingestive behaviors will be suppressed both peripherally and centrally, which is defined as the termination phase (Sternson and Eiselt 2017; Augustine et al. 2020) (Fig. 1). The termination phase is composed of two distinct ingestion-suppressing processes termed satiation and satiety, respectively. Satiation refers to the sensation of fullness during ingestion, primarily derived from food palatability and/or the distension of stomach (Janssen et al. 2011; Livovsky et al. 2020). Satiation puts an end to the ongoing meal (Higuchi et al. 2020; Li et al. 2020; Klaassen and Keszthelyi 2021), and thus occurs at the interface of the consumption and termination phase (Fig. 1). After the meal ceases, satiation disappears soon as stomach emptying, but the termination phase can be maintained by satiety which describes the postprandial feeling of non-hunger and delays the next eating episode (Janssen et al. 2011; Livovsky et al. 2020; Klaassen and Keszthelyi 2021). Satiety is principally induced by the appetite-suppressing actions of satiety signals, which are the peripheral peptides or hormones released due to the increased nutrients in the intestine or blood plasma (Begg and Woods 2013; Hellstrom 2013; Xu and Xie 2016). Collectively, satiation is usually attributed to the satiating value (e.g., taste, texture, palatability, and total volume) of food before digestion while satiety is more associated with the nutrient composition and total calories consumed. Furthermore, satiation leads to a decreased

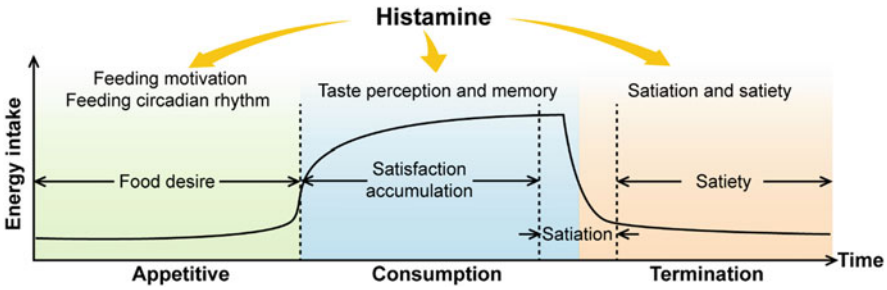

Fig. 1 A schematic overview of the functions of histamine in feeding. Eating can be divided into three phases, namely the appetitive, consumption, and termination phases. The appetitive phase is dominated by the desire for food, motivated by either physical energy demand or pleasure after food rewards. Once the food is obtained, the consumption phase initiates and continues as satisfaction provided by food accumulates. After satisfaction peaks, satiation and satiety suppress food consumption to terminate the meal. Histamine is involved in these phases in different ways, which will be addressed in detail in the following sections

meal size (g or kcal) and shortens meal duration, and satiety, on the other hand, prolongs the inter-meal interval and reduces meal frequency (De Graaf et al. 1999). As time goes by, satiety progressively diminishes and another energy intake cycle initiates.

Histamine is a neurotransmitter and neuromodulator with various functions in the mammalian central nervous system (CNS). Since the 1970s, mounting evidence has revealed that histamine acts as an anorexigenic agent. Acute injection of histamine into the lateral ventricle reduces food intake in cats (Clineschmidt and Lotti 1973), and in rodents continuous central infusion of histamine suppresses feeding (Itowi et al. 1988). Consistent with these observations, increasing central histamine levels, either by boosting histamine synthesis (Sheiner et al. 1985; Orthen-Gambill 1988; Vaziri et al. 1997) or by inhibiting histamine catabolism (Lecklin et al. 1995), also decreases food consumption. Subsequent investigations of histamine-mediated feeding behaviors have revealed that histamine has heterogeneous functions in different feeding phases. Histamine can terminate eating by enhancing both satiation and satiety, while in the appetitive phase it can drive motivated behaviors toward food and engage in the modulation of feeding circadian rhythm. Evidence also shows the involvement of histamine in taste perception during food consumption (Fig. 1). In this review, we first summarize the diverse functions of histamine in feeding behaviors as well as the neural circuit mechanisms behind different functions. Furthermore, we review the main findings regarding the regulation of the histaminergic feeding network by histamine receptors and discuss the insights from clinical feeding interventions targeting histamine receptors.

1 Histamine in Feeding

1.1 Histamine in Satiety and Satiation

Early in the 1990s, it has been shown that histamine is closely associated with satiety. α-fluoromethylhistidine (FMH) is a suicide inhibitor ($IC_{50} = 1.3 \times 10^{-5}$ M in vitro) (Kollonitsch et al. 1978) of histidine decarboxylase (HDC, histamine-synthesizing enzyme) and has been widely used for histamine depletion in vivo. Infusion of α-FMH into the third cerebroventricle of rats fed *at libitum* triggers ingestive behaviors in the early light phase (Ookuma et al. 1993). Interestingly, α-FMH microinfusion into the ventromedial (VMH) or paraventricular hypothalamus (PVH), but not the lateral (LH), dorsomedial (DMH), or preoptic anterior hypothalamus (POAH), recapitulates feeding induced by the depletion of hypothalamic histamine (Ookuma et al. 1993). Given that VMH and PVH serve as satiety centers in the CNS (Becker and Kissileff 1974), these results imply that histamine inhibits feeding by enhancing satiety. Furthermore, continuous automatic detection of daily meal pattern revealed that the inhibition of histamine biosynthesis by α-FMH increased meal frequency in rats fed *at libitum* (Fukagawa et al. 1988; Doi et al. 1994), whereas antagonism of histamine H3 receptors (auto-receptor) by thioperamide decreased it (Machidori et al. 1992), reflecting the involvement of histamine in satiety induction. However, the observations above must be interpreted with caution since the alteration of meal pattern may also result from circadian rhythm derangement (see below for details). By employing an alternative satiety-assessing paradigm (behavioral satiety sequence analysis), Prof. Maria Beatrice Passani and her colleagues found that oleoylethanolamide, a satiety molecule released from the small intestine, induced a reduction in food intake and a shift of behavioral sequence from eating to resting in rats provided with palatable wet mesh for 40 min, which was abolished by α-FMH co-administration (Provensi et al. 2014). These results indicate that histamine is required for oleoylethanolamide-induced satiety. In addition to oleoylethanolamide, inhibition of either histamine biogenesis or the post-synaptic histamine H1 receptor blunts the anorexigenic effects of various satiety signals, including leptin (Morimoto et al. 1999; Yoshimatsu et al. 1999; Yoshimatsu 2008), amylin (Lutz et al. 1996; D'Este et al. 2001), bombesin (Merali and Banks 1994; Kent et al. 1997; Okuma et al. 1997), cholecystokinin (Attoub et al. 2001), glucagon-like peptide-1(Gotoh et al. 2005), and nesfatin-1 (Gotoh et al. 2013), suggesting that histamine relays satiety messages from the periphery to the CNS.

Although it is clear that histamine plays a key role in the transmission of peripheral satiety messages, the mechanisms underlying the peripheral regulation of histaminergic neurons are less clear. It has been shown that leptin receptors are barely expressed in histaminergic neurons (Elmquist et al. 1998; Hakansson et al. 1998) and whether receptors of other satiety molecules residue in histaminergic neurons is unknown, although some of them are present in hypothalamus, and even in the tuberomammillary nucleus (Moody et al. 1988; O'Shea and Gundlach 1993;

Campos et al. 1994; Paxinos et al. 2004; Goebel-Stengel et al. 2011). Evidence to date has tended to support indirect regulation of histaminergic neurons by peripheral satiety signals. Histaminergic neurons receive synaptic input from α-melanocyte stimulating hormone (α-MSH)-containing neurons of the arcuate nucleus (ARC), the main central target of leptin (Fekete and Liposits 2003; Xu et al. 2018). Histaminergic neurons are surrounded by amylin-positive fibers (D'Este et al. 2001), implying a potential synaptic connections between these two kinds of neurons. In addition, corticotropin-releasing hormone neurons and thyrotropin-releasing hormone neurons in the PVH, as well as feeding-related neurons in the nucleus tractus solitarius (NTS), transmit peripheral signals of satiety to histaminergic neurons (Gotoh et al. 2005, 2013; Yoshimatsu 2008; Provensi et al. 2016; Umehara et al. 2016) (Fig. 2).

Although the findings above demonstrate that histamine is required for satiety, histamine itself cannot be classified as a satiety signal. Actually, feeding-induced increase of hypothalamic histamine occurs much earlier (<15 min) than the peripheral release of satiety hormones (Itoh et al. 1991). More importantly, ingestion is the prerequisite of the secretion of endogenous satiety signals. However, the extracellular histamine concentration in the medial hypothalamus of rats fasted for 24 h increases (by 63%) even after the presentation of inaccessible food (in a closed wire mesh box), although ingestion triggers a more dramatic (143%) increase of extracellular histamine (Itoh et al. 1991).

In addition to satiety, histamine also engages in satiation induction. A pilot study conducted by Prof. Toshiie Sakata and his colleagues showed that ad libitum feeding of hard pellet intake, but not intubation of liquid diet with equal calorific value, increased the concentration of tele-methylhistamine (a predominant metabolite of histamine) in hypothalamus and the mesencephalic trigeminal nucleus (Me5) (Fujise et al. 1998). These results indicate that oral sensations during ingestion can affect central histamine turnover. Moreover, depletion of histamine in the hypothalamus by α-FMH not only reduces the latency to eat (due to the loss of satiety) but also enlarges the size of the first meal and prolongs meal duration in the early light phase in rats fed *at libitum* (Sakata et al. 1990; Ookuma et al. 1993). As mentioned above, satiation is a feeling of fullness that occurs during food intake and controls meal size and duration. The evidence above indicates that histamine can suppress feeding by enhancing satiation (Sakata 1995; Sakata et al. 1997). However, the satiation induced by histamine seems to be primarily involved when the rats are in an energy-deficient state, since continuous infusion of α-FMH fails to affect daily intake in rats fed *at libitum* (Doi et al. 1994) but acute α-FMH treatment increases the size of the first meal after 5-h fasting in rats (Fujise et al. 1998) or during the early light phase when nearly 5 h has passed since the last meal (Sakata et al. 1990; Ookuma et al. 1993). Thus, the satiation induced by histamine could be crucial for preventing physical discomfort caused by excessive ingestive behaviors during energy deficiency.

Again, infusion of α-FMH into the VMH merely attenuates satiation in 5-h fasted rats, indicating that there is an overlap in the downstream histaminergic circuits regulating satiety and satiation (Ookuma et al. 1993; Fujise et al. 1998). However, the upstream circuits of histaminergic neurons controlling satiation remain unclear

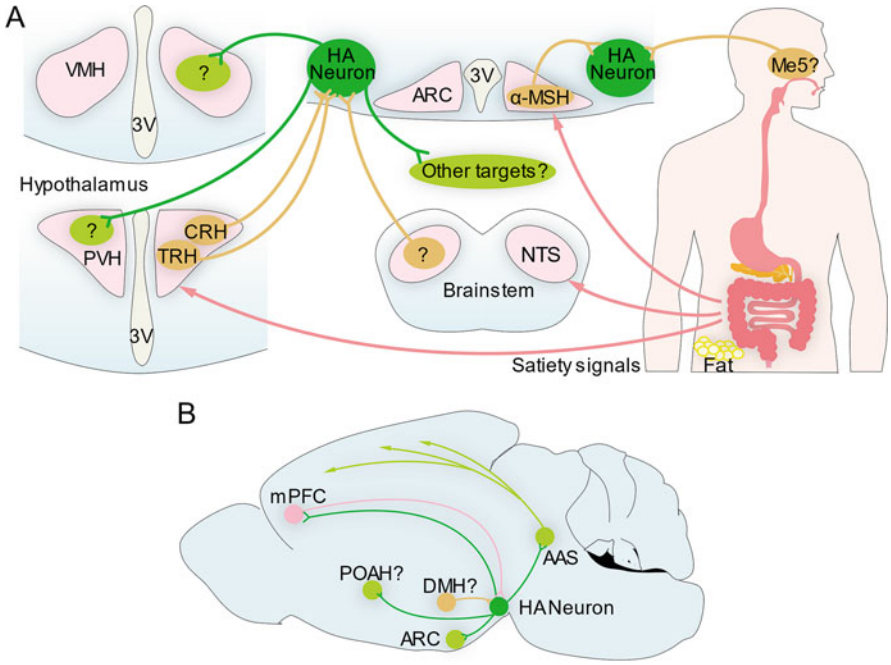

Fig. 2 A schematic diagram of the histaminergic network underlying satiety, satiation, and feeding motivation. (**a**) Histamine is required for the anorexigenic actions of peripheral satiety signals, including leptin, oleoylethanolamide, amylin, bombesin, cholecystokinin, glucagon-like peptide-1, and nesfatin-1. The α-MSH neurons in the ARC, corticotropin-releasing hormone (CRH) neurons, and thyrotropin-releasing hormone (TRH) neurons in the PVH, as well as feeding-related neurons in the NTS can transmit peripheral signals of satiety to histaminergic (HA) neurons. The mesencephalic trigeminal nucleus (Me5) may convey sensation from the oral cavity to histaminergic neurons. The histaminergic neurons further regulate food intake through projections to the VMH and PVH. However, the cell types required in the different nodes of this network are unclear. (**b**) Histaminergic neurons increase arousal to energize feeding motivation through the activation of the ascending arousal system (AAS) and ARC. The histaminergic projections to the POAH might also engage in feeding motivation. Histaminergic neurons and mPFC may form a positive feedback loop to maintain the intensity of the efforts to obtaining food. Moreover, histaminergic neurons also receive input from a food-entrainable circadian oscillator, and DMH might be one candidate for this upstream oscillator

(Fig. 1). Given the fact that the texture of food affects central histamine turnover (Fujise et al. 1998), it is likely that an innervation conveys sensation from the oral cavity to histaminergic neurons directly. Indeed, the mesencephalic trigeminal nucleus, which plays crucial roles in the proprioception of the face and oral cavity, sends projections to histaminergic neurons (Ericson et al. 1989; Ericson et al. 1991; Sakata et al. 2003) (Fig. 2a).

1.2 Histamine in Feeding Motivation

As mentioned above, enticing hungry (24 h of fasting) rats with inaccessible food boosts the release of hypothalamic histamine (Itoh et al. 1991; Valdes et al. 2010), suggesting that histamine may also be involved in food anticipation during the appetitive phase of feeding in addition to terminating a meal through satiety and satiation. Supporting this hypothesis, food-seeking behaviors together with the number of cfos-positive histaminergic neurons increase before the predicted meal-time in rats under a restricted feeding schedule (training for 4 days with food availability from 9:00 to 10:00 h and from 15:00 to 17:00 h) (Inzunza et al. 2000; Meynard et al. 2005). In this paradigm, the activation of histaminergic neurons seems to primarily result from food anticipation rather than circadian rhythm, since few cfos-positive neurons could be observed during the same period of time in rats fed ad libitum (Meynard et al. 2005).

Prof. Fernando Torrealba and his colleagues further advanced the theory that histamine maintains feeding motivation during the appetitive phase (Torrealba et al. 2012). They found that the intense attempts made by 24-h fasted rats to reach food in a closed wire mesh box increased in parallel with the increase of extracellular histamine in the posterior hypothalamus (Valdes et al. 2010). Moreover, when rats were challenged with an instrumental lever press task, in which they had to press a lever enough times to obtain a food reward, 24-h starvation enhanced both the number of lever presses and the extracellular histamine concentration in the medial prefrontal cortex (mPFC) (Riveros et al. 2019). Food reward in both tests induced little interest and histamine release remained unchanged in rats fed ad libitum (Valdes et al. 2010; Riveros et al. 2019). Furthermore, the inhibition of histamine signaling (intracerebroventricular infusion of pyrilamine) decreased the efforts to obtain food in starved (24-h of fasting) rats in a dose-dependent manner (Riveros et al. 2019). The correlation of histaminergic activation with the intensity of endeavor indicates that histamine is fundamental to the maintenance of motivation during the appetitive phase of feeding. In addition to hunger-triggered food-seeking, histamine may also be required for reward-induced feeding since a stronger-tasting food further reinforces TMN activation and strengthens the efforts of hungry rats (24-h of fasting) to obtain food (Valdes et al. 2010). However, histamine was found to be dispensable for the consumption phase; if each level press in the instrumental lever press task was followed by one accessible food pallet, the inhibition of histamine signaling failed to affect the number of level presses and pallets ingested in 24-h fasted rats (Riveros et al. 2019).

The histamine-induced reinforcement of feeding motivation is hypothesized to result from histamine-induced arousal given the fact that the intensity of efforts to obtain food relies on the arousal state and the essential role of histamine in alert and attentive waking (Torrealba et al. 2012). Supporting this hypothesis, food enticement activates several wake-promoting nuclei and leads to increased active waking with suppressed rapid eye movement (REM) and non-REM (NREM) sleep (Valdes et al. 2005). The intense arousal induced by food enticement is characterized by

desynchronized and fast EEG, elevated locomotor activity (behavioral arousal), and increased body core temperature (vegetative arousal), which are blunted by TMN lesions (Valdes et al. 2005; Valdes et al. 2010). In addition, the activation level of the histaminergic system mirrors the arousal state and the intensity of efforts to obtain food in 24-h fasted rats (Valdes et al. 2010; Riveros et al. 2019). These results raise the hypothesis that histamine increases arousal to energize efforts in the appetitive phase of feeding.

The arousal induced by food enticement could also be shown as the general activation of cortex including the mPFC and orbitofrontal, sensory, and motor cortices (Valdes et al. 2010). It is well established that cortical arousal requires a collection of wake-active nuclei in the so-called AAS including the TMN, LH, the ventral tegmental area (VTA), the locus coeruleus (LC), and the dorsal raphe (DR). Interestingly, TMN has been proved to be the earliest activated nucleus in food enticement followed by delayed responses of other AAS nuclei including the LH and DR (Valdes et al. 2010). However, forced wakefulness by noises was found to trigger the release of serotonin rather than histamine in the mPFC, implying the involvement of the LC or VTA in forced arousal (Riveros et al. 2015). These findings suggest that AAS nuclei are hierarchically recruited in response to different external stimuli, and that histaminergic neurons are crucial to arousal induction in feeding motivation (Fig. 2b).

Meal anticipation in restricted-fed (training for 2 weeks with food availability from 22:00 to 24:00 h) rats was found to trigger neural activation in the ARC, which could be abolished by systematic administration of H1 receptor antagonists (diphenhydramine and mepyramine), suggesting that the ARC may also serve as a downstream target of histaminergic neurons in feeding motivation (Umehara et al. 2011). By employing optogenetics and chemogenetics techniques, recent studies have revealed that Agouti-related protein (AGRP) neurons, a group of hunger-activated orexigenic neurons in the ARC, are also required for motivated behaviors (Atasoy et al. 2012; Sternson 2013; Betley et al. 2015). The rapid reduction of AGRP neuron activity by food consumption indicates that they are primarily involved in the appetitive rather than consumption phase (Betley et al. 2015). More importantly, photo-stimulation of AGRP neurons decreases the preference for the flavor favored before conditioning, indicating that the activation of AGRP neurons transmit a negative-valence teaching signal about hunger to maintain the intensity of feeding motivation (Betley et al. 2015; Sternson 2016). Similarly, H1 receptor depletion was found to increase methamphetamine-induced conditioned place preference, while morphine-induced conditioned place preference was stronger in $HDC^{-/-}$ mice (Takino et al. 2009; Gong et al. 2010), implying that histamine may also transmit a negative-valence signal that regulates motivated behaviors. Collectively, these observations suggest that the histamine-induced arousal during food-seeking could also be an outcome of the TMN-ARC axis other than the AAS activation (Fig. 2b).

As mentioned above, increased body core temperature is a characteristic of histamine-induced arousal in feeding motivation (Valdes et al. 2005; Valdes et al. 2010). Histaminergic regulation of thermogenesis heavily relies on projections to the POAH (Yasuda et al. 2004). Recently, the medial preoptic area (MPON), a

subregion within the POAH, was shown to play an essential role in prey-seeking and hunting-like actions (Park et al. 2018). Thus, the histaminergic circuit from the TMN to the POAH may also be related to feeding motivation, although the POAH is dispensable for histamine-mediated satiety (Ookuma et al. 1993).

When it comes to arousal, the histaminergic system is a major output of LH orexinergic neurons for arousal induction (Huang et al. 2001; Mochizuki et al. 2011; Yoshikawa et al. 2021). However, the delayed activation of LH orexinergic neurons after food enticement suggests that LH may not be the upstream input of histaminergic neurons in feeding motivation (Valdes et al. 2010). Given the food anticipation in restricted-fed rats, it is highly possible that a food-entrainable circadian oscillator is involved in the regulation of the histaminergic system in motivated behaviors (Inzunza et al. 2000; Meynard et al. 2005). The DMH, which is thought to be an essential food-entrainable circadian pacemaker, may be a candidate upstream modulator of histaminergic neurons (Gooley et al. 2006; Mieda et al. 2006). The infralimbic (IL) cortical area has been found to mediate the activity of histaminergic neurons involved in the induction of circadian oscillator-independent feeding motivation, as shown by suppressed behavioral arousal and decreased activation of the TMN after generation of IL lesions (Valdes et al. 2006). Since the mPFC, which consists of the prelimbic and IL cortex areas, also serves as a downstream target of histaminergic neurons in feeding motivation (Riveros et al. 2014; Riveros et al. 2015), there possibly exists a positive feedback loop between the TMN and the mPFC, which holds particular significance for survival from starvation by maintaining the intensity of arousal and food seeking (Fig. 2b).

1.3 Histamine in Food Taste Perception and Memory

As mentioned above, the histaminergic system responds differentially to hard and soft diets (Fujise et al. 1998; Ishizuka et al. 2010). In addition to texture, taste also influences histamine release. Aversive tastants such as HCl and quinine elicit the release of histamine in the anterior hypothalamus, whereas the sweeteners induce a delayed reduction of extracellular histamine in the same region (Treesukosol et al. 2003, 2005). After rats are conditioned with a sweet solution paired with an injection of LiCl to produce a taste aversion, re-exposure to sweeteners increases histamine release (Treesukosol et al. 2005; Ishizuka and Yamatodani 2012), indicating that histaminergic activity is modulated by the palatability of tastants rather than merely chemical stimulation.

Nevertheless, the significance of histamine-mediated taste perception is not settled. Given the role of histamine in satiation, the reduction in the release of histamine by sweeteners may prolong the consumption phase of a meal and lead to the overconsumption of sweet food; however, this hypothesis needs further confirmation by abolishing histaminergic signaling and evaluating the effects on the consumption of palatable food. Interestingly, histamine seems not only to decide the ongoing meal but also to affect future food choices. The histaminergic system

was reported to tune the acquisition and retrieval of taste aversive memory through its regulation of cholinergic release in the insular cortex (Puron-Sierra and Miranda 2014). These observations give birth to another assumption whereby the fluctuation in histamine release induced by different foods may serve as a cue for the formation of the corresponding taste memories, and thus may further contribute to food preference and direct food choices.

There is limited knowledge of the neural circuits involved in histamine-mediated taste perception and memory. The chorda tympani, a key oral sensor of chemicals, may be an important source of input to histaminergic neurons involved in taste perception, as its transection attenuates the increase of histamine release elicited by tastants (Treesukosol et al. 2003). On the other hand, the histaminergic projections emanating from the TMN to the nucleus basalis magnocellularis (NBM) engage in taste memory (Puron-Sierra and Miranda 2014).

1.4 Histamine in Feeding Circadian Rhythm

Feeding is under the control of circadian rhythmicity which synchronizes the behaviors and visceral functions to food availability (Segers and Depoortere 2021). Electrophysiological data has shown that the histaminergic neuronal activity correlates with the arousal state with a higher firing rate during the wake than the sleep period (Vanni-Mercier et al. 1984; Szymusiak et al. 1989; Sakai et al. 1990; Krilowicz et al. 1994; Steininger et al. 1999). Thus, histaminergic neurons show higher activity at night in rodents but, in humans, they are more active in the daytime (Haas et al. 2008). Consistent with the circadian pattern of the histaminergic neuronal activity, the activity of hypothalamic HDC peaks at night and decreases during daylight hours (Orr and Quay 1975a, b). Moreover, in the hypothalamus of freely-moving rats, the average extracellular histamine level in the dark phase is significantly higher than that in the light phase (Mochizuki et al. 1992), but the total amount of histamine in the hypothalamus peaks in the early light phase (Orr and Quay 1975a, b), which may result from the high activity of HDC throughout the night. The observation of circadian variation in hypothalamic histamine concentration has led to the assumption that histamine might play a role in feeding rhythm. Supporting this hypothesis, sustained infusion of α-FMH or H1 receptor antagonist chlorpheniramine into the third cerebral ventricle of rats fed ad libitum increases diurnal food intake but suppresses feeding at night, resulting in flattened fluctuation of food intake (Doi et al. 1994). Similarly, depletion of the H1 receptor in aged mice specifically promotes the food consumption in the daytime, leading to the increased ratio of light/night food intake (Masaki et al. 2004). More intriguingly, the disruption of feeding rhythm occurs much earlier than the onset of hyperphagia and obesity in *Hrh1*$^{-/-}$ mice (Masaki et al. 2004; Yoshimatsu 2008). Re-setting the feeding rhythm by scheduled feeding corrects hyperphagia and leads to bodyweight reduction in obese *Hrh1*$^{-/-}$ mice (Masaki et al. 2004; Yoshimatsu 2008), reflecting the fundamental role of histamine-mediated feeding rhythm in obesity.

The hypothalamic suprachiasmatic nucleus (SCN), the master regulator of the mammalian circadian clock, is considered to be one candidate for the downstream target of histamine in feeding rhythm control (Doi et al. 1994). In agreement with this assumption, the SCN is innervated by histaminergic neurons (Watanabe et al. 1984) and infusion of histamine into the SCN reduces daily food consumption in rats fed ad libitum (Itowi et al. 1988). Furthermore, histamine alters the firing rates of SCN neurons (Liou et al. 1983; Scott et al. 1998) and induces a circadian phase-shift of SCN neural activity in rodent hypothalamic slices (Cote and Harrington 1993; Meyer et al. 1998; Biello 2009; Kim et al. 2015). By contrast, intracerebroventricular α-FMH infusion only reduces the amplitude of feeding rhythm in rats fed ad libitum, but fails to shift the circadian feeding cycle as it does in ambulatory rhythm regulation (Doi et al. 1994). In addition, accumulated evidence demonstrates that the SCN is dispensable for the entrainment of daily feeding cycles (Mistlberger 2020; Power and Mistlberger 2020). These results indicate that the SCN may be more involved in the sleep-wake cycle than in feeding rhythm mediated by histamine. Since HDC deletion disrupts the mRNA expression rhythms of clock genes such as Per1/2 and MAL1 in the cortex and striatum rather than in the SCN (Abe et al. 2004), these regions might contain downstream circuits involved in histamine-mediated feeding rhythm. Further investigations are needed to uncover how histaminergic neurons and downstream targets coordinate feeding rhythm.

2 Histamine Receptors in Feeding

Histamine fulfills its functions through the activation of four different histamine receptors (H1–H4 receptors), which belong to the G protein-coupled receptor family. H3 receptors primarily reside in the CNS, while the other three receptors are present both centrally and peripherally. In the brain, the H1 and H2 receptors are predominantly expressed at the post-synapses in almost all brain regions. However, the expression profile of H3 receptors is much more complicated (Panula and Nuutinen 2013). H3 receptors were initially found to serve as auto-receptors in the pre-synapses of histaminergic neurons and to negatively regulate histamine release. Further studies have revealed that H3 receptors are also located pre-synaptically in non-histaminergic neurons where they mediate the release of various neurotransmitters, such as glutamate, γ-aminobutyric acid (GABA), acetylcholine, and noradrenaline (Schlicker et al. 1994; Giorgetti et al. 1997; Yamamoto et al. 1997). H3 receptors also function as post-synaptic receptors in some brain regions such as the cortex and striatum (Ellenbroek and Ghiabi 2014; Yan et al. 2014). The expression pattern of H4 receptors in the brain is still controversial and their functions in the CNS are less clear. In the following section, we summarize the roles of histamine receptors in feeding behaviors (Table 1) and further discuss potential insights into feeding interventions in obesity and other feeding-related disorders.

Table 1 Main findings regarding the roles of histamine receptors in feeding

Receptors	Localization			Roles	Evidence	Ref.
	Nucleus	Neurons	Synapse			
H1	VMH	GRN &?	Post	Satiety	(1) Hyperphagia in $H1^{-/-}$ mice (2) Inhibition or depletion of the H1 receptor attenuates anorexia induced by satiety signals (3) Local H1 antagonism evokes feeding (4) H1 antagonism reduces the discharge rate of GRNs in brain slices	(Garbarg et al. 1980; Sakata et al. 1988a, b, c; Fukagawa et al. 1989; Ookuma et al. 1989; Lecklin et al. 1998; Morimoto et al. 1999; Yoshimatsu et al. 1999; Masaki et al. 2001, 2004; Mollet et al. 2001, 2003; Davidowa 2007; Gotoh et al. 2013)
	PVH	?	Post			
	mPFC	?	Post	Feeding motivation	(1) Food enticement increases exocellular histamine in the mPFC (2) Central H1 antagonism decreases efforts to obtain a food reward	(Valdes et al. 2006; Riveros et al. 2019)
	ARC	?	Post		Systematic H1 antagonism inhibits ARC activation induced by food anticipation	(Umehara et al. 2011)
	?	?	Post	Feeding rhythm	Feeding dysrhythmias in $H1^{-/-}$ mice	(Masaki et al. 2004; Masaki and Yoshimatsu 2006)
	NBM	ChAT	Post	Taste memory	Local H1 antagonism suppresses ACh release and impairs taste aversion memory	(Puron-Sierra and Miranda 2014)
H2	/	/	/	None	(1) Central H2 antagonism fails to alter food intake (2) Food intake	(Sakata et al. 1988c; Fukagawa et al. 1989;

(continued)

Table 1 (continued)

Receptors	Localization			Roles	Evidence	Ref.
	Nucleus	Neurons	Synapse			
					and body weight is unchanged in $H2^{-/-}$ mice	Lecklin et al. 1998)
	?	?	Post	Satiety	Systematic H2 antagonism abolishes the anorexigenic effect of cholecystokinin	(Attoub et al. 2001)
	MPON	Glu	Post	Feeding motivation?	(1) H2 agonism increases the firing rate of glutamatergic neurons in MPON slices (2) Glutamatergic neurons in the MPON facilitate hunting-like behaviors	(Tabarean et al. 2012; Park et al. 2018)
H3	?	HA	Pre	Satiety	Systematic or central H3 antagonism reduces food intake	(Ookuma et al. 1993; Ghoshal et al. 2018; Kotanska et al. 2019; Kumar et al. 2019)
	?	Non-HA	Pre?	Satiety	Systematic H3 agonism reduces food intake but increases central dopamine and norepinephrine metabolites levels	(Yoshimoto et al. 2006)
	Insular cortex	GABA	Post	Taste memory	(1) Local H3 agonism inhibits taste aversion memory and Ach release (2) The impairment of Ach release is alleviated by local $GABA_A$ receptor antagonism	(Giorgetti et al. 1997; Puron-Sierra and Miranda 2014)
H4	?	?	?	?	(1) Hyperphagia in $H4^{-/-}$ mice (2) Systematic H4	(Sanna et al. 2017;

(continued)

Table 1 (continued)

Receptors	Localization			Roles	Evidence	Ref.
	Nucleus	Neurons	Synapse			
					antagonism blunts cisplatin-induced anorexia in mice	Yamamoto et al. 2019)

ChAT cholinergic neurons, *Glu* glutamatergic neurons, *HA* histaminergic neurons, *Non-HA* non-histaminergic neurons, *GABA* GABAergic neurons

2.1 Histamine H1 Receptor: A Putative Downstream Target

A putative molecular mechanism underlying histamine-mediated feeding is the activation of H1 receptors. Central antagonism of H1, but not H2 receptors, elicits feeding (Sakata et al. 1988a, b, c; Fukagawa et al. 1989; Lecklin et al. 1998). Moreover, H1 knockout mice gradually exhibit hyperphagia during aging and develop mature-onset obesity. However, an abnormal feeding rhythm, characterized by the shift of food consumption into the daytime, precedes the phenotype of hyperphagia, highlighting the role of H1-regulated feeding rhythm in the development of obesity (Masaki et al. 2004; Masaki and Yoshimatsu 2006). As the major downstream circuits of histamine-regulated feeding rhythm are still unresolved, the mechanisms underlying feeding dysrhythmias after H1 deletion remain to be elucidated.

The hyperphagia in H1 knockout mice may be an outcome of reduced satiety since the daily meal frequency also seems to be increased by H1 depletion (Masaki et al. 2004). In line with these observations, inhibition or depletion of the H1 receptor attenuates anorexia induced by peripheral satiety signals including leptin (Morimoto et al. 1999; Yoshimatsu et al. 1999; Masaki et al. 2001), amylin (Mollet et al. 2001, 2003; Davidowa 2007), and nesfatin-1 (Gotoh et al. 2013). What's more, microinjection of an H1 antagonist (chlorpheniramine) into the hypothalamic satiety center (VMH or PVH) evokes feeding, which cannot be recapitulated by the inhibition of H1 receptors in other hypothalamic subregions including the LH, DMH, or POAH (Ookuma et al. 1989). The H1 antagonist chlorpheniramine reduces the discharge rate of glucose-responding neurons in the VMH (Fukagawa et al. 1989). Since glucose-responding neurons are crucial for energy-sensing and glucose homeostasis regulation by the VMH (Chan and Sherwin 2013), these results indicate that the H1 receptor may regulate satiety by affecting energy-sensing in the VMH (Fukagawa et al. 1989), which is in agreement with our previously stated assumption that the role of histamine in satiety and satiation relies on the energy state.

H1 receptors are also the main drivers of histamine-mediated feeding motivation, as shown by the diminished efforts to obtain a food reward after the infusion of H1 antagonist (pyrilamine) into lateral ventricles of 24-h fasted rats (Riveros et al. 2014). The mPFC may be where H1 receptors work since food enticement but not loud noise awakening specifically increases histamine concentration in the mPFC of 24-h fasted rats (Riveros et al. 2015). In addition, H1 antagonism by

diphenhydramine or mepyramine inhibits ARC activation induced by food anticipation in rats under a restricted feeding schedule (Umehara et al. 2011), indicating that H1 receptors in the ARC may also be involved in feeding motivation.

Local infusion of the H1 receptor antagonist pyrilamine into the NBM suppresses acetylcholine (Ach) release in the insular cortex and simultaneously impairs taste aversion memory (Puron-Sierra and Miranda 2014), indicating that histamine mediates taste memory through the activation of H1 receptors in the NBM.

2.2 Histamine H2 Receptor: A Dispensable Receptor for Feeding?

H2 receptors are presumed to be dispensable for feeding behaviors because there are several lines of evidence showing that central antagonism of the H2 receptor (intracerebroventricular infusion of famotidine or cimetidine) fails to affect food consumption (Sakata et al. 1988c; Fukagawa et al. 1989; Lecklin et al. 1998). Similarly, neither food intake nor body weight was found to be altered by H2 depletion in mice (Kobayashi et al. 2000). However, systematic H2 receptor antagonism by ranitidine abolishes the anorexigenic effect of cholecystokinin in the restricted-fed rats (with food availability from 10:00 to 17:00 h), indicating that the H2 receptor may be involved in histamine-induced satiety (Attoub et al. 2001). More surprisingly, another H2 antagonist, cimetidine, has been reported to suppress appetite and induce body weight loss in overweight adults (Stoa-Birketvedt 1993; Stoa-Birketvedt et al. 1998). Thus, after excluding the unperceived pharmacological effects of the H2-targeting compounds, the functions of the H2 receptor could be much more complicated than originally supposed. As discussed above, the MPON may be orchestrated in the downstream histaminergic circuits underlying feeding motivation. In the MPON, histamine seems to selectively activate H2 receptors rather than H1 receptors to induce hyperthermia (Tabarean et al. 2012). Interestingly, H2 receptors influence the activity and firing of glutamatergic neurons, but not GABAergic neurons, in the MPON during thermoregulation (Tabarean et al. 2012). Similarly, the photo-stimulation of a subpopulation of glutamatergic neurons in the MPON has been reported to facilitate hunting-like behaviors without the requirement for activity of GABAergic neurons in the same area (Park et al. 2018). In light of the finding that histamine induces vegetative arousal during food anticipation, it is likely that H2 receptors participate in feeding motivation in a cell type-specific manner (Table 1). Given these findings, it will be of great significance to re-examine the feeding-related roles of H2 receptors in the scale of a single cell type.

2.3 Histamine H3 Receptor: A Unique Mechanism Involved?

Given the roles of H3 receptor as an auto-receptor, it is reasonable to believe that it participates in feeding behaviors through the regulation of histamine release and subsequent activation of post-synaptic H1 receptors; this notion is supported by the observation of reduced food consumption after H3 receptor antagonism (Ookuma et al. 1993; Ghoshal et al. 2018; Kotanska et al. 2019; Kumar et al. 2019). However, in contrast with previous studies, systematic administration of the H3 receptor agonist imetit was also reported to decrease daily food intake (Yoshimoto et al. 2006) and depletion of the *Hrh3* gene was found to lead to hyperphagia and obesity (Takahashi et al. 2002). Moreover, the hyperphagia phenotype of $Hrh3^{-/-}$ mice, characterized by an increase in nocturnal food intake, was found to occur earlier than that in $Hrh1^{-/-}$ mice who consume more food during the daytime (Takahashi et al. 2002; Masaki et al. 2004). These findings have suggested the possibility of other molecular mechanisms underlying H3 receptor-mediated feeding besides regulation of histamine release.

Indeed, H3 receptors are abundantly expressed outside the TMN as either heteroreceptors or post-synaptic receptors. It has been reported that imetit-induced anorexia in diet-induced obese mice (*at libitum* fed) is not correlated with histamine release (Yoshimoto et al. 2006). By contrast, imetit suppresses feeding simultaneously with the fluctuation of central dopamine and norepinephrine metabolites levels (Yoshimoto et al. 2006), implying a potential heteroreceptor-related mechanism. Local agonism means selective activation of H3 receptors of insular cortex by only injecting the agonist in this area rather than systematic administration (Puron-Sierra and Miranda 2014). Based on the observations that H3 receptors are mainly expressed in the GABAergic neurons of the insular cortex and that the impairment of Ach release could be alleviated by local $GABA_A$ receptor antagonism (Giorgetti et al. 1997), H3 receptors may serve as post-synaptic receptors when modulating taste memory. At post-synapses, H3 receptors also heterodimerize with both the dopamine D1 and D2 receptors and alter dopaminergic signaling transduction (Ryu et al. 1994; Ferrada et al. 2009; Moreno et al. 2011). Given that dopamine determines the reward value of food, the post-synaptic H3 receptors may be required for feeding motivation. Thus, extensive investigations are encouraged to illuminate the feeding-related roles of the H3 receptor in non-histaminergic neurons (Table 1).

2.4 Histamine H4 Receptor: A Receptor Awaiting Exploration

Limited evidence to date has suggested the potential anorexigenic actions of the H4 receptor. H4 receptor deficiency increases 1-h food consumption after 4-h food deprivation in mice (Sanna et al. 2017) and subcutaneous injection of the H4 receptor antagonist JNJ7777120 blunts cisplatin-induced anorexia in mice fed at

libitum (Yamamoto et al. 2019). Nevertheless, the detailed characteristics of H4-mediated feeding behaviors and the underlying mechanisms still remain to be determined (Table 1).

2.5 *Clinical Trials of Chemicals Targeting Histaminergic Receptors*

Weight gain has been identified as a major adverse effect of second-generation antipsychotic drugs (SGA), such as risperidone, clozapine, and olanzapine. The weight gain induced by these drugs is highly correlated with their binding affinity for the H1 receptor (He et al. 2013; Luo et al. 2019), highlighting the possibility of weight control in human beings by targeting the histaminergic system. Supporting this hypothesis, betahistine, a histamine analog with both H1 receptor agonistic and H3 receptor antagonistic effects, has been shown to be effective in preventing weight gain in schizophrenic patients prescribed with SGA drugs (Table 2). Moreover, betahistine has an impressive safety profile when used as a therapy for vestibular disorders such as Ménière's disease and the symptomatic treatment of vertigo (James and Burton 2001; Jeck-Thole and Wagner 2006).

However, in non-schizophrenic populations with/without a high body mass index (BMI), betahistine together with other histamine-related agents fails to induce a weight change in most clinical trials (Table 2). Although the unsatisfactory outcomes may result from the poor blood-brain barrier penetration of H1/H2 receptor-targeting compounds, numerous clinical trials assessing anti-obesity pharmacological actions of H3 antagonists, which show higher CNS availability, have also been aborted and ended up without results disclosed (Provensi et al. 2016). The heterogeneous phenotypes caused by unhealthy eating may explain the varying outcomes in human beings. Some obese patients show a general reduction in satiety with higher susceptibility to hunger while others encounter uncontrollable episodes of compulsive eating even when they feel full. In addition, a portion of the population shows an overwhelming attraction to energy-dense foods such as high-fat foods and dessert (Hebebrand et al. 2014). These hyperreactions to certain kinds of food share some similarities with addiction. Consistent with these similarities, food addiction occurs more often in patients with obesity and binge eating disorder (Pedram et al. 2013; Albayrak et al. 2017). Feeding dysrhythmias also contribute along with dietary structure to high BMI in humans (Muscogiuri et al. 2020). Taken together, results from previous studies suggest that abnormal changes in body weight can stem from distinct eating habits and that effective body weight management must be based on the precise regulation of various feeding behaviors. Despite the multiple functions of histamine in feeding, the best strategy to achieve the precise regulation of certain feeding behaviors is still not clear. Thus, extensive investigations are needed to accelerate the clinical transformation of histamine receptor-related compounds.

Table 2 Main clinical studies regarding the impacts of histamine-related compounds on weight control

Drug	Target	Population	Characteristics	Duration	Treatment	Food intake	BW vs. baseline	ΔBW vs. placebo	BMI vs. baseline	ΔBMI vs. placebo	Ref.
Betahistine	H1&H3	Diagnosed with schizophrenia or bipolar disorder	18–55 years ♀ 17 ♂25 BMI = 25.23 ± 2.33	12 weeks	Placebo + SGA (n = 29) Betahistine (36 mg/day) + SGA (n = 13)	/	/	Less**	/	Less**	(Kang et al. 2018)
Betahistine	H1&H3	Treated with antipsychotic medications	30 ± 12.8 years ♀ 27 ♂24 BMI = 32.9 ± 6.0	12 weeks	Placebo + Olan/Cloz (n = 22) Betahistine + Olan/Cloz (n = 29) 0–2 weeks: 8–48 mg/day 2–12 weeks: 48 mg/day (US) 0–2.5 weeks: 8–36 mg/day 2.5–12 weeks: 36 mg/day (China)	/	/	Less**	/	Less**	(Smith et al. 2018)
Betahistine	H1&H3	Diagnosed with schizophrenia, schizoaffective disorder, schizophreniform disorder, or a psychotic disorder	16–45 years ♀ 10 ♂25 18.5 < BMI < 35	16 weeks	Placebo + Olan (n = 20) Betahistine (48 mg/day) + Olan (n = 15)	/	/	NS	/	/	(Barak et al. 2016a)
Betahistine	H1&H3	Healthy females	18–45 years ♀46 16.8 < BMI < 27	4 weeks	Days 1–7: Placebo (n = 22) Betahistine (144 mg/day) (n = 24) Days 8–14: Placebo + Olan Betahistine (144 mg/day) + Olan Days 15–28: Olan only	/	/	Less*	/	/	(Barak et al. 2016b)

Betahistine	H1&H3	Diagnosed with schizophrenic disorder	16–45 years ♀8 ♂35 18.5 < BMI < 35	6 weeks	Placebo + Olan ($n = 14$) Betahistine (144 mg/day) / Reboxetine (8 mg/day) + Olan ($n = 29$)	/	/	Less**	/	Less**	(Poyurovsky et al. 2013)
Betahistine	H1&H3	Obese female	18–70 years ♀76 30 < BMI < 40	1 day	Placebo ($n = 19$) Betahistine (48 mg/day) ($n = 19$) Betahistine (96 mg/day) ($n = 17$) Betahistine (144 mg/day) ($n = 21$)	NS	/	/	/	/	(Ali et al. 2010)
Betahistine	H1&H3	Obese adults	18–65 years ♀ + ♂ = 234 30 < BMI < 40	12 weeks	Placebo ($n = 63$) Betahistine (16 mg/day) ($n = 55$) Betahistine (32 mg/day) ($n = 58$) Betahistine (48 mg/day) ($n = 58$)	/	/	NS	/	NS	(Barak et al. 2008)
Betahistine	H1&H3	Hospitalized for a first episode of schizophrenic disorder	22 ± 1.7 years ♂3 BMI = 22.2 ± 4.0	6 weeks	Betahistine (144 mg/day) + Olan ($n = 3$)	/	<7%	/	/	/	(Poyurovsky et al. 2005)
Ranitidine	H2	Diagnosed with a first episode of schizophrenic disorder	18–60 years ♀8 ♂67 BMI < 30	8 weeks	Placebo + Olan ($n = 25$) Ranitidine (150 mg/day) + Olan ($n = 25$) Ranitidine (300 mg/day) + Olan ($n = 25$)	/	/	NS	/	NS	(Mehta and Ram 2016)

(continued)

Table 2 (continued)

Drug	Target	Population	Characteristics	Duration	Treatment	Food intake	BW vs. baseline	ΔBW vs. placebo	BMI vs. baseline	ΔBMI vs. placebo	Ref.
Nizatidine	H2	Diagnosed with schizophrenia, schizoaffective disorder, or schizophreniform disorder	18–65 years ♀22 ♂32 BMI < 40	12 weeks	Placebo + Olan ($n = 27$) Nizatidine (300 mg/day) + Olan ($n = 27$)	/	/	NS	/	NS	(Assuncao et al. 2006)
Famotidine	H2	Hospitalized for a first episode of acute psychosis	40–65 years ♀5 ♂9 BMI < 30	6 weeks	Placebo + Olan ($n = 7$) Famotidine (40 mg/day) + Olan ($n = 7$)	/	/	NS	/	NS	(Poyurovsky et al. 2004)
Nizatidine	H2	Diagnosed with schizophrenia	28.7 ± 8.8 years ♀14 ♂21 BMI = 26.8 ± 1.7	8 weeks	Placebo + Olan ($n = 17$) Nizatidine (300 mg/day) + Olan ($n = 18$)	/	Less*	Less*	Less*	Less*	(Atmaca et al. 2003)
Nizatidine	H2	Diagnosed with schizophrenia, schizoaffective disorder, or schizophreniform disorder	18–65 years ♀ + ♂ = 169 BMI < 40	16 weeks	Placebo + Olan ($n = 56$) Nizatidine (300 mg/day) + Olan ($n = 56$) Nizatidine (600 mg/day) + Olan ($n = 57$)	/	/	NS	/	NS	(Cavazzoni et al. 2003)

Cimetidine	H2	Overweight adults with type 2 diabetes	18–65 years ♀14 ♂29 27.2 < BMI < 48.2	12 weeks	Placebo ($n = 24$) Cimetidine (1,200 mg/day) ($n = 19$)	/	Less*	Less*	Less*	/	(Stoa-Birketvedt et al. 1998)
Cimetidine	H2	Overweight adults	18–59 years ♀55 ♂5 25 < BMI < 37	8 weeks	Placebo ($n = 30$) Cimetidine (600 mg/day) ($n = 30$)	Reduced hunger	/	Less***	/	Less***	(Stoa-Birketvedt 1993)

BW body weight, *BMI* body mass index, *ΔBW* body weight change, *ΔBMI* body mass index change, *Ref* references, *SGA* second-generation antipsychotic drugs, *Olan* olanzapine, *Cloz* clozapine, ♀: female, ♂: male, /: not investigated in the trial, *NS* not significant compared with the indicated group

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

3 Functional Diversity of Histamine: What Shall We Do Next?

3.1 Diverse Functions of Histamine in Different Phases of Feeding

Evidence so far has supported the notion that histamine plays more important roles in the appetitive and termination phases of feeding. On the one hand, histamine can suppress feeding by promoting satiation and satiety. On the other hand, when feeding is highly motivated (e.g., in the energy-deficient state), histamine also serves as an arousal inducer to drive motivated behaviors toward food rewards as it does for other motivated behaviors such as drinking, mating, or drug seeking (Torrealba et al. 2012; Contreras et al. 2016). In the physical conditions, however, histamine does not seem to participate in drinking regulation (Ookuma et al. 1993; Lecklin et al. 1998). Collectively, histaminergic system goes through dynamic functional switching in response to food-related cues (Fig. 3a).

Compared to the other two phases, the contribution of histamine to the consumption phase is less clear (Riveros et al. 2019). Given the role of histamine in taste perception and memory, it is reasonable to assume that histamine also engages in the consumption phase. However, pharmacological inhibition of histamine synthesis (α-FMH) or inhibition of H1 receptors (chlorpheniramine) in the LH, a putative driver of the consumption phase (Betley et al. 2015; Sternson 2016), fails to affect feeding (Ookuma et al. 1989; Ookuma et al. 1993). Interestingly, the cell types in the LH are highly heterogeneous and cell type-specific activation of inhibitory neurons, but not the entire neural population in the LH, evokes feeding (Jennings et al. 2013, 2015). Thus, it is possible that the effects of histamine on different LH neurons counteract each other. Taken together, the functions of histamine in different phases of feeding may be worth re-verifying using cell type-specific neural circuit tracing and manipulating techniques, such as optogenetics and chemogenetics (Fig. 3b).

3.2 Circuit Basis for the Functional Switching of Histamine in Feeding

Exhaustive studies have emphasized the functions of histaminergic projections to VMH and PVH in feeding, however, the limited outputs mismatch the functional diversity of histamine. Morphological evidence shows that histaminergic neurons in the TMN are divided into five subgroups (E1–E5). Food anticipation in restricted-fed rats was found to specifically induce the activation of E3 subgroups (Umehara et al. 2011), while E2 histaminergic neurons seemed to be more related to food consumption during the dark phase (Ujita et al. 2016). Stress challenges, such as restraint and foot shook, exclusively activate the E4–E5 subgroups (Miklos and Kovacs 2003). Moreover, the histaminergic projections to the mPFC and dorsal

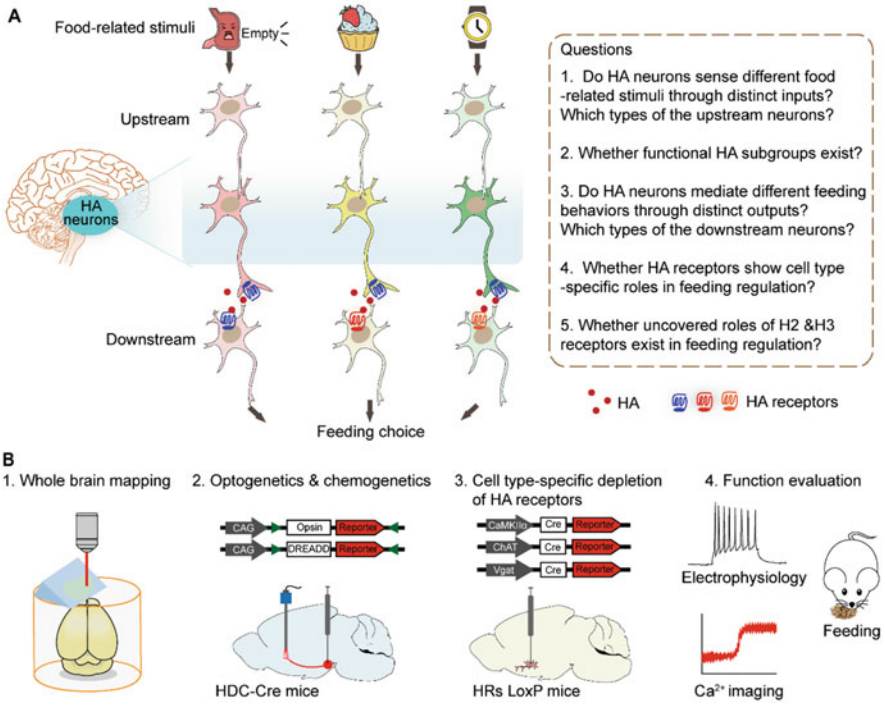

Fig. 3 Perspectives on future research into the role of histamine in feeding. (**a**) Evidence to date implies the existence of functional subpopulations of histaminergic neurons. These subgroups may sense distinct stimuli through discrete upstream inputs and respond to food cues by projecting to different brain areas. To verify this assumption, many questions need to be answered. (**b**) For addressing these issues, the following attempts are encouraged: (1) high-resolution visualization of three-dimensional histaminergic circuits in the whole brain with novel microscope technologies such as fMOST, (2) dissection of single histaminergic circuits with optogenetics or chemogenetics in mice expressing opsin or DREADD in histaminergic neurons. (3) examination of the roles of histamine receptors after selective depletion of histamine receptors in different neural types (for example, CaMKIIα: glutamatergic neurons, ChAT: cholinergic neurons, Vgat: GABAergic neurons) with the Cre-LoxP system, (4) evaluation of behavioral phenotypes and detection of neuronal activities using electrophysiology or Ca^{2+} imaging based on the manipulations above. DREADD, designer receptors exclusively activated by designer drugs, HA: histamine, HA receptors: histamine receptors, HR LoxP mice: transgenic mice with LoxP sites inserted around the gene encoding a particular histamine receptor

striatum produce disparate effects on locomotor and repetitive behaviors (Rapanelli et al. 2017). Collectively, there possibly exist the histaminergic subgroups sensing different food-related cues and mediating discrete feeding behaviors through separate outputs (Fig. 3a). However, morphological data to date doesn't support the biased projections of histaminergic subpopulations (Kohler et al. 1985; Ericson et al. 1987; Inagaki et al. 1990). A higher-resolution visualization of three-dimensional histaminergic circuits in the whole brain with novel microscope technologies such as fluorescent micro-optical sectioning tomography (fMOST) may allow the

visualization of histaminergic connections in more detail and shed light on the uncovered circuit mechanisms underlying the functional switching of histamine in feeding (Fig. 3b).

3.3 Precise Regulation of Feeding Behaviors Through Histamine Receptors

The functional diversity of histamine makes it a viable target for feeding behavior regulation in treatment of obesity and other feeding-related disorders. However, targeting histamine receptors generally in the brain does not seem to be a wise choice, as the functional diversity of histamine also appears to be a "double-edged sword" and the disparate histaminergic circuits could interplay with each other resulting in the net energy intake remaining unchanged. Illuminating the cell type-specific roles of histamine receptors through a combination of spatiotemporally specific gene-editing technologies and various functional analyses will help to uncover novel biological and pathological functions of histamine receptors (Cheng et al. 2021; Jiang et al. 2021) (Fig. 3b) and provide insight into the development of compounds or dosage forms selectively targeting certain histamine receptors in specific cells.

4 Conclusions

In summary, histamine is undoubtedly a crucial mediator of feeding with a wide range of functions. In the termination phase, histamine is required for both satiation and satiety and prevents further eating. As satiety diminishes, histamine switches its role to driving motivated behaviors geared toward obtaining food in the appetitive phase and organizing rhythmic food intake. In addition, histamine also participates in taste perception and memory during food consumption. However, the circuit basis for functional switching of histamine is unclear and the mechanisms of histamine receptors in feeding are still murky. Employing cutting-edge technologies, dissecting histaminergic circuits, and manipulating histamine receptors in a more spatiotemporally selective manner will help to address these issues and shed light on clinical strategies for the precise regulation of feeding behaviors.

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Conflict of Interests The authors declare that there are no conflicts of interest.

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