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Brain histaminergic system: An emerging target for the treatment of feeding and eating-related disorders

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ABSTRACT

Feeding is an intrinsic and fundamental behavior regulated by complex neurobiological networks that integrate peripheral metabolic signals with neurotransmitter systems within key brain regions. Histamine, a biogenic amine acting as a neuromodulator in the central nervous system, plays a crucial role in the regulation of food intake and energy homeostasis. Within the hypothalamus, histaminergic neurons influence appetite-related circuits, primarily through H_1R and H_3R. Central administration of histamine suppresses food consumption, an effect largely mediated via H_1R. The blockade of H_1R has been associated with increased appetite and weight gain, as observed with certain antihistaminic and antipsychotic drugs. Conversely, H_3R antagonists, which enhance histaminergic tone by preventing autoinhibition, exhibit anorexigenic properties. Histamine also modulates peripheral mechanisms such as gluconeogenesis and ketone body production. Clinically, pharmacological modulation of histaminergic receptors has gained interest as a potential therapeutic approach for treating obesity and related metabolic disorders. Promising results are emerging from clinical trials evaluating the efficacy of betahistine, a drug with a dual pharmacological profile as a weak H_1R agonist and potent H_3R antagonist, in restoring histaminergic tone and counteracting weight gain and metabolic side effects induced by antipsychotic therapies. Reduced H_1R binding in certain brain areas has been observed in patients with anorexia nervosa. In this review, we surveyed the role of brain histamine in the control of eating behavior and energy expenditure. We also described the implications of histamine release in the gut-brain axis and discussed available clinical data regarding the efficacy of histaminergic compounds in eating-related disorders.

1. Introduction

Over the past decades, there has been a rise in the availability and consumption of hyper-palatable foods (HPF), which emerged as a global health concern, triggering altered eating behavior driven by hedonic mechanisms that can lead to eating disorders (EDs) and obesity.

EDs, which include anorexia nervosa (AN), bulimia nervosa (BN), and binge eating disorder (BED) among others, are described in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). EDs are serious and complex mental illnesses characterized by abnormal feeding behaviors and significant weight alterations that have a profound impact on personal and social well-being, quality of life and psychiatric comorbidities [1,2]. The disorders commonly arise during the early adulthood, although their mean onset is decreasing, and predominantly affect women [3,4]. Their prevalence has recently increased, also in connection with the COVID-19 pandemic [5,6]. The incidence of EDs has risen globally, particularly in Western countries [7,8]. Individuals affected by EDs are at risk of severe medical complications, including elevated mortality and suicide rates [9]. Among all EDs, AN presents the highest mortality rate [10], whereas BED is the most

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prevalent [3,11].

EDs are also characterized by profound disturbances in body weight, severe weight loss and underweight due to food restriction in AN, and overweight or obesity resulting from food craving and overeating in BN and BED [12]. Episodes of binge eating, characterized by rapid consumption of HPF and loss of control, are followed in both AN and BN by compensatory behaviors, such as vomiting, use of laxatives or excessive exercise. In BED the frequency and severity of binge episodes can lead to physical and psychological complications, which in turnlimit the ability to lose weight and contribute to its increase [11–13]. Such excessive intake of foods high in fat and sugar combined with sedentary lifestyles leads to an increase and subsequent maintenance of overweight. This makes it challenging to consider obesity and EDs as entirely distinct conditions [14]. Increasing evidence suggests a rising occurrence of EDs among individuals with obesity, underscoring the necessity to adopt integrated methodologies for examining the coexistence of these disorders [14]. Multiple overlapping features that could promote their simultaneous occurrence range from neurobiological and genetic factors to behavioral and psychological influences [14–16]. Fig. 1

Moreover, the overvaluation of body shape and weight is the primary psychological feature of AN and BN, which is not present in BED. Instead, it is the most closely linked or leads to obesity [12]. Prior research has indicated a significant prevalence of lifetime obesity among individuals diagnosed with EDs, particularly BED and BN. The reported lifetime obesity rates for patients with BED vary between 36.2 % and 87.8 %, while those for BN range from 32.8 % to 33.2 % [14,17,18].

Obesity is classified as a physical and metabolic disease, whereas EDs are categorized as psychiatric disorders. However, a better understanding of the psychosocial dimensions of obesity, together with the biological and genetic underpinnings of EDs, may enhance research and therapeutic strategies for both conditions. Emerging findings suggest that shared neurobiological alterations may play a pivotal role in elucidating the effectiveness of research and treatment for both disorders. Continued investigation in this area is essential to elucidate the mechanisms that contribute to their coexistence [14,19]. Thus, a deeper understanding of the neurobiological pathways associated with compulsive eating may lead to substantial therapeutic advancements integrated with psychological interventions, as well as improved prevention and remission rates for patients affected by EDs and/or obesity.

In April 2023, the World Federation of Societies of Biological Psychiatry (WFSBP) published an updated set of guidelines on the pharmacological treatment of EDs [20]. An international task force of clinical and scientific experts conducted a comprehensive and systematic literature review (PubMed, January 2011–January 2022) providing a detailed evaluation of the quality of evidence (Level of Evidence, LoE) and strength of recommendations (Grade of Recommendation, GoR) in accordance with the new WFSBP classification system [21]. The update highlights the limited but evolving role of pharmacotherapy across different EDs subtypes and aims to guide clinicians in selecting appropriate medications based on efficacy, safety, and regulatory approvals. For AN, the evidence supporting pharmacological interventions remains weak. Among nearly 40 drugs considered, olanzapine is the only agent with sufficient data to reach a qualified recommendation: LoE A (strong evidence that the intervention is Effective) and GoR 2 (limited recommendation for using the intervention). These scores are largely based on clinical trials indicating a modest efficacy in promoting weight gain (an effect probably related to its action as an H_1R antagonist at central level). However, the impact on core psychopathological symptoms such as body image disturbance, obsessive thinking, or anxiety are less clear. Importantly, olanzapine has not received marketing authorization for use in AN from any medicine regulatory agency, so its use remains off-label, warranting cautious, primarily adjunctive clinical application [20]. In contrast, for BN there is stronger evidence supporting pharmacological intervention. The guidelines endorse fluoxetine (LoE A; GoR 1 - strong recommendation for using the intervention) due to its efficacy in reducing binge-purge behaviors and improving psychopathological symptoms. Topiramate (LoE: A; GoR: 1) is also endorsed as an effective alternative, particularly for decreasing binge episodes;

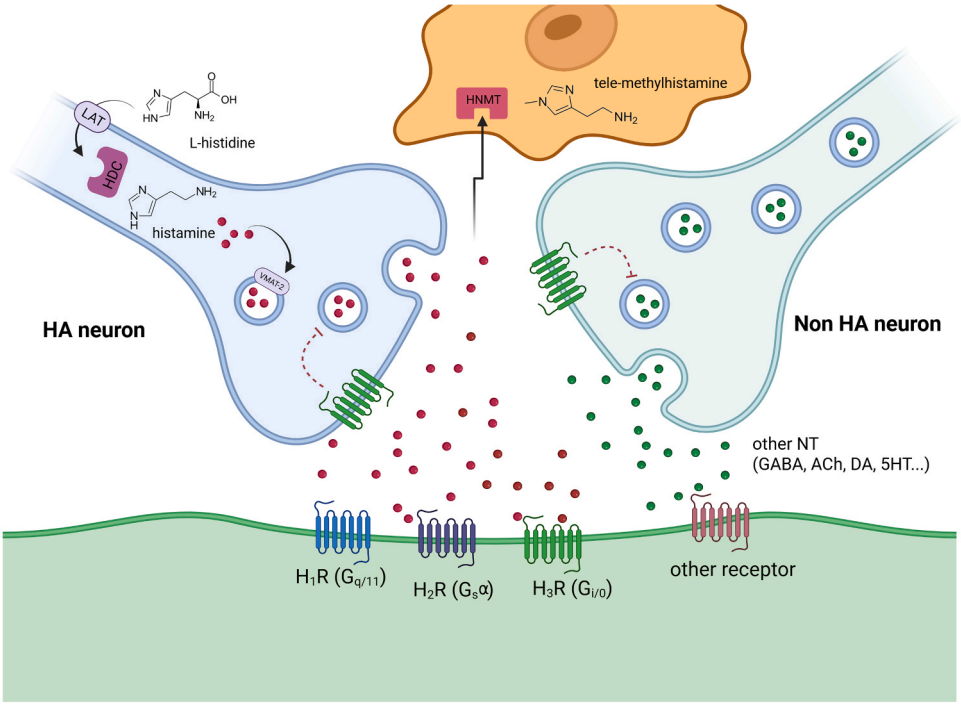

Fig. 1. Histaminergic neurotransmission. L-histidine is transported into neurons by L-amino acid transporter (LAT) and converted into histamine (HA) by the specific enzyme histidine decarboxylase (HDC). Subsequently histamine is taken up into vesicles by the vesicular monoamine-transporter (VMAT-2) and stored until release. In the extracellular space HA interacts with specific receptors, H1Rs and H2Rs located on post-synaptic membrane, and H3Rs located on histaminergic and other cell somata, dendrites and axons (varicosities) where they provide feedback modulation to inhibit histamine and other transmitters synthesis and release. Finally, HA is catabolized into the inactive metabolite tele-methylhistamine by the enzyme histamine N-methyltransferase (HNMT) in glial cells.

however its use is limited by potential adverse effects, including cognitive impairment and teratogenic risks, which make it contraindicated during pregnancy and lactation. Like olanzapine, topiramate is used off-label. Regarding BED, two agents are recommended: lisdexamfetamine and topiramate, both rated LoE A and GoR 1. Lisdexamfetamine shows robust efficacy in reducing binge frequency and improving weight-related outcomes and is the only the U.S. Food and Drug Administration (FDA)-approved drug for BED pharmacotherapy. Although the drug has received regulatory approval, it is not without adverse effects; the most commonly reported are headache, insomnia, and dry mouth. Topiramate is also effective, but it carries the same concerns reported above. For other EDs, such as avoidant/restrictive food intake disorder (ARFID), pica, and rumination disorder, the available evidence is insufficient to support any formal pharmacological recommendations [20].

Pharmacotherapeutic options for EDs remain limited, and the few available agents are often constrained by modest efficacy and significant side effects, highlighting the urgent need to identify novel therapeutic targets. In this context, histamine is emerging as a promising and innovative target. Histamine is a biogenic amine released in the brain and in peripheral organs and it is one of the main actors involved in homeostatic and metabolic processes related to the regulation of food intake and energy metabolism. This review aims to present a comprehensive update on the involvement of histamine and its receptors in the modulation and regulation of feeding behavior and body weight and discuss its potential as pharmacological target for the treatment of metabolic and eating-related disorders.

2. The brain histaminergic neurotransmitter system

The hypothesis that histamine plays functional roles within the brain was first proposed in the 1940s, based on the sedative effects observed following the administration of classical antihistamine drugs. However, technical limitations in demonstrating the presence of histamine in brain tissues hindered the acceptance of this amine as a neurotransmitter. It was only in the early 1980s that two pivotal discoveries led to the recognition of a central histaminergic neurotransmitter system, analogous to other monoaminergic systems. The first was the identification of a novel histaminergic receptor, the H_3 receptor (H_3R), functioning as an autoreceptor on histaminergic neurons [22]. The second was the development of specific antibodies targeting either histamine or histidine decarboxylase (HDC), the enzyme responsible for its synthesis that enabled the anatomical identification of histaminergic neurons, localized within the tuberomammillary nucleus (TMN) of the posterior hypothalamus [23,24]. It is now well established that histaminergic neurons originating from the TMN project extensively throughout the central nervous system. A recent study combining state-of-the-art methodologies such as genetic labeling strategies, tissue-clearing techniques, and fluorescence micro-optical sectioning tomography generated a comprehensive whole-brain map of histaminergic projections in the mouse brain. The map revealed that areas exhibiting dense histaminergic innervation were primarily located in the hypothalamus; regions with moderate innervation were predominantly found in the midbrain and limbic system, whereas cortical and cerebellar regions displayed the lowest density of histaminergic fibers [25].

Neuronal histamine is synthesized from its precursor, the amino acid L-histidine, through a single-step decarboxylation reaction catalyzed by HDC. Once synthesized, histamine is transported into synaptic vesicles via the vesicular monoamine transporter 2 (VMAT2), where it is stored until release. Upon neuronal activation and the influx of Ca^{2+} through voltage-gated calcium channels, histamine is released into the extracellular space via varicosities along histaminergic axons [26]. In the extracellular space, histamine can bind to specific G protein-coupled receptors - H_1R, H_2R, H_3R, and H_4R - or undergo enzymatic inactivation through methylation by histamine N-methyltransferase (HNMT), yielding the inactive metabolite tele-methylhistamine [27].

H_1Rs are postsynaptic and widely distributed throughout the central nervous system (CNS), though their density does not always correlate with the extent of histaminergic innervation. Autoradiographic studies using [^{3}H]mepyramine revealed high H_1R densities in regions involved in cognition, arousal, feeding, and behavioral regulation such as the hypothalamus, thalamus, cortex, and aminergic and cholinergic brainstem nuclei. Histamine activates neurons in these regions via H_1Rs, which are coupled to G_q proteins and mediate excitatory signaling [26–28].

H_2Rs, also postsynaptic, share a similar distribution to H_1Rs but show a closer anatomical correspondence with histaminergic projections, particularly in rodents. High densities of H_2Rs are found in the amygdala, hippocampus, cortex, and basal ganglia. H_2Rs also mediate excitatory responses, primarily via G_s protein activation of the cAMP–PKA–CREB signaling cascade, which is involved in regulating synaptic plasticity [26–28].

H_3Rs are functionally and anatomically distinct. Unlike H_1Rs and H_2Rs, which are found in both neurons and glial cells, H_3Rs are exclusively neuronal and act primarily as presynaptic autoreceptors to inhibit histamine release from histaminergic neurons. They also function as heteroreceptors, modulating the release of other neurotransmitters such as GABA, glutamate, acetylcholine, and noradrenaline. H_3Rs are broadly distributed in the cerebral cortex, hippocampus, amygdala, striatum, nucleus accumbens, olfactory tubercle, cerebellum, substantia nigra, and brainstem, exerting their effects through $G_{i/o}$ protein signaling [26–28].

H_4Rs, the most recently identified histamine receptor subtype, are primarily expressed in peripheral immune-related tissues such as bone marrow and leukocytes. However, they have also been detected in the dorsal root ganglia, spinal cord, and selected cortical and thalamic brain regions. Despite structural and pharmacological similarities to H_3Rs, the physiological role and therapeutic relevance of H_4Rs in the CNS remain poorly understood and require further investigation [26–28].

3. Brain histamine modulates food consumption

The inverse relationship between central histaminergic activity and feeding behavior has been known for several decades. Early studies demonstrated that intracerebroventricular (i.c.v.) administration of histamine into the lateral ventricles of cats [29] or rats [30] as well as direct injection into the suprachiasmatic nucleus of the hypothalamus of rats [31], elicited prolonged suppression of food intake. Similar anorexigenic effects were observed following systemic administration of L-histidine, a histamine precursor [32–36], or metoprine, an HNMT inhibitor [37]. Conversely, inhibition of neuronal histamine synthesis via administration of α-fluoromethylhistidine (α-FMH), an HDC irreversible inhibitor, into the lateral ventricles or into hypothalamic nuclei such as the ventromedial (VMH) or paraventricular nucleus (PVN), significantly increased food consumption [38–40]. Consistently, genetically modified mice lacking the ability to synthesize histamine (*Hdc*$^{-/-}$ mice) exhibited increased caloric intake and body weight starting at 16 weeks of age [41], along with enhanced susceptibility to high-fat diet-induced obesity (DIO) [42]. Histamine appears to regulate both meal size and duration. Depletion of histamine in the mesencephalic trigeminal sensory nucleus slowed the rate of consumption, while histamine depletion in the VMH increased both the quantity and duration of feeding [43]. Neuronal histamine also plays a critical role in modulating circadian feeding rhythms. Continuous infusion of α-FMH into the lateral ventricles disrupted the light–dark cycle of feeding, drinking, and locomotion in rats fed *ad libitum* [44]. Food availability is a potent circadian signal, and when feeding is restricted to a predictable time, animals display anticipatory locomotor activity which is indicative of increased arousal and feeding motivation [45]. A series of studies demonstrated a key role for brain histamine in food-related arousal and motivation. For instance, cluster-specific activation of histaminergic neurons within the E3 subregion of the TMN was observed immediately

before mealtime in food-restricted rats subjected to a scheduled feeding [46–48]. Additionally, histamine levels in the hypothalamus increased when hungry rats were exposed to inaccessible palatable food. Such an increase was not observed in animals fed *ad libitum,* indicating that histamine activity is closely related to motivational state [49]. Furthermore, optogenetic studies showed that histaminergic activation during the appetitive phase enhances motivation by engaging prefrontal circuits, particularly the infralimbic cortex [50]. There is also evidence supporting a role for brain histamine during the consummatory phase of feeding behavior revealed by a transient increase in hypothalamic histamine release was observed when fasted animals were refed [51,52].

Sensory inputs, including taste and texture, can also influence histaminergic tone. For instance, feeding on hard pellets increased histamine release from the amygdala, whereas soft pellets had no significant effect [53]. Regarding gustatory stimuli, it was demonstrated that they can modulate the histaminergic activity by two mechanisms: the physiological excitation of the chorda tympani nerve, one of the taste nerves [54], and by the emotional response elicited by taste perception, i.e., taste palatability [55]. In rodents, taste stimuli that are described by humans as “bitter” or “nauseous” are rejected while those described as “sweet” or “pleasurable” by humans are avidly accepted [56]. Aversive taste stimuli like NaCl, HCl or quinine enhanced hypothalamic histamine release in mice, whereas palatable stimuli such as sucrose and saccharin suppressed it. These findings support the hypothesis that histamine release is associated with aversive taste stimuli, potentially serving to limit intake of unpalatable foods. Conversely, the suppression of histamine release by palatable foods may contribute to overconsumption [52].These findings suggest that palatable food blunts histamine release which may results in overeating [52].

The involvement of different histaminergic receptors on feeding regulation is a current area of research. A list of histaminergic ligands and their effects on food intake is reported in Table 1. Initial investigations indicated that dietary composition influences central histaminergic signaling. An increased expression of H_1R expression in brain tissue was reported in rats exposed to low-protein or poor-quality diets. Such an alteration was associated with reduced food consumption [57]. In contrast, animals maintained on low-energy diets exhibited decreased H_1R levels, accompanied by increased caloric intake. These observations were validated by pharmacological studies: central administration of H_1R agonists suppressed feeding, whereas localized infusion of H_1R antagonists into the VMH or PVN, but not the lateral (LH) or dorsomedial hypothalamus (DMH), elicited feeding responses characterized by increased meal size and duration [44, 58–63]. In keeping with these findings, the phenotype of H_1R knockout mice (*Hrh1*$^{-/-}$) includes elevated food intake, visceral adiposity, and alterations in metabolic impairments, such as hepatic steatosis, hyperglycemia, and insulin resistance when submitted to high-fat diets [64,65].

The role of H_2R in feeding control is less clear. Early pharmacological studies reported negligible effects for both H_2R agonists and antagonists on feeding behavior in rodent models [30,59,62,66,67]. However, recent advances employing opto- and chemogenetic manipulation and fiber photometry revealed a functional TMN-medial septum circuit that is transiently suppressed during food intake [68]. The same study demonstrated that the activation of H_2R specifically expressed in the glutamatergic neurons of the medial septum resulted in anorexigenic effects. Notably, the downregulation of H_2R within this neuronal population as well as the treatment with H_2R agonist attenuated body weight gain in a mouse model of DIO [68].

The pharmacological blockade of H_3R, which increases histamine turnover in the brain, resulted in consistent reduction of food intake and improvement of metabolic parameters in preclinical models. For instance, treatment with several H_3R antagonists reduces energy intake, body weight, and circulating triglyceride levels in both lean and leptin-resistant DIO mice (reviewed in [69,70]). These effects seem to be mediated through downstream H_1R signaling, as co-administration of H_1R antagonists mitigates the anorectic action of H_3R blockade [71]. It was also demonstrated that H_3R antagonists blunt the hyperphagic effects of neuropeptide Y (NPY) [72,73] and potentiate cholecystokinin (CCK)-induced satiety signals [74]. On the other hand, experiments evaluating the impact of H_3R agonists on feeding behavior provided mixed results: peripheral administration of H_3R agonists has been associated with increased food intake in mice [42], whereas central administration in rats fails to reproduce this effect [30]. Despite the lack of effects *per se,* H_3R agonists such as R-α-methylhistamine and imetit attenuate satiety signals elicited by amylin [75], bombesin [76], and CCK [74], suggesting a modulatory role for the central histaminergic system.

Additional insights into the role of H_3R in body weight regulation come from studies in hibernating and seasonally adapting mammals. During hibernation, when overall brain activity is markedly reduced, histaminergic tone appears paradoxically enhanced. In ground squirrels (*Citellus lateralis*), histamine and its metabolite tele-methylhistamine accumulate in the hypothalamus and hippocampus, along with an increase in histaminergic fiber density [77]. Although Siberian hamsters (*Phodopus sungorus*) are not classified as true hibernators, they exhibit natural reductions in food intake and body weight in response to winter photoperiods [78]. Interestingly, in these animals, *Hrh3* mRNA expression in the posterior hypothalamus is significantly decreased during the lean state associated with short-day photoperiods. Upon transition to a stimulatory long-day photoperiod, H_3R expression levels increase rapidly, coinciding with the recovery of body weight. Pharmacological evidence further supports a role for H_3R in seasonal energy regulation: administration of the H_3R agonist imetit increased food intake, whereas H_3R antagonists such as clobenpropit and thioperamide suppressed feeding in lean hamsters [79]. A similar pattern of seasonal regulation has been observed in golden hamsters (*Mesocricetus auratus*), where *Hrh3* mRNA expression varies with both developmental stage and brain region, being prominent in the cortex and hippocampus during puberty and in the amygdala during adult hibernation [80]. Notably, thioperamide significantly reduced food intake in adults, but not pubertal animals, suggesting a developmental or state-dependent modulation of H_3R signaling.

Despite substantial evidence supporting an anorexigenic effect of H_3R antagonism, not all experimental data align with this interpretation. In a study using a DIO model, Yoshimoto et al. (2006) unexpectedly reported that H_3R activation reduced whereas the blockade increased food intake and body weight. These effects appeared to occur via mechanisms independent of histamine release, challenging the canonical view of H_3R function [81]. Similarly, Sindelar and et al. found that thioperamide reduced food intake and induced conditioned place aversion when administered intraperitoneally (i.p.), but not when administered orally (gavage), despite achieving similar pharmacokinetic profiles, receptor occupancy, and central histamine turnover. These findings led the authors to propose that central H_3R blockade may not be directly responsible for the anorectic effects observed, contradicting earlier reports in which i.c.v. administration of H_3R antagonists reliably suppressed food intake in a histamine-dependent manner [82].

Genetic models have also yielded inconsistent results. No significant difference in terms of body weight were found between H_3R knockout (*Hrh3*$^{-/-}$) mice and their wild-type littermates, suggesting a marginal role for H_3R in baseline energy homeostasis [83]. In contrast, Takahashi and colleagues (2002) described a markedly hyperphagic and obese phenotype for *Hrh3*$^{-/-}$ mice, characterized by decreased energy expenditure and disrupted regulation of food intake resembling the phenotype described to *Hrh1*$^{-/-}$ animals [84]. The authors also reported elevated hypothalamic histamine levels in *Hrh3*$^{-/-}$ mice and hypothesized that chronic histamine overexposure could lead to H_1R desensitization, which in turn promotes hyperphagia [84]. These paradoxical findings underscore the complexity of H_3R receptors on feeding behavior and suggest that effects on energy balance may involve not only histamine release but also receptor plasticity and interactions with other neurotransmitter systems.

Table 1
Effects of histaminergic ligands on food consumption and body weight.

Compound	Model	Treatment	Main Outcomes		Reference
			Food Intake	Body Weight	
H1R AGONIST					
2-(3-trifluoromethylphenyl) histamine	rat	200nmol, i.c.v.	↓	NI	[30]
H1R ANTAGONISTS					
Cetirizine	mouse (HFD)	4 mg/kg, i.p.	NE	↑	
Chlorpheniramine	rat	0.12–0.52 μmol, i.c.v.	↑	NE	[58, 59, 61–63, 66, 67, 191]
	rat	0.26–0.52 μmol, intra VMH/PVN	↑	NE	[59,62,63,66,67]
	rat	0.26–0.52 μmol, intra DMH/LH/ POAH/CX	-	NE	[59,62,63,66,67]
	Zucker rat	0.26 μmol, i.c.v.	-	NE	[58,61,191]
	rat	5–10 mg/kg, i.p.	↓	NE	[33]
Cyproheptadine	rat	0.625–5 mg/kg, i.p.	↑	NE	[35]
	rat	2.5 mg/kg, i.p.	↑	↑	[192]
Diphenydramine	rat	2 mg/kg, i.p.	↑	↑	[192]
Fexofenadine	mouse (HFD)	40 mg/kg i.p.	-	↑	[193]
Mepyramine	rat	0.12–0.26 μmol, i.c.v.	↑	NE	[59,62,66,67]
	rat	20 mg/kg, i.p.	↑ (light phase)	NE	[194]
Promazine	rat	3 mg/kg, i.p.	↑	↑	[192]
Promethazine	rat	0.12–0.26 μmol, i.c.v.	↑	NE	[59,62,66,67]
	rat	0.5–1 mg/kg, i.p.	↑	NE	[35]
Tiprolidine	rat	82 μg, i.c.v.	↑	NE	[195]
H2R AGONIST					
Dimaprit	rat	0.1 μmol, i.c.v.	-	NE	[30]
Amthamine	mouse	10 μmol, intra MS, 42 days	↓	↓	[68]
H2R ANTAGONISTS					
Cimetidine	rat	0.04–0.48 μmol, i.c.v.	-	NE	[59,62,66,67]
Famotidine	rat	0.015–0.06 μmol, i.c.v.	-	NE	[59,62,66,67]
Lamtidine	rat	0.4 μmol, i.c.v.	↓	NE	[30]
Ranitidine	rat	100 mg/kg, i.p.	↓ (dark phase) - (light phase)	NE	[194]
H3R AGONISTS					
Imetit	rat	50–100 nM, i.c.v. 10 mg/kg, i.p.	↑	NE	[196]
Imepip	rat	200–300 nmol, i.c.v.	↑	-	[197]
RAMH	rat	100 nmol, i.c.v.	-	NE	[194]
	mouse	10 mg/kg, i.p.	-	NE	[42]
H3R ANTAGONISTS					
(4,4-Difluoropiperidin−1-yl)[1-isopropyl−5-(1-isopropylpiperidin-4-yloxy)−1*H*-indol−2-yl]methanone	rat (HFD)	10–20 mg/kg, p.o., 17 days	↓	↓	[198]
A−304121	rat	10–30 mg/kg, i.p., 15 days	-	-	[199]
A−331440	mouse (HFD)	5–15 mg/kg, p.o., 28 days	↓	↓	[71, 200–202]
A−423579	mouse (HFD)	10 mg/kg, p.o., 28 days	NE	↓	[202,203]
	rat (HFD)	10 mg/kg, p.o., 28 days	NE	↓	[202,203]
A−417022	mouse (HFD)	30 mg/kg, p.o., 28 days	NE	↓	[202,203]
A−631972	mouse (HFD)	0.5–1.5 mg/kg, p.o., 28 days	NE	-	[71]
ABT−239	mice	3–10 mg/kg, i.p.	↓	NE	[109]
Ciproxifan	rat	3–10 mg/kg, i.p., 15 days	↓	↓	[199]
Clobenpropit	mice	5 mg/kg, i.p.	↓	NE	[204]
	mouse (HFD)	5 mg/kg, i.p.	↓	NE	[204]
Compound 4c	mouse	20 mg/kg, p.o., 42 days	↓	↓	[205]
	ob/ob mouse	20 mg/kg, p.o., 28 days	↓	↓	[205]
Compound 6 K	Mouse (HFD)	10–20 mg/kg, p.o.	↓	NE	[206]
Compound 9	rat (HPD)	10 mg/kg, i.p. 28 days	↓	↓	[207]
Compound 17	mouse (HFD)	1–10 mg/kg, p.o., 4 days	NE	↓	[208]
GT−2016	rat	3–10 mg/kg, i.p.	↓	NE	[71]
GT−2394	rat	10 mg/kg, i.p.	↓	NE	[71]
	Zucker rat	3–10 mg/kg, p.o.	↓	↓	[71]
JNJ−5207852	*ob/ob* mouce	3–10 mg/kg, i.p., 28 days	-	-	[209]
KSK−19	rat (HFHS)	10–15 mg/kg, i.p. 28 days	↓	↓	[210]
KSK−59	rat (HPD)	10 mg/kg, i.p. 28 days	NE	↓	[211]
KSK−61	rat (HPD)	10 mg/kg, i.p. 28 days	NE	↓	[212]
KSK−63	rat (HPD)	10 mg/kg, i.p. 28 days	NE	↓	[212]
KSK−64	rat (HPD)	10 mg/kg, i.p. 28 days	NE	↓	[212]
KSK−69	rat (HPD)	10 mg/kg, i.p. 28 days	NE	↓	[212]
KSK−70	rat (HPD)	10 mg/kg, i.p. 28 days	NE	↓	[212]
KSK−73	rat (HPD)	10 mg/kg, i.p. 28 days	NE	↓	[211]
NNC 38–1049	rat	15–60 mg/kg, p.o.	↓	NE	[213,214]

(*continued on next page*)

Table 1 (*continued*)

Compound	Model	Treatment	Main Outcomes		Reference
			Food Intake	Body Weight	
	rat (HFD)	10–20 mg/kg, p.o., 15 days	↓	↓	[214]
NNC 38–1202	rat	15–30 mg/kg, p.o.	↓	NE	[213]
	rat (HFD)	5 mg/kg, p.o., 22 days	↓	↓	[213]
pitolisant	Mouse (HFHS)	10 mg/kg, i.p., 14 days	-	↓	[215]
Proxyfan	rat	5 mg,kg, i.p.	-	NE	[197]
Thioperamide	rat	0.1 μmol, i.c.v.	↓	NE	[39,58,61,191,216]
	Zucker rat	0.1 μmol, i.c.v.	-	NE	[39,58,61]
	rat	400 nM, i.c.v.	↓	NE	[196]
		0.5–2.5 mg/kg, i.p.			
	rat	200 nmol, i.c.v.	↓	NE	[30]
	rat	5 mg/kg, i.p.	-	NE	[194]
	rat	30 mg/kg, i.p.	↓	NE	[82]
	rat	10–30 mg/kg, p.o.	-	NE	35)
	mouse	10 μmol, intra MS	↓	NE	[68]

↑ = increase, ↓ = reduction, - = no effect, NE = not evaluated, i.c.v. = intracerebroventricular, i.p. = intraperitoneal, p.o. = *per os*, HFD = high fat diet, HFHS = high fat and high sugar diet, HPD = high palatable diet, CX= cerebral cortex, DMH = dorsomedial hypothalamus, LH = lateral hypothalamus, MS = medial septum, POAH = preoptic anterior hypothalamus, VMH = ventromedial hypothalamus.

4. Histamine signaling in the gut–brain axis: crosstalk with hormones regulating feeding behavior

The gastrointestinal tract and adipose tissue secrete over 20 distinct hormones which are involved in the modulation of a wide range of physiological functions. Beyond their local paracrine actions and systemic endocrine effects, these hormones serve as key messengers conveying the body's nutritional status to central appetite-regulating centers, including the hypothalamus and brainstem. These brain regions integrate peripheral metabolic signals with internal cues, such as mood and reward pathways, to modulate sensations of hunger and satiety [85,86].Thus, feeding behavior is governed by a highly intricate network of peripheral and central signals, within which brain histamine appears to function as an integrative hub, bridging external metabolic inputs with central regulatory mechanisms.

Leptin, a hormone primarily secreted by adipocytes, exhibits circulating concentrations that closely correlate with total body fat mass [87]. Both peripheral and central leptin administration significantly elevate central histamine levels [88]. Serum leptin levels are markedly increased in *Hdc*$^{-/-}$ mice [89], whereas reduced hypothalamic histamine concentrations were found in *db/db* mice carrying an inactivating mutation in the leptin receptor which results in hyperphagia, severe obesity and diabetes [90]. Interestingly, the hyperphagic and obese phenotypes can be reversed by chronic i.c.v. histamine infusion [91]. Leptin's anorexigenic effects are significantly blunted in animals depleted of histamine by injections of α-FMH [92,93] and in *Hrh1*$^{-/-}$ mice [88,91]. Also, leptin-induced upregulation of uncoupling protein 1 (UCP1) in brown adipose tissue (BAT) and UCP3 in white adipose tissue (WAT) are impaired in *Hrh1*$^{-/-}$ mice [91]. It is well known that leptin stimulates the production of proopiomelanocortin (POMC) in the hypothalamus, which subsequently activates melanocortin 4 receptors (MC4R), a key pathway in the regulation of energy homeostasis [94]. Agouti yellow (A^y/a) mice develop obesity because they overexpress agouti-related protein, a physiological melanocortin receptor MC4R antagonist. In these mice, central administration of histamine leads to decreased food intake and body weight, as well as enhanced UCP1 expression in BAT. These effects are significantly attenuated in H_1R-deficient A^y/a obese mice [95]. Glucagon-like peptide-1 (GLP-1), a gut-derived incretin hormone, is secreted by intestinal enteroendocrine cells shortly after nutrient intake. It plays a critical role in reducing food consumption, inhibiting glucagon secretion, and delaying gastric emptying. These physiological effects have led to the development of GLP-1 receptor agonists for the treatment of type 2 diabetes and obesity [96]. Interestingly, it was demonstrated that central administration of GLP-1 in rats, which determines a pronounced anorexigenic effect, increase histamine turnover in the hypothalamus [97], raising the hypothesis that central histaminergic system can contribute to the effects induced by GLP-1 agonists.

Thyrotropin-releasing hormone (TRH), a hormone produced by produced by PVN neurons in the hypothalamus, suppresses food intake [98]. TRH-containing axons innervate the TMN [98] and the two TRH receptors are expressed in most histaminergic neurons [99]. Electrophysiological experiments revealed that TRH increases histaminergic neurons firing rate [99]. Central infusion of TRH suppressed food intake and increased hypothalamic histamine turnover. Such effects were blunted in histamine-deprived rats [100] and *Hrh1*$^{-/-}$ mice [101].

Similar observations were reported for the hypophagic effect of nesfatin-1 [101]. In fact, nesfatin-1 increased histamine turnover, whereas histamine increased nesfatin-1 levels in the hypothalamus. Nesfatin-1-suppressed feeding was partially attenuated in rats treated with α-FMH, *Hrh1*$^{-/-}$ mice [101].

Estrogens also exert anorexigenic effects and ovariectomy-induced estrogen deficiency leads to increased food intake and weight gain in female mice. Such mechanism is hypothesized to be involved in the increased incidence of obesity in post-menopausal women. Estrogen supplementation reverses the effects of ovariectomy on energy balance. Interestingly, the estrogen receptor α (Esα) is expressed on histaminergic neurons and the anorexic effect of estrogens is attenuated in *Hrh1*$^{-/-}$ mice [102].

Histaminergic and orexinergic systems provide distinct yet synergistic contributions to the regulation of wakefulness. These two neuronal populations are anatomically interconnected and exhibit reciprocal influences. For instance, microinjection of orexin A into the TMN enhances histamine release in brain regions such as the medial preoptic area and frontal cortex, resulting in increased arousal [103]. Similarly, i.c.v. administration of orexin A promotes wakefulness, stimulates feeding behavior, and upregulates NPY mRNA expression in wild-type mice but not in *Hrh1*$^{-/-}$ mice. Notably, baseline NPY expression was found to be approximately fourfold higher in these animals than in wild-type controls [42]. Further supporting this notion, central administration of NPY led to a delayed and transient increase in histamine release in rats, while promoting a more pronounced hyperphagic response in *Hrh1*$^{-/-}$ mice compared to wild-type animals. These findings suggest that histamine may exert a negative feedback influence on NPY-induced feeding behavior [104]. Oleoylethanolamide (OEA) is a fatty-acid ethanolamide produced in the small intestine in response to dietary fat [105]. It locally activates vagus nerve afferents that project to the nucleus tractus solitarius (NTS) in the brainstem. From there,

noradrenergic neurons relay the signal to the PVN stimulating oxytocin release which is required for OEA effect [106,107]. Consistently, blockade of oxytocin receptors prevents OEA-induced hypophagic effect [108]. In histamine-deficient mice (*Hdc*$^{-/-}$ and α-FMH treated mice) the anorexigenic effects of OEA are markedly reduced [109]. indicating that histaminergic neurotransmission contributes to OEA's regulation of feeding behavior. OEA treatment also resulted in increased c-Fos expression in histaminergic neurons and enhanced histamine release in the cortex of food-deprived mice [109]. Moreover, OEA-induced activation of oxytocin-producing neurons in the PVN and other appetite-regulating regions was significantly blunted in *Hdc*$^{-/-}$ mice, providing a mechanistic explanation for the reduced anorectic response to OEA in the absence of histamine [109,110].

5. Central and peripheral histamine modulate energy homeostasis

Brain histamine plays a dual role in energy balance by suppressing food intake and promoting energy expenditure [111]. Thermogenesis, a major component of energy expenditure in homeothermic organisms, is partly mediated by uncoupling proteins (e.g., UCP1), which facilitate heat production in BAT and are essential for maintaining core body temperature [112]. Both central and peripheral histamine contribute to the regulation of this process. Histamine-deficient mice exhibit reduced UCP1 expression in BAT [41]. Histamine infusion into the lateral ventricles or the preoptic area, but not into the LH or VMH, upregulates UCP1 expression in BAT and UCP2 in WAT, and enhances sympathetic nerve activity to BAT [64,113] suggesting that the preoptic area is a key site for histaminergic modulation of thermogenesis. Indeed, elevated histaminergic activity within this region also increases core body temperature, lowers the respiratory exchange ratio, and suppresses food intake [113].

During cold exposure, mast cells in human adipose tissue respond to thermal stress by releasing histamine and other mediators that induce the expression of UCP1, promoting thermogenesis by uncoupling mitochondrial electron transport and stimulating lipolysis, thereby initiating the beiging of WAT [114,115]. In addition to their thermogenic function, beige adipocytes within BAT contribute to improved lipid and glucose metabolism. In this regard, Kimura and colleagues proposed that central histamine downregulates hepatic gluconeogenic gene expression through the activation of H_1R [116]. This highlights the broader role of histamine in coordinating communication between the brain and peripheral organs. Supporting this, H_1R signaling in both the central nervous system and pancreatic tissue has been shown to regulate glucose metabolism. In contrast, H_2R activation appears to mediate peripheral effects, particularly in the liver and skeletal muscle, by engaging the adiponectin system, which modulates both lipid and glucose metabolism [65]. *Vice versa,* the brain histaminergic system is responsive to fluctuations in blood glucose levels. Glycemic variability has been shown to downregulate histamine receptor expression in hippocampal neurons and astrocytes [117], which may impair astrocytic glutamate clearance and contribute to excitotoxicity and cognitive dysfunction in diabetes [118,119].

Peripheral histamine also plays a critical role in metabolic adaptation to both nutrient intake and energy deprivation. During fat absorption, intestinal mucosal mast cells degranulate, releasing histamine into the circulation [120]. Mast cells also have an unexpected role in the regulation of ketogenesis, a crucial metabolic adaptation in response to prolonged periods of food shortage. It was shown in mice that after 12 h of food deprivation, histamine is released from the mast cells into the portal circulation and stimulates, by activating H_1R, the hepatic production of OEA, a high-affinity peroxisome proliferator-activated receptor alpha (PPARα) agonist. Activation of PPARα, in turn, increases the production of energy-rich ketone bodies [121]. Pharmacological or genetic disruption of any one of these steps in the histamine-OEA-PPARα axis, including histamine depletion or H_1R antagonism blunts ketogenesis [122]. Notably, long-term exposure to a high-fat diet suppresses fasting-induced release of histamine into the portal circulation, thereby reducing histamine-dependent OEA synthesis in the liver [123]. The specific mast cell subpopulation responsible for fasting-induced histamine release has yet to be identified, but the most probable candidates are intestinal mucosal mast cells. Chronic high-fat diet exposure also promotes mast cells infiltration and degranulation into the kidney, two processes that along with increased histamine levels are presumably responsible for renal dysfunctions in rats [124].

6. Brain histamine in feeding and eating-related disorders: clinical findings

Growing clinical evidence suggests that pharmacological modulation of the histaminergic system may significantly impact body weight regulation and body mass index (BMI). For instance, Ratliff et al. analyzing data from the 2005–2006 National Health and Nutrition Examination Survey (NHANES), identified a significant association between the use of H_1R antagonists (cetirizine, fexofenadine, desloratadine) and risk of obesity in adults. Indeed, the odds ratio (OR) for being overweight was significantly increased in antihistamine users when compared to age and sex matched healthy subjects (males: 1.70; 95 % CI, 1.23–2.31; females: 1.21; 95 % CI, 0.98–1.49). The use of H_1R antagonists was also associated with higher waist circumference and increased circulating insulin levels [125].

Associations between the use of antihistamines and alterations in body weight have been reported in pediatric populations. A large retrospective cohort study involving over 333,000 children demonstrated that prescriptions of antibiotics, H_2R antagonists, or proton pump inhibitors (PPIs) within the first two years of life were associated with a higher incidence of early childhood obesity. The risk was further elevated in case of combined drug exposure or prolonged treatments (>30 days). Interestingly, the relationship between treatment with H_2R antagonists and obesity seems to be sex-specific, as the increased risk was observed predominantly in male children. The authors speculate that drug-induced gut microbiota alterations may be a mechanism underlying the link between early-life drug exposure and obesity [126]. Saad et al. provided further evidence supporting the association between childhood use of antihistamines and the risk of obesity. This retrospective analysis included 39 obese pediatric patients diagnosed with non-alcoholic fatty liver disease (NAFLD), who were either exposed or not exposed to H_1R antagonists (diphenhydramine, hydroxyzine, cetirizine, loratadine) or H_2R antagonists (famotidine or ranitidine). Children exposed to antihistamines exhibited significantly higher BMI, BMI percentiles, and BMI z-scores (a more standardized anthropometric indicators for growing children) compared to non-exposed peers. Notably, total cholesterol and low-density lipoprotein (LDL) levels were lower in the antihistamine group, while hepatic enzyme levels, fasting glucose, triglycerides, and high-density lipoprotein (HDL) cholesterol were similar between the two groups [127]. Preclinical data corroborates these findings. Chronic administration of desloratadine in rats induced an obesity-like phenotype, characterized by significant weight gain, increased abdominal subcutaneous fat, intracapsular brown fat accumulation, and metabolic alterations including elevated serum triglycerides, HDL, fasting glucose, liver-to-body weight ratio, and hepatic steatosis [128]. Similarly, chronic exposure to cetirizine or fexofenadine exacerbated the progression of hepatosteatosis in mice fed with a high-fat diet. This effect was associated with significantly increased serum glucose and hepatic bile acid levels [129]. Second-generation H_1R antagonists have low affinity for muscarinic receptors, which are involved in the regulation of glucose metabolism through activation of vagal efferent pathways. Although these drugs have a reduced ability to cross the blood–brain barrier, their central penetration is not negligible and thus, central histaminergic blockade cannot be entirely ruled out. Consequently, the metabolic and homeostatic effects of antihistamines are likely mediated through a combination of central H_1R blockade and

peripheral mechanisms, potentially involving indirect modulation of muscarinic signaling. The precise contribution of central versus peripheral pathways in mediating these metabolic outcomes warrants further investigation.

Preclinical evidence has highlighted the H_1R as a promising target for the development of novel anti-obesity therapies. However, from a clinical perspective, no selective and potent brain-penetrant H_1R agonists have been identified. Moreover, these compounds would be associated with intolerable side effects affecting the cardiovascular, respiratory, or gastrointestinal systems that would limit their use. As an alternative, strategies aimed at enhancing endogenous histamine release, using H_3R antagonists or inverse agonists, offer a valid strategy. These drugs disinhibit histaminergic neurons, hence indirectly increasing histamine levels in the brain. In studies testing the efficacy of compounds, such as pitolisant and MK-0249 for the treatment of narcolepsy [130], attention-deficit/hyperactivity disorder [131], schizophrenia [132], and epilepsy [133], no significant weight changes were reported among participants. Nevertheless, these compounds may still hold therapeutic potential in contexts more directly related to eating behavior or metabolic regulation.

One attempt to explore this potential involved a multicenter, randomized, placebo-controlled phase II clinical trial assessing the efficacy of the H_3R antagonist SCH497079 in overweight and obese individuals. However, the results, as reported on ClinicalTrials.gov, were underwhelming. After 12 weeks of treatment, there were no meaningful differences between the active drug and placebo groups in terms of weight loss (–0.51 kg vs. –0.92 kg), body mass index reduction (–0.12 vs. –0.32), or waist circumference (–1.22 cm vs. –0.94 cm). Furthermore, the proportions of participants achieving more than 10 % (1.6 % vs. 0.8 %) or more than 5 % (7.1 % vs. 11.5 %) weight loss from baseline were comparable across groups. These outcomes fall well short of the efficacy thresholds defined by the FDA for weight management therapies. Specifically, the FDA requires either a statistically significant decrease in body weight of $\geq$ 5 % beyond the placebo effect, or [2] that at least 35 % of patients lose $\geq$ 5 % of their body weight after one year of treatment [134].SCH497079 did not meet the criteria for further development as a weight-loss medication. The sharp contrast between favorable preclinical findings and disappointing clinical data underscores the complexity of translating histaminergic modulation into effective anti-obesity interventions. Further research is warranted to clarify the role of H_3R antagonists in energy balance and to determine whether specific patient populations or comorbid conditions might benefit from their use.

Given the inconsistent outcomes of clinical trials involving H_3R antagonists, researchers have explored alternative approaches. In this context, betahistine, a structural analog of histamine combining a weak partial H_1R agonist and potent H_3R antagonist properties [135] emerged as an interesting alternative. In clinical settings, betahistine is primarily used for the symptomatic treatment of vestibular disorders and is known for its favorable safety profile, with minimal adverse effects on the cardiovascular, respiratory, or gastrointestinal systems. Additionally, betahistine is orally bioavailable and efficiently crosses the blood–brain barrier [136], making it a good candidate for evaluating interventions acting in the central histaminergic system for the management of overweight and metabolic syndrome.

A proof-of-concept, randomized, placebo-controlled trial evaluated the acute effects of different oral doses (48, 96, or 144 mg) of betahistine on appetite and energy intake in obese but otherwise healthy women (BMI 30–39.99 kg/m^2). Contrary to preclinical findings, the study reported no statistically significant changes in food intake or appetite following betahistine administration [137]. Another study assessed the impact of 12 weeks betahistine treatment (16, 32 and 48 mg) on body weight and metabolic parameters in a multiethnic obese population. Although the pharmacological intervention did not result in statistically significant changes in weight in the overall cohort, a post hoc subgroup exploratory analysis found that factors as age, sex and ethnicity affected the outcomes, with women, non-Hispanic under 50 years having a better response to the drug treatment in terms of weight reduction. This study also confirmed betahistine safety profile since minimal adverse event were reported [138]. These findings suggest a potential age- and sex-dependent responsiveness to betahistine that may be related to by hormonal status, metabolic rate, or differential histamine receptor expression. All these factors can be potentially explored in future stratified clinical trials.

Prader–Willi syndrome (PWS) is a rare genetic disorder characterized by a complex clinical phenotype including metabolic, physical, and neuropsychiatric alterations. Common symptoms include hypotonia, sleep disturbances, developmental delays and cognitive impairment. A distinctive feature of PWS is the dysregulation of appetite control. In early infancy, affected individuals typically exhibit poor feeding and reduced appetite, largely attributed to hypotonia. However, as children grow, this phase is often followed by hyperphagia and compulsive food-seeking behaviors, eventually leading to severe obesity.

Recent case reports have suggested that pitolisant, a H_3R antagonist, may offer therapeutic benefits in PWS. In two separate studies, treatment with pitolisant led to cognitive improvements in a total of four individuals with PWS [139] and a proof-of-concept study showed the efficacy of pitolisant in treating excessive-daytime sleepiness in PWS patients [140]. These positive outcomes raise the possibility that pitolisant could also impact hyperphagic behavior and may stimulate further studies specifically addressing it. If such studies confirm its efficacy in addressing both cognitive and metabolic aspects of the syndrome, pitolisant may represent a novel and promising therapeutic approach for managing the multifaceted symptoms of PWS. Such hypothesis was recently discussed by [141].

Changes in the central histaminergic system have been also implicated in specific EDs, such as AN. In a study conducted by Yoshizawa and coworkers, positron emission tomography (PET) was used to assess histamine receptor activity in female patients diagnosed with AN. The results revealed a significantly increased binding potential of [^{1} ^{1}C] doxepin, a radioligand that binds H_1R receptors, in the amygdala and lentiform nucleus of these patients, compared to healthy female control subjects. A significant negative correlation between the binding potential of [^{11}C]doxepin in the amygdala and the State-Trait Anxiety Inventory (STAI) scores of AN patients was also reported [142]. This observation is particularly noteworthy, as the amygdala is a brain region deeply involved in emotional regulation and the processing of emotional responses [143]. Therefore, the increased [^{1} ^{1}C]doxepin binding observed in individuals with AN may reflect altered histaminergic neurotransmission possibly contributing to the heightened anxiety and emotional dysregulation frequently seen in this disorder. Indeed, preclinical studies indicate that histaminergic neurotransmission plays a role in modulating anxiety-related behaviors, with both anxiolytic [144, 145] and anxiogenic [146,147] outcomes reported, depending on the dose, the site of administration and the experimental paradigm used. For example, local infusions of histamine into rats' central [148] or basolateral [149] amygdala has an anxiogenic-like effect as measured in the elevated plus maze, a behavioral test for assessing anxiety-like behavior in rodents. Such effect was prevented, in a dose-dependent manner, by infusion of the H_1R antagonist pyrilamine, but not by infusion of the H_2R antagonist ranitidine [148]. Further evidence for the role of H_1R in anxiety modulation arises from clinical trials on hydroxyzine, a first-generation H_1R antagonist extensively studied for generalized anxiety disorder (GAD) and related conditions. In a randomized controlled trial hydroxyzine significantly reduced the Hamilton Anxiety Rating Scale (HAM-A) scores, a clinician scale to evaluate the severity of a patient's anxiety symptoms, in GAD patients [150]. Indeed, hydroxyzine is approved by the FDA for anxiety treatment and is commonly used in clinical settings as an alternative to benzodiazepine therapies for anxiety, panic attacks, and insomnia in both adults and children [151]. PET studies using [^{1} ^{1}C]doxepin demonstrated that therapeutic anxiolytic doses of hydroxyzine achieve substantial H_1R

occupancy in the brain (approximately 60–70 % binding potential in the prefrontal and cingulate cortices) which strongly correlates with both sedative and anxiolytic effects [152]. However, several pieces of the puzzle remain missing. For example, direct measurements of H_1R binding in the amygdala have not yet been performed. Moreover, it remains unclear whether the neurochemical changes in AN patients are a cause or a consequence of the illness. To address all these questions, future studies are needed and should include individuals who have achieved full remission from AN to examine whether these alterations in histamine receptor binding persist after recovery, potentially indicating a trait marker or long-term neurobiological adaptation associated with the disorder.

7. Boosting central histaminergic transmission with betahistine: a promising strategy to prevent antipsychotics-induced weight gain

Over the past decades, a marked increase in the prevalence of obesity and metabolic disturbances has been observed among individuals diagnosed with schizophrenia, particularly those undergoing treatment with second-generation antipsychotics [153]. Such an outcome contributes to poor treatment adherence, reduced quality of life, and an increased risk of cardiovascular morbidity and mortality [154]. Substantial research efforts have been made to elucidate the neurobiological mechanisms underlying antipsychotic-induced weight gain revealing dysregulation across multiple neurotransmitter systems, with growing emphasis on the role of the central histaminergic system [155]. Consistently, antipsychotics with high binding affinity for the histamine H_1R such as olanzapine, clozapine, quetiapine and risperidone have been consistently associated with pronounced weight gain and metabolic impairments, including hyperglycemia, hyperinsulinemia, and elevated plasma triglycerides [156,157]. Among these, olanzapine is one of the most extensively studied agents due to its robust metabolic side effect profile.

The progression of olanzapine-induced weight gain follows a triphasic trajectory. The early acceleration phase is characterized by a rapid increase in body weight (approximately the first 2 weeks in rodents and 3 months in humans), followed by an intermediate "new equilibrium" phase in which the rate of weight gain slows (weeks 3–4 in rodents, months 3–18 in humans), and finally a late plateau phase, during which weight gain stabilizes ($>$ 5 weeks in rodents, $>$ 18 months in humans) [158–161]. Dynamic alterations in the central histaminergic system have been reported throughout all these stages: during the early phase (after 8 days of olanzapine treatment), there is a significant increase in *Hdc* mRNA expression as well as elevated H_1R binding in key regulatory brain regions such as the arcuate nucleus (Arc) and the VMH. These molecular changes are positively correlated with increased food intake and weight gain. With continued exposure to olanzapine (16–36 days), H_1R binding remains elevated in these areas and extends to the dorsal vagal complex (DVC) in the brainstem, although *Hdc* mRNA expression returns to baseline. Increased H_1R binding in the Arc, VMH, and DVC continues to be strongly correlated with weight gain during chronic treatment [162].

Emerging evidence implicates AMPK as a downstream mediator of H_1R signaling, particularly in the context of antipsychotic-induced hyperphagia. The hypothalamic 5′-adenosine monophosphate-activated protein kinase (AMPK) is a key enzyme in the regulation of energy homeostasis [163,164]. AMPK is activated in response to energy deficiency, promoting catabolic pathways to generate ATP while suppressing energy-consuming anabolic processes. In the brain AMPK acts as an integrative hub linking peripheral metabolic signals with central neurocircuitry to orchestrate energy balance [165]. Preclinical studies revealed a robust increase in phosphorylated AMPK (pAMPK) levels in the hypothalamus during the initial phase of olanzapine administration. This upregulation is temporally associated with increased H_1R mRNA expression and augmented food intake and body weight. However, this activation appears to be transient as treatment continues into the intermediate and late phases, hypothalamic pAMPK levels normalize despite persistent H_1R antagonism [159,166,167]. These findings suggest a temporally dynamic modulation of the H_1R–AMPK signaling axis by olanzapine. In the acute phase, H_1R blockade leads to disinhibition of AMPK activity, thereby promoting hyperphagia and positive energy balance. Over time, chronic H_1R antagonism may engage compensatory or parallel metabolic pathways, contributing to sustained weight gain and metabolic dysregulation independently of AMPK activation. These findings collectively support a model in which olanzapine-induced antagonism of H_1Rs disrupts normal histaminergic regulation of appetite and energy homeostasis by modulating the AMPK signaling cascade in a time-dependent manner [162].

Beyond homeostatic dysregulation, motivational processes have also been implicated in antipsychotic-induced weight gain. Preclinical studies revealed that atypical, but not typical, antipsychotics can potentiate the reinforcing value of palatable food [168]. Such an effect seems to be stimulus-selective; for example, clozapine has been found to diminish nicotine-seeking behavior while simultaneously increasing the motivational drive for food-related rewards [169]. Further studies found that clozapine augments food-seeking behavior under a progressive ratio schedule of reinforcement, even in the absence of caloric need, suggesting that its effects on feeding are independent of energy balance. This effect is likely due to the convergent antagonism of serotonin $5\text{-}HT_{2C}$ receptors and histamine H_1Rs [169]. Clinically, these findings align with reports of binge eating episodes in clozapine-treated patients [170], reinforcing the hypothesis that increased motivational salience of food, rather than solely impaired metabolic regulation, contributes to the pronounced weight gain associated with atypical antipsychotic treatments.

Given the accumulating evidence implicating central histaminergic signaling in antipsychotic-induced weight gain and metabolic alterations, enhancing histaminergic neurotransmission has emerged as a potential therapeutic approach to mitigate these adverse effects. In this context, promising results were obtained following treatment with betahistine in case studies and controlled clinical trials [138,171,172]. Initial clinical observations by Poyurovsky et al. reported that co-administration of betahistine with olanzapine in three schizophrenic patients prevented weight gain [173]. In a subsequent randomized study, the same group found that betahistine combined with reboxetine significantly attenuated olanzapine-associated weight gain compared to placebo, although the contribution of reboxetine to this effect remains unclear in that study [174].

These preliminary findings were confirmed and expanded in subsequent randomized, double-blind, placebo-controlled trials. For example, Barak et al. reported significantly lower weigh gain in patients with schizophrenia or schizoaffective disorder receiving betahistine as adjunctive therapy to olanzapine compared to placebo [175]. Similarly, Smith et al. demonstrated that betahistine attenuated increases in body weight, BMI, and waist circumference in patients treated with olanzapine or clozapine [176]. In another study, Kang et al. showed that both betahistine and metformin significantly improved anthropometric and metabolic parameters, including body weight, waist circumference, BMI, insulin levels, and insulin resistance in antipsychotic treated patients [177]. More recently, Bai et al. reported that a 4-week treatment with betahistine lowered LDL cholesterol and waist-to-hip ratio without significantly altering body weight or BMI, suggesting that longer treatment durations may be required to elicit comprehensive metabolic benefits [178].

Across clinical studies, betahistine has demonstrated a favorable safety and tolerability profile, with no exacerbation of psychotic symptoms and no significant adverse effects compared to placebo. Beyond mitigating antipsychotic-induced weight gain, betahistine may also alleviate other histaminergic side effects, particularly excessive daytime somnolence, a common complaint associated with antipsychotics exhibiting strong H_1R antagonism. In a placebo-controlled study,

Barak et al. reported that betahistine significantly reduced olanzapine-induced somnolence in healthy female participants [179]. These findings are supported by several case reports, in which betahistine adjunctive treatment was associated with reductions in both clozapine-induced weight gain and sedation [180,181]. Notably, one case also documented concomitant improvements in mood and cognitive functioning, suggesting broader neuropsychiatric benefits of histaminergic modulation [182].

The therapeutic efficacy of betahistine in mitigating antipsychotic-induced metabolic disturbances may be attributed to underlying alterations in central histaminergic signaling associated with both schizophrenia and obesity. Elevated levels of tele-methylhistamine, a major histamine metabolite and indirect marker of histaminergic activity have been reported in the cerebrospinal fluid of patients with schizophrenia [183], although the functional implications of this finding remain unclear. Genetic studies have further identified associations between specific H_1R polymorphisms (e.g., rs346074 and rs346070) and increased susceptibility to obesity in patients receiving antipsychotics with high H_1R affinity [184]. Postmortem investigations have shown reduced H_1R binding in multiple cortical regions [185] and increased H_3R binding in the dorsolateral prefrontal cortex of individuals with schizophrenia [186]. However, it remains uncertain whether these alterations reflect intrinsic pathophysiological features of the disorder or are secondary to chronic antipsychotic exposure. Notably, histaminergic signaling alterations have yet to be systematically investigated in individuals with obesity in the absence of psychiatric comorbidities.

Preclinical studies have provided mechanistic insight into betahistine's mode of action. In rodent models, both subchronic and chronic co-administration of betahistine effectively attenuated olanzapine-induced weight gain and adiposity, while normalizing feeding efficiency and hypothalamic markers such as H_1R expression and pAMPK levels [159]. Additionally, betahistine restored expression of thermogenic genes, including *UCP1* and *PGC-1α*, in BAT, suggesting modulation of the hypothalamic H_1R–AMPK–BAT axis as a potential mechanism for improved energy homeostasis [187]. One hypothesized pathway involves enhanced histaminergic activation of the PVN, which increases sympathetic outflow to BAT and stimulates thermogenesis [64]. Antipsychotic-induced H_1R blockade may impair this regulatory circuit, contributing to reduced thermogenic capacity and increased energy intake. Moreover, peripheral H_1R antagonism may exacerbate metabolic dysfunction by promoting lipogenesis in WAT and disrupting hepatic and pancreatic metabolic regulation [188]. A mechanistic explanation for the effects of betahistine may be proposed based on its pharmacological profile. Betahistine acts as a weak agonist at H_1R and a potent antagonist at H_3R receptors, thereby enhancing histaminergic neuronal activity and promoting histamine synthesis in the TMN [189,190]. H_3R antagonists have been shown to reduce food intake (see Table 1), suggesting a role in appetite regulation. Consequently, the pharmacodynamic properties of betahistine may contribute to the attenuation of antipsychotic-induced metabolic side effects. As a weak H_1R agonist, betahistine may competitively inhibit antipsychotic binding at these receptors in both the central nervous system and peripheral tissues. Simultaneously, H_3R antagonism would facilitate increased histamine release in the brain, thereby contributing to appetite suppression.

8. Concluding remarks

Alterations in feeding behavior represent a core feature of EDs, a group of severe psychiatric conditions that include AN, BN, and BED. In addition to the chronic dysregulation of energy intake, these disorders are also characterized by maladaptive cognitive control over food consumption and aberrant reward processing. Under normal physiological conditions, feeding behavior is orchestrated by a complex interplay between homeostatic mechanisms, primarily integrated by hypothalamic nuclei, and non-homeostatic influences such as emotional state, stress, cognition, and environmental stimuli.

At the neurobiological level, multiple neurotransmitter systems modulate central feeding circuits, including the histaminergic system. Histaminergic neurons, originating in the TMN of the posterior hypothalamus, project extensively to brain regions involved in appetite regulation, including the PVN and VMH, where histamine exerts anorexigenic effects primarily through the H_1R and H_3R. Pharmacological blockade of H_1R is associated with hyperphagia and weight gain, two side effects commonly observed during the treatment with certain antipsychotic and antidepressant medications that act as potent H_1R antagonists. Conversely, blockade of H_3R, which function as presynaptic autoreceptors, enhances histamine release and promotes anorexigenic effects. Several investigational compounds (Table 1) targeting H_3R have shown promise in modulating feeding behavior and may hold clinical potential as therapeutic strategies for conditions characterized by excessive food intake, such as BED and obesity.

Despite these emerging insights, direct clinical studies investigating histaminergic markers in patients with EDs remain limited. For instance, altered expression of H_1R in the amygdala has been observed in individuals with AN compared to healthy female controls. This finding suggests that histaminergic receptors may represent viable therapeutic targets; however, further research is required to determine whether these neurochemical changes are a cause or consequence of the illness. It is also important to note that, beyond its role in regulating food intake, neuronal histamine influences cognitive and emotional processes, including arousal, stress response, anxiety, and motivation, which are factors closely linked to disordered eating patterns. Therefore, histamine-based therapies may have the potential to act on multiple biological pathways, enhancing the efficacy of interventions through a multidimensional approach.

Collectively, the findings summarized in this review highlight the role of the histaminergic system as a key modulator of appetite regulation and energy expenditure, positioning it as a promising pharmacological target for the treatment of EDs and related metabolic syndromes. However, further studies are essential to elucidate the role of neuronal histamine in the pathophysiology of EDs and to facilitate the development of more targeted, mechanism-based therapeutic strategies.

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Declaration of Competing Interest

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Data Availability

No data was used for the research described in the article.

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