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Review Article

Modulation of Histaminergic System: A Potential Target for Obesity Treatment

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Abstract

Obesity develops due to the defects in genetic factors and environmental factors or may be due to imbalance between energy intake and energy expenditure. Energy intake is determined by the central regulation of appetite and several orexigenic and anorexigenic neuropeptides. The neurotransmitter histamine regulate appetite and food intake and exerts its anorexigenic action via H1 receptors. Blockade of the presynaptic auto inhibitory H3 receptors reduce food intake. Leptin decreases body weight and food intake in animals but leptin resistance leads to development of obesity. It was reported that the histaminergic system is one of the targets of leptin. Histamine is a mediator of the anorexigenic action of leptin it may attenuate and delay the development of leptin resistance in high fat diet induced obesity. Based on this evidence modulation of the histaminergic system seems to be an essential target for treatment of obesity.

Keywords: Obesity, Neuropeptides, Histamine, Leptin

1.Introduction

Obesity is a major public health problem in the western world as it increases the risk of developing life threatening diseases and conditions such as type 2 diabetes, hypertension, cardiovascular diseases cancer [1]. The increased body weight of obese people is the result of energy intake exceeding energy expenditure which is regulated by complex central and peripheral factors. Various peptides and neurotransmitters control the regulation of body weight. Energy intake is partially determined by the central regulation of appetite, a process which involves several orexigenic and anorexigenic neuropeptides in the hypothalamus [2]. Histamine is a neurotransmitter released by neurons originating excessively in the tuberomammillary body in the posterior hypothalamus [3]. The histaminergic system plays an important role in the regulation of body weight. Some antipsychotics and antidepressants which proved to be potent histamine H1 receptor antagonists were found to have more side effects in the form of appetite stimulation and weight gain [4]. Several studies supported the involvement of the histaminergic system in appetite and body weight regulation. The aim of this review is to give a brief overview of these studies related to histaminergic system and weight regulation and thereby evaluate the potential of the histaminergic system as a target for obesity treatment.

2.Histamine and Histaminergic System

Histamine consist of an imidazole ring and an amino group connected by a short chain of two carbon atoms, is stored in and released from various types of cells like the IgE receptor bearing mast cells and basophils, endocrine cells and neurons in the central and peripheral nervous system [5]. Histamine is synthesized from the essential amino acid L-histidine, which is actively transported into the cells by decarboxylation of histidine by the enzyme histidine decarboxylase (HDC). The synthesized histamine is transported into secretory vesicles, from which it is released on stimulation of the cell. In the central nervous system, histamine is found in mast cells and neurons. Histamine derived from mast cells is possibly involved in vascular control and immune responses while histamine derived from neurons functions as a neurotransmitter [6, 7]. Histamine does not cross the blood-brain barrier, so brain histamine must be synthesized in brain to be effective [8]. Neuronal histamine originates in neurons of the tuberomammillary body in the posterior hypothalamus and from there the histaminergic neurons project to each and every part of the brain and the highest density of fibers is found in the hypothalamus [3]. In brain, three subclasses of histamine receptors designated as H1, H2 and H3 receptors present. The H1 and H2 receptor types are present on the postsynaptic membrane and mediate the actions of histamine. The H1 receptor has widely distributed throughout the brain, with a high density in the hypothalamus and the H2 receptors distribution resembles same but a lower density is found in the hypothalamus [9, 10]. The H3 receptor is present on the presynaptic membrane of the histaminergic neuron and is known as auto inhibitory receptor [8]. Binding of histamine to H3 receptors results in inhibition of synthesis and release of histamine. This feedback mechanism resembles that of many other neurotransmitters, e.g. serotonin, noradrenaline and dopamine [5]. H3 receptor is a heteroreceptor so besides its localization on the histaminergic neurons, it is also found on non-histaminergic neurons and modulate the release of other neurotransmitters like serotonin, noradrenaline, dopamine, GABA and acetylcholine containing neurons [11]. The H4 receptor is expressed in cells of the immune system, mast cells, lymphocyte T cells, dendritic cells, basophils and it induces the chemotaxis of eosinophils and mast cells. The H4 receptor along with H2 receptor involved in the control of Interleukin-16 release from human lymphocytes. Histamine H4 receptors antagonists such as JNJ 7777120 reported to be efficacious in various study models of inflammation [12].

2.1. The Histaminergic System and Regulation of Appetite

Administration of histamine into lateral ventricle of cats produces a long-term suppression of food intake [13]. In addition, study report showed that continuous administration of histamine into the suprachiasmatic nucleus of the hypothalamus reduced food intake and an acute injection of histamine into the lateral ventricle of rats reduce food intake [14, 15]. Administration of L–histidine (the histamine precursor) by intraperitoneal route has been shown to have the same effect as histamine, reducing food intake possibly due to conversion of L-histidine to histamine by histamine decarboxylase enzyme. Metoprine is an inhibitor of N-methyltransferase, the enzyme that breaks down histamine to N–methylhistamine and so increases the endogenous histamine concentration. Administration of metoprine by intraperitoneal injection and by intracerebroventricular infusion, suppresses food intake in rats [16-

-20]. A specific and irreversible inhibitor of the histamine decarboxylase (HDC) enzyme, α-fluoromethylhistidine (α-FMH) has the competency for depletion of histamine from the central neurons. α-FMH administered by intracerebroventricular route significantly increases food intake in rats [21–25]. These findings prove good evidence for use of histamine as an anorexigenic agent. Several pharmacological approaches have been used to study the involvement of histamine receptors in appetite regulation. Injection of an H1 receptor agonist into the lateral ventricle decreased food intake in rats while intracerebroventricular administration of an H1 receptor antagonist increased food intake in rats and administration of an H1 receptor antagonist attenuated the histamine induced suppression of food intake [26–30]. The H2 receptor is not believed to be involved in the regulation of appetite, because neither H2 receptor agonists nor H2 receptor antagonists have any effect on food intake and the administration of an H2 receptor antagonist did not abolish the histamine induced suppression of food intake [14, 15, 30]. The involvement of the H3 receptors in the regulation of appetite is complex. The presumed mechanism is that stimulation of the H3 receptor leads to inhibition of histamine release and thereby resulting in an increase in appetite. While blocking the H3 receptor would lead to enhanced release of histamine from the histaminergic neurons to synaptic cleft which would stimulate the H1 receptors and thereby lead to decrease in appetite. Activation of H3 receptors by the agonist R-α-methyl histamine has increased food intake when administered intraperitonally to mice [31, 32]. H3 receptor antagonist, thioperamide experiments have shown mixed results and in some studies decrease in food intake was recorded, while in other studies it have no significant effect on food intake [15, 24, 33, 34]. H3 receptor is a heteroreceptor so these inconsistent findings might be due to the release of substances other than histamine. Tomoko Ishizuka reported that an H3-inverse agonist clobenpropit (5 mg/kg, i.p.), significantly reduced 3 hr energy intake in normal and DIO mice. It has been shown that histamine deficient mice develop age-related obesity when fed a normal diet [35]. However, it has never been investigated how histamine deficiency affects the tendency to gain weight on a high fat diet (HFD). Jørgensen et al. reported that HDC-KO mice had gained more weight after 2 weeks on an HFD and at the end of the 8-week feeding period; weight gain was 110% percent higher than the controls [36]. There is no evidence about how the H2 receptor ligands can affect appetite behavior. It was hypothesized that pharmacological manipulation of H1 receptors affects food intake in animals. However, it is inapproachable, because no H1 receptor agonists have been identified that can penetrate the brain and that would have antiobesity effects. Hence, the histaminergic H3 receptor thought to be a potential target for obesity treatment due to the unavailability of selective H1 receptor agonists which are devoid of peripheral action. H3 receptor antagonists enhance histamine release from nerve terminals and may afford an effective therapeutic alternative for treatment of obesity. The exact role of H3 receptor acting agents in the treatment of metabolic diseases is still remained unclear due to the inconsistent results from different studies in regulation of food intake. In several studies it was observed that blockade of hypothalamic H3 receptors is useful in decreasing plasma triglycerides, energy intake and body weight while H3 receptor agonists raise feeding in rats [37-39]. It was observed that H3 receptor antagonists triggers histamine release from the hypothalamus and reduces energy intake in normal and leptin resistant mice in diet induced obesity models [40]. Administration of H1 receptor antagonists debilitates the feeding suppressing action induced by H3 antagonists [37]. H3 receptor affects the appetite signaling pathways through different mechanisms. H3 receptor agonists reduce satiety induced by amylin or bombesin while H3 receptor antagonists reduce the orexigenic effect of neuropeptide Y and enhance cholecystokinin induced satiety [41-43]. This results support an appetite suppressant effect by blockade of H3 receptor. However results obtained in some reports are totally different. Study report showed that H3 receptor agonist in diet induced obese mice reduces food intake and decreases body weight, which is assumed to be a mechanism independent of histaminergic modulation [44]. H3 receptor deficient mice revealed disrupted regulation of energy expenditure, body weight and food intake. H3 receptor deletion resulted in hyperphagic obese mice having lesser energy expenditure, which coincide with the H1 receptor deficient mice [45]. These results may be due to down regulation of H1 receptor in the hypothalamus of H3 receptor deficient mice which leads to hyperphagia and obesity. It shows that the effects of H3 receptor modulators are complex on food intake and energy balance and mediated by histamine release and also regulated through a several receptors and neurotransmitters. The role of the H3 receptor in AAPD induced weight gain still remains uncertain [46]. Co-administration of olanzapine (H3 receptor antagonist) with betahistine (weak H1 receptor agonist) for 6 weeks in schizophrenic patients produced a weight gain in initial 2 weeks of study with further it has not affected body weight up to 6 week of treatment [47]. H3 receptor antagonism disinherits the release of several neurotransmitters that are involved in the control of food intake and energy balance. During clinical trials of new H3 receptor antagonists such as pitolisant, MK-0249 and (1R, 3R) - N-ethyl-3-fluoro-3-[3-fluoro-4-(pyrrolidin-1yl-methyl) phenyl] cyclobutane-1-carboxamide (PF-03654746) in narcolepsy or attention deficit hyperactivity syndrome (ADHS) significant weight change was not reported and instead of that these compounds proved to be effective in treating eating related diseases. Recently for compound SCH-497079 phase II clinical trials were performed to check effect on body weight in obese and overweight subjects. More experimental efforts required to prove the role of H3 receptor antagonists as antiobesity drugs. Amphetamines have the abuse and addiction potential while H3 receptor antagonists lack stimulant, abusive, sensitization and addictive properties and reduce body weight as compared to other anti-obesity drugs [48].

2.2. Involvement of Histamine and Leptin in appetite regulation

Leptin is secreted by adipose tissue reduces food intake and increases energy expenditure through actions in the hypothalamus [49]. Studies showed an involvement of the histaminergic system in the mediation of the anorexigenic effect of leptin. In addition, complete absence of an anorexigenic effect of leptin in H1 receptor knockout mice was observed. Study showed that histamine knockout mice fed with a high-fat diet, leptin resistance seems to develop earlier as indicated by down regulation of leptin receptor gene expression [50-52]. The involvement of the histaminergic system in mediation of the anorexigenic effect of leptin has been demonstrated pharmacologically and by knockout approach. Histamine and its H1 receptor are part of the leptin-signaling pathway since both blockade of histamine synthesis and blockade of the H1 receptors attenuated the response to leptin and leptin facilitated histamine release from the hypothalamus [44, 50, 53, 54]. It has been shown that genetically obese animals with defects in the leptin system (ob/ob and db/db mice, fa/fa rats) display lowered levels of hypothalamic histamine [43, 45]. These observations provide evidence of histamine may act as a mediator of leptin effects. The histaminergic nerve cell bodies in the CNS are exclusively located in the tuberomammillary nucleus (TMN) of posterior hypothalamus [48]. These cells axons projects in the paraventricular nucleus (PVN) and ventromedial hypothalamus (VMH) area [49]. Leptin interacts with thyrotropin releasing hormone (TRH) neurons in the PVN through histamine [50, 51]. The VMH is mainly involved in sexual arousal and mating behavior [52]. Patch clamp recordings on the membrane potential of VMH neurons showed that estrogen treatment increases membrane potential in ovariectomized female mice [53]. It suggests that neurons in the VMH integrate nutritional signals with estrogenic signaling. It would not be adaptive for women to reproduce at times when they do not have an adequate food supply [51]. It indicates that histamine has

role in two different systems that relates to energy homeostasis and also that relates to reproductive function (Fig. 1).

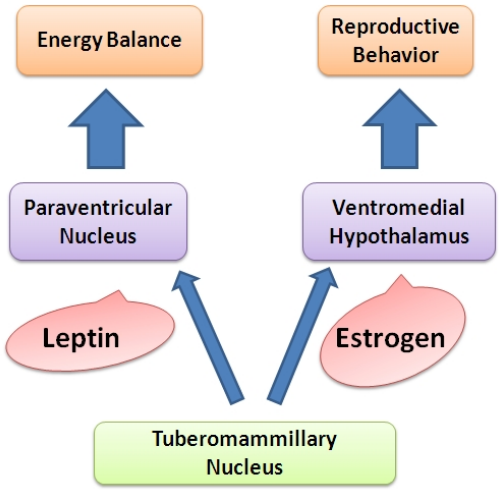

Fig. 1. Histaminergic neurons in the brain

Histaminergic neurons are located in tuberomammillary nucleus and their axons project into the ventromedial hypothalamus (VMH) and paraventricular nucleus (PVN). In PVN, axons interact with leptin responsive neurons to modulate energy balance. In VMH, axons interact with estrogen sensitive neurons and link reproduction with feeding behavior.

The link between estrogens, histamine and VMH neurons shows that weight effect was observed only in women age below 50 years or in premenopausal women. Leptin levels were also higher in High fat diet (HFD) fed HDCKO mice compared to standard diet fed HDC-KO mice. Hence, HDC-KO mice would consume fewer calories if their leptin-signaling system was intact. However, the fact that they do not consume fewer calories as they gain weight implies that they are somehow resistant to the anorexigenic effect of leptin. It was observed that 8 weeks HFD fed HDC-KO mice had a significant decrease in hypothalamic Ob-R mRNA levels as compared to the standard diet fed HDC-KO controls and showed that the body weight gain and leptin resistance which is known to develop in HFD-fed WT mice develop earlier in HFD-fed HDC-KO mice. Compensatory mechanisms may prevent excess weight gain and development of leptin resistance in HFD-fed WT mice as they are dependent on an intact histaminergic system. So, it supports the hypothesis of histamine playing a role in the development of HFD induced obesity [54]. Leptin, the ob gene product secreted from white adipose tissue links peripheral adiposity levels for the regulation of energy homeostasis [55]. Both the central and peripheral injections of leptin decrease body weight and food intake in lean mice [56-58]. Leptin receptors which take part in leptin signal transduction exist in the hypothalamus [59]. Leptin is thought to produce an anorectic effect by acting on the hypothalamus. However, in a rodent model of high fat diet induced obesity (DIO) an analogue of human obesity, leptin did not counteract adiposity despite an elevated level of circulating leptin [55]. This ineffectiveness is explained as "leptin resistance". It is thought to occur because of a disturbance to the transport of leptin to the brain and the inability of peripheral leptin to reach the hypothalamus [60-62]. Therefore, direct control of factors downstream of leptin may be effective in treating obesity in leptin resistant subjects. Several studies indicate involvement of the histaminergic system in the regulation of food intake. L-histidine, the precursor of histamine and the intracerebroventricular (ICV) infusion of histamine itself suppresses food intake, whereas the depletion of neuronal histamine by α-fluoromethylhistidine (FMH), a specific inhibitor of histamine forming enzyme increases food intake [63-68]. The effects of these compounds were blocked by an H1-antagonist, but not an H2-antagonist [64], suggesting that neuronal histamine suppresses food intake via the histamine H1 receptors. Studies showed that leptin decreases food intake via the activation of the histaminergic system through histamine H1-receptors [57, 62, 69, 70]. The anorectic effect of leptin was abolished both in neuronal histamine-depleted mice [35] and in histamine H1 receptor-knockout mice and leptin increased histamine release from the rat anterior hypothalamus [25-27]. These findings reveal the importance of the histaminergic system in the expression of the effect of leptin and suggest that the system is a promising target in the treatment of high fat diet induced obesity. It is observed that in DIO mice, leptin affected neither histamine release nor 12 h energy intake, suggesting that DIO mice are resistant to exogenous leptin and inactivation of the histaminergic system leads to obesity in DIO mice. Another type of H3 antagonist was revealed to decrease food intake in obese mice and the chronic icv injection of histamine into DIO mice reduced food intake and adiposity [37, 38]. Therefore, the direct activation of the histaminergic system contributes to the improvement of leptin resistance in DIO mice, and the activation of the histaminergic system is a promising strategy to treat obesity. Leptin modulates not only the histaminergic system but also other factors which regulate food intake such as neuropeptide Y corticotropin-releasing hormone norepinephrine, and dopamine [71-73]. This can explain why leptin had a prolonged effect on energy intake despite its lesser influence on histamine release compared to clobenpropit. Leptin increased histamine release and decreased energy intake only in lean mice, while clobenpropit had an effect in both lean and DIO mice. These results suggest that the histaminergic system is a promising target for the treatment of high fat diet induced obesity in humans.

2.3. Role of Histaminergic system in Lipolysis

The effect of histamine on regulation of body weight may be exerted through effects on appetite and direct effects on metabolism. Central administration of histamine increases serum free fatty acid levels [74]. So, histamine release is related with lipolysis. The neuronal histamine has been shown to accelerate lipolysis in white adipose tissue (WAT) by centrally activating the sympathetic nervous system [75, 76]. In addition, histamine seems to participate in maintaining energy homeostasis by regulation of food intake and affecting peripheral energy expenditure. Histamine H1 receptor and histamine H3 receptor knockout mice have been shown to develop obesity with increasing age [77, 78]. HDC-KO mice had greater epididymal adipose tissue sizes compared to STD-fed WT mice [36]. Therefore, histamine-deficient mice apparently display lowered lipolysis, resulting in increased deposition of adipose tissue.

2.4. Brain Histamine and Eating Behavior

Histamine is associated with eating disorders. It was reported that some of the atypical antipsychotic agents stimulate appetite and promote weight gain through hypothalamic AMP kinase stimulation which linked with the regulation of appetite and resist the actions of leptin. This action is exerted through the histamine H1 receptor by abolished augmentation of AMP kinase in histamine H1 receptors depleted mice [79, 80]. Histamine neurons are important for sustaining of arousal during motivated behavior, because of the circadian rhythm observed in histaminergic system with low levels during sleep and high levels during the active period [81]. Histamine neurons are mainly located in the tuberomammillary nucleus (TMN) in the posterior hypothalamus and innervates throughout the CNS, area that are organized in functionally distinct circuits on different brain regions [82]. Histamine in brain affects the energy balance by decreasing food intake and increasing energy expenditure. Histamine in brain induces a loss of appetite that is a part of adaptive anorexia. Studies showed that H1 receptors activation and increased histamine

level in brain suppresses food intake in mice and rat [83-86]. While the H1 receptor antagonists or α-fluoromethylhistidine (α-FMH) (histidine decarboxylase inhibitor) administration decreases central histamine increased food consumption and ultimately increased body weight [87-89]. Blockade of H1 receptors in the VMH region increases meal size and meal duration, and decreases the activity of glucose responding neurons. But blockade of H1 receptors in PVN region or lateral hypothalamus are not involved in that activity. So, the main site of brain histamine mediated food intake suppression is probably through the VMH region [90]. The VMH region includes glucose responding neurons having axons projections linked to hindbrain regions that contain premotor sympathetic neurons and it was considered to be a satiety center. However, VMH seemed to be acting as a somatomotor center for motivated behavior related activity [91]. Histamine administered as intracerebral infusion inhibits the development of obesity in db/db obese and diet induced mice. These mice are having higher leptin levels and develop severe type 2 diabetes and obesity because of a molecular defect in a leptin receptor. Brain histamine by modulating peripheral energy expenditure regulates body weight and adiposity. Uncoupling protein 1 (Ucp1) is a marker of energy expenditure and it is present in brown adipose tissue (BAT). The Ucp1 expression is regulated by neuronal and humoral factors. Central administration of H1 receptor agonists or histamine increases the expression of Ucp1 mRNA levels in BAT of rodents, while the central administration of H3 receptor antagonist thioperamide or histamine increases the lipolytic response in white adipose tissue (WAT) in rodents. However, pretreatment with H1 receptor antagonist blocks the thioperamide induced activity, suggesting that effect may be mediated by sympathetic nerves that innervate WAT [92]. TMN neurons are crucial for the rise in temperature during motivated behavior by acting on premotor sympathetic neurons present in the raphe pallidus nucleus (RPN) [93]. RPN promotes BAT thermogenesis partially by increasing arousal which leads to increased motor activity and increase energy expenditure (Fig. 2).

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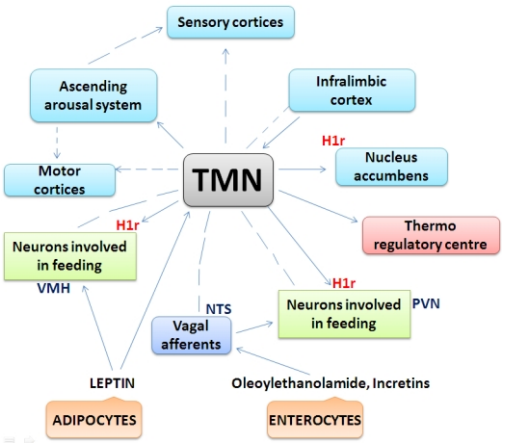

Fig. 2. Hypothalamic histamine neurons activity in feeding behavior

It is assumed that Histamine reduces food intake through H1 receptors expressed on feeding related neuron in the VMH. The infralimbic cortex regulates the arousal and vegetative responses required for the appetitive behavior. TMN involved in cortical arousal described by increased sensory, motor and emotional response and it may induce thermal responses. Double lines show the assumed link between TMN and feeding related centers. Dot/dash lines show assumed connections between TMN and cortical areas involved in appetitive behavior. H1r-Histamine H1 receptor. The appetite stimulating and consumption phases of feeding behavior involve different brain, physiological or behavioral mechanisms. Behavioral or physiological functions include catabolic mechanisms through sympathetic system activation and energy spending functions. The appetitive phase is one type of a behavioral challenge which requires an optimal arousal state, but exactly how the brain circuits generate and organize such a motivated behavior is still not known. The appetitive phase evokes sensory, motor, emotional and sympathetic responses that are regulated by forebrain mechanisms. Parasympathetic system predominates during the ingestive phase. Ingestion also expressed in decerebrated adult rats which show that consummatory behavior such as food acceptance/rejection, mastication, swallowing and satiety involve the hindbrain region [94]. Histamine through the TMN region affect the activity of other ascending activating nuclei which regulate the release of various neurotransmitters such as serotonin, dopamine and acetylcholine and hypothetically it acts in relation with reward systems and learning circuits to modulate the appetitive behaviors (Fig. 2). [95-98]

2.5. Involvement of Histamine and appetite regulating peptides

Peptides such as leptin, orexin, glucagon like peptide 1 (GLP-1), neuropeptide Y, thyrotropin releasing hormone (TRH) and hormones such as estradiol act as satiety or hunger signaling molecules modulate the hypothalamic nuclei through the histaminergic system. Histaminergic neurons partially associated with orexin neurons in the posterior hypothalamus. Histamine and orexin neurons regulate the consciousness. Histamine involved in consciousness and cognitive functions while the peptide neurons are involved in behavioral arousal which include muscle tone, locomotion and emotional reactions [99]. Administration of orexin A into TMN evokes wakefulness and stimulates food intake in rats effects that are dependent on histaminergic neuronal system mediated through the H1 receptor [100, 101]. Leptin produces adiposity signal which is associated with peripheral adiposity levels for the regulation of energy balance in the brain. Leptin affects feeding behavior by activating histamine containing neurons. The administration of α-FMH to mice and rat decreases the leptin induced reduction in food intake. In addition, leptin induced hypophagia is suppressed in H1 receptor deficient mice [102]. PVN neurons release the anorexigenic TRH which activates TMN neurons and ultimately evokes the histamine turnover [103]. TRH induced suppression of feeding is significantly abated in H1 receptor knockout fasting mice and histamine depleted rats. Glucagon-like peptide-1(GLP-1) is expressed in nucleus of solitary tract and ventrolateral medulla of the brainstem and inhibits gastric emptying, increase satiety through central nervous system actions and suppresses glucagon release thereby decreases the food intake. GLP-1 induced suppression of feeding behavior is partially mediated by hypothalamic neuronal histamine as the effects are attenuated by loss of H1 receptor function [104]. Microdialysis study in freely moving rats showed that the oleoylethanolamide decreases histamine release in the TMN and other brain area that innervates histaminergic system and control appetitive behavior [105]. The orexigenic cannabinoid CB1 receptor agonists raise histamine release in the TMN (Fig. 2) [106]. These orexigenic and anorexigenic effects of endogenous molecules act in relation to the histaminergic system. These results show histamine is not a satiety signal and it is also involved in regulation of food intake and energy expenditure.

2.6. Histamine and Anorexia

Histamine neurons in brain may be part of compensatory response system that inhibits appetite to intensify on more pressing situation or it may possible that histamine is a satiety signal that released during eating [107, 108]. To act as a satiety signal, histamine should be released after the onset of meal consumption. Histamine is released when rats are trying to obtain food either by attempting to open a container filled with food or lever pressing in operant conditioning box and while easily available food was not followed by histamine release. These results show that histamine release during feeding is correlated with appetitive phase rather than food consumption and satiety [109]. It might be possible that brain histamine released during the appetitive phase such as feeding (or

escape from threat), resulting in raised arousal and sympathetic activity and decreased ability of food consumption. In that case it is possible that TMN activation under the influence of the infralimbic cortical area and histamine release allow the optimal activation of motivated behavior (Fig. 2) [110]. Anorexia also observed in some physiological or pathological conditions. For example, cyclic increase in estrogens decreases food intake in rodents, primates and humans [111]. Various hypothalamic nuclei express estrogen receptors but mainly the PVN mediate the anorectic effect of estradiol. Estradiol induced reduction in food intake is partially mitigated in histamine H1 receptors depleted mice and α-FMH treated rats [112, 113].

3. Conclusion

Histamine is involved in the regulation of body weight. So, pharmacological manipulation of the histaminergic system seems to be an important target as antiobesity drugs. Central H1 and H3 receptors could be potential targets for the treatment of obesity. Various preclinical models of obesity in rodents showed significant reduction in abdominal and subcutaneous fat in rodents and proved effectiveness of H3 receptor antagonist. However, H1 receptor agonist would also affect the peripheral mast cells and generate an unwanted allergic response due to mast cell derived histamine release. This limits the use of H1 receptor agonists as a drug target. Hence, the H3 receptors may be a promising drug target and the use of H3 receptor antagonists to stimulate the histaminergic system may provide a pharmacological means for treatment of obesity. Further work is required before manipulation of the histaminergic system and it might be considered as a pharmacological target for the control of obesity.

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Conflicts of Interest

The author declares no competing interests.

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