Neuronal Histamine and Histamine Receptors in Food Intake and Obesity

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Abstract: Histamine is a neurotransmitter and neuromodulator within the central nervous system that affects the regulation of food intake and obesity. This review focuses on the roles of neuronal histamine and its receptors in regulating food intake and obesity.

Key Words: Histamine, food intake, obesity, histamine H_1 receptors, histamine H_3 receptors, histidine decarboxylase, feeding rhythm, brain.

INTRODUCTION

Cell bodies of histamine neurons exist in the tuberomammilary nucleus of the hypothalamus (TMN), and diffusely project throughout the brain [1-3]. Neuronal histamine is involved in hypothalamic functions such as locomotor activity, circadian rhythm, drinking behavior, and feeding behavior and obesity [4-9] through the histamine H_1, H_2, and H_3 receptors (H_1-R, H_2-R, and H_3-R, respectively) [9-11].

Several pharmacological and physiological studies have investigated the function of histamine receptors, using an agonist/antagonist of H_1-R, H_2-R, and H_3-R [12-15]. Among them, H_1-R and H_3-R especially have been shown to be involved in food intake and obesity. Other studies have shown that H_1-R, H_3-R, and histidine decarboxylase (HDC) are all targets of food intake and obesity [16-19]. Thus, this review demonstrates the involvement of neuronal histamine, H_1-R, and H_3-R in food intake and obesity.

NEURONAL HISTAMINE AND ITS RECEPTORS IN THE BRAIN

Histamine (**1**) is synthesized in the brain from l-histidine (**2**) by the enzyme HDC [3]. The termination of histamine's action in the brain may require its catabolism to telemethylhistamine (**3**) by the enzyme histamine N-methyltransferase [3]. In turn, the inhibition of histamine synthesis by alpha-fluoromethylhistidine (FMH) (**4**), an irreversible inhibitor of HDC, decreases histamine levels [3, 20] (Fig. **1**).

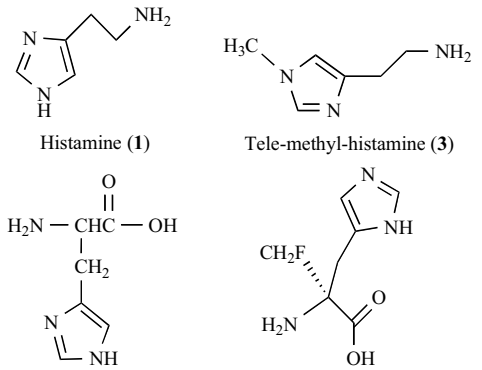

Fig. (1). Substances related to histamine turnover.

Four types of histamine receptors, H_1-R, H_2-R, H_3-R, and H_4-R, have been cloned and identified [9, 19, 21-24]. Histamine H_1-Rs are located postsynaptically, and high densities of these receptors are seen in the hypothalamus [9]. H_2-Rs are also located postsynaptically and seen in the basal ganglia and parts of the limbic system [9, 11]. Histamine H_3-Rs are located on the axon terminals of histamine neurons, where they serve as autoreceptors to modulate histamine synthesis and release, but are located pre- and postsynaptically in other brain regions [9, 10]. Unlike the other aforementioned receptors, H_4-R has not been demonstrated in the brains of rats or mice [22-24].

H_1-R and H_3-R are important for regulating food intake and obesity. H_1-R encodes a member of the large 7-transmembrane-spanning, G-protein-associated receptor family [3, 25]. Intracellularly, stimulation of H_1-R leads to hydrolysis of phosphatidyl 4,5-biphosphate and the formation of inositol-1,4,5-triphosphate (IP3) and 1,2-diacylglycerol (DAG). DAG potentiates the activity of protein kinase C (PKC), while IP3 binds to the IP3 receptor located on the endoplasmic reticulum. IP3 mobilizes intracellular calcium, and DAG activates PKC. In this way, histamine induces the production of inositol phosphates; activation of H_1-R has been shown to increase intracellular calcium [3, 25]. In addition, H_1-R activation can lead to the formation of arachidonic acid (AA), most likely through the action of phospholipase A2, and cyclic guanosine monophosphate (cGMP) [26]. The increase in intracellular calcium explains the pharmacological effects of H_1-R stimulation. H_1-R stimulation-dependent elevation in intracellular calcium may lead to increased cyclic adenosine monophosphate (cAMP) levels.

H_3-R is also a G-protein coupled receptor that is sensitive to pertussis toxin. Interestingly, the H3 receptor gene shows a low overall homology to all other biogenic amine receptors [27]. In various cell lines, H_3-R activation leads to an inhibi-

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tion of forskolin-stimulated cAMP formation [27]. However, a physiological action *in situ* that is dependent on this effect remains to be shown. A study that labeled H_3-Rs in the rat brain with [3H](R)alpha-methylhistamine showed that H_3-Rs are present in all areas and layers of the cerebral cortex, with a higher density rostrally and in the deep layers [28]. High densities of H_3-Rs are also found in the nucleus accumbens, striatum, olfactory tubercles, and the substantia nigra, whereas only moderate levels are found in the hypothalamus. H_3-Rs are present, however, on the cell bodies of the histamine neurons in the TMN.

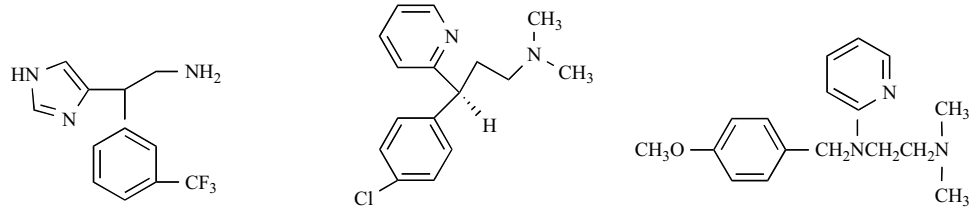
PHARMACOLOGICAL ASPECTS OF NEURONAL HISTAMINE, H_1-R, AND H_3-R ON FOOD INTAKE AND OBESITY

Extensive pharmacological experiments have demonstrated that the histamine system in the brain plays a critical role in the regulation of food intake and obesity [29, 30]. Centrally injected histamine suppresses food intake and body weight in rodents [31]. Histidine, a precursor of histamine, has the same effect on food intake in rodents [32, 33], suggesting that peripheral histidine may penetrate the blood brain barrier and be converted into histamine in the brain by HDC [34]. In fact, the histidine-induced suppression of food intake results from elevated histamine levels in the brain [34]. In contrast, the HDC inhibitor alpha-FMH increases food intake in rodents. Pharmacological experiments using histamine H_1-R-agonists and antagonists have shown that H_1-Rs also help control food intake; central injection of the H_1-R-agonist 2-(3-trifluoromethylpheryl)-histamine (4) decreases feeding in rodents [35]. In contrast, central administration of the H_1-R-antagonists chlorpheniramine (5) and pyrilamine (6) elicit food intake in rats [36, 37] (Fig. **2**). Injecting H_1-R antagonist in the ventromedial hypothalamic nucleus effectively regulates appetite [37].

The cloning of the gene for H_1-R has enabled the production of mice lacking this gene [4]. These mice appear to develop normally but have deficits in the normal circadian rhythm of locomotor activity, and reduced exploratory behavior in a novel environment [4]. H_1-R-deficient mice show no significant change in daily food intake, growth curve, body weight, or adiposity at a younger age [38]. However, H_1-R-deficient mice develop aging-related obesity accompanied with hyperphagia [16]. In addition, loading H_1-R-deficient mice with a high-fat diet increases fat deposition more than in wild mice [38]. These results provide insight into the control of energy homeostasis; H_1-R-deficient mice are models of aging-related and diet-induced obesity, and H_1-R is a key receptor that contributes to the regulation of food intake and obesity. Similar to the H_1-R-deficient mice, HDC-deficient mice also show marked abdominal obesity [19]. In addition, HDC-deficient mice display a metabolic phenotype characterized by hyperinsulinemia, impaired glucose tolerance, and increased epididymal white and brown fat depots, supporting the important role that histamine plays in the regulation of energy metabolism [19]. Cold-exposure regulation of body temperature is attenuated in HDC-deficient mice [19]. These observations suggest that HDC and H_1-R both contribute to the regulation of food intake and obesity.

H_3-Rs are pharmacologically identified and predominantly expressed in the brain, where they negatively regulate histamine release, acting as presynaptic autoreceptors [39]. Therefore, H_3-R antagonists/inverse agonists (IAs) have therapeutic potential for treating obesity. Investigations into the role of histamine as a neurotransmitter have shown that histamine inhibits its own neuronal synthesis and release from depolarized slices of the rat cortex *via* presynaptic feedback mechanisms [40-42]. The existence of H_3-R was validated by the development of the agonist *R*-alpha-methylhistamine and the antagonist thioperamide [43]. With the availability of these pharmacological tools, H_3-R was shown to modulate the release of various major neurotransmitters such as serotonin and noradrenaline [43].

H_3-R IAs are believed to suppress appetite by activating H_1-Rs in post-synaptic areas, because H_3-Rs negatively regulate the release of HA in the brain [44]. To address the therapeutic potential of H_3-R ligands as anti-obesity agents, several studies have reported the pharmacological profiles of H_3-R IAs in animal studies [40, 41]. Thioperamide (**8**), an imidazole-containing H_3-R inverse agonist, suppresses food consumption in spontaneous, fast-induced, schedule-induced, and NPY-induced feeding in rodents [40]. Although these reports have suggested the therapeutic potential of H_3-R IAs, their anti-obesity effects remain controversial [44]. In a recent study, oral administration of thioperamide enhanced HA release in the brain, but the treatment did not decrease food intake [45]. In addition, the H_3-R agonist Imetit (**9**) reduces adiposity in DiO mice by inhibiting food intake and increasing energy expenditure. The anti-obese effects of the H_3-R agonist were also confirmed using an H3 agonist, *R*-methylhistamine (**10**) [46] (Fig. **3**). In contrast, chronic dosing with thioperamide leads to a slight but significant increase in body weight in lean mice, and a trend of weight gain in DiO mice [46]. Moreover, the study that used H_3-R-deficient (H_3-R KO) mice demonstrated a crucial role for H_3-Rs in food intake and obesity [18]. However, enhanced histamine re-



2-(3-trifluoromethylphenyl)histamine (**5**) Chlorpheniramine (**6**) Pyrilamine (**7**)

Fig. (2). Examples of histamine H_1 receptor agonist and antagonist.

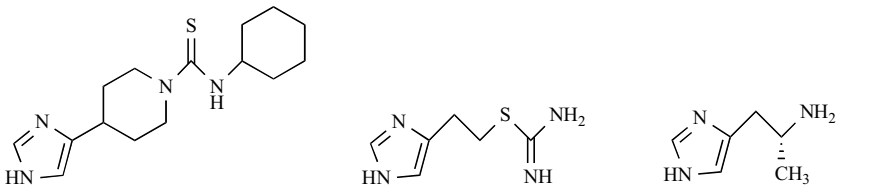


Fig. (3). Examples of histamine H_3 receptor agonist and antagonist.

lease was accompanied by obese and hyperphagia phenotypes in H_3-R KO mice [18]. Further studies are needed to clarify the involvement of H_3-Rs in food intake and obesity.

NEURONAL HISTAMINE AND ADIPOCYTOKINE LEPTIN IN CONTROLLING FOOD INTAKE AND OBESITY

Obesity is defined as an increased mass of adipose tissue, which confers a higher risk of cardiovascular and metabolic disorders such as diabetes and hyperlipidemia in metabolic syndrome [47-49]. Although the molecular mechanisms underlying obesity have not been fully elucidated, obesity and related metabolic disorders include multiple factors such as PPARs and adiponectin related to insulin resistance at several levels: hepatic, muscular, adipose, and vascular tissue [50-53]. In addition, a number of studies have revealed that the hypothalamic functions that regulate energy balance play a central role in the development of obesity [54, 55]. Several orexigenic and anorexigenic neuropeptides in the hypothalamus are involved in feeding and obesity, although their relative contributions are different.

Obesity research has gained new momentum from the discovery of the adipocytokine leptin, which was detected by identifying the mutation responsible for producing obesity in the *ob/ob* mouse [56]. Leptin-binding sites, which correspond to various classes of leptin receptor, have been identified in the hypothalamus [57]. There is increasing evidence that the effects of leptin are governed by several hypothalamic mediators, including orexigenic substances such as neuropeptide Y [58] and agouti-related protein [58], in addition to anorexigenic substances such as corticotropin releasing hormone [59], proopiomelanocortin [60], and the melanocortin-4 receptor and neuronal histamine [61, 62].

Leptin and histamine are both satiety factors, and we postulate that leptin expresses an anorectic effect through the histaminergic system. Concentrations of hypothalamic histamine are lower in leptin-deficient *ob/ob* mice [61]. *Ob/ob* obese mice also show lower histamine turnover, but this insufficient turnover can be recovered by leptin infusion [61]. An infusion of leptin elevates the turnover rate of neuronal histamine in the hypothalamus [61, 62]. Administrating FMH prior to injecting leptin attenuates the leptin-induced suppression of food intake in mice and rats [61, 63], suggesting the involvement of the central histaminergic system as a target for leptin in its control of feeding. In addition, in wild-type mice, leptin reduces food intake and obesity, whereas in H_1-R-KO mice, the effect of leptin is attenuated [38]. Taken together, these results suggest that leptin may affect feeding behavior by activating the central histaminergic system *via* H_1-R.

DIURNAL RHYTHM OF FEEDING BY HYPOTHALAMIC HISTAMINE AND HISTAMINE H_1-R

Previous studies have demonstrated that the circadian rhythm of feeding behavior is a crucial factor in the development of obesity, and abnormalities in the rhythm of feeding is associated with obesity [64-67]. In addition, correcting disturbances in circadian feeding rhythms can partially reverse obesity and related metabolic disorders [7, 17]. Several neuronal factors such as NPY have been shown to crossly regulated by circadian rhythm [67].

As for neuronal histamine, since the concentrations of neuronal histamine across the sleep-wake cycle in H_1-R deficient mice are significantly altered [17], it is possible that an altered circadian rhythm in H_1-R deficient mice affects their feeding behavior and consequently contributes to the development of obesity. Indeed, histamine H_1-R deficient mice had abnormal circadian rhythms of food intake relative to wild-type controls [17]. It is indicated that the disruption of feeding rhythm in H_1-R deficient mice contributed to the obesity.

Zucker obese rats also exhibited hyperphagia, disruption of feeding rhythm and severe obesity [68]. *Ad libitum* fed Zucker obese rats gained more weight compared with scheduled feeding groups, although food intake did not differ significantly between groups [69]. It is suggesting that disruption of feeding rhythm may contribute to body weight regulation in Zucher obese rats. Abnormalities in Zucker obese rats including disruptions of circadian feeding patterns and adaptive behaviors mimicked those in the H_1-R deficient mice. In fact, studies in Zucker obese rats revealed deficiency in both histamine concentration and HDC activity in the hypothalamus [68]. So, the abnormalities in the rhythm of feeding in Zucker obese rats is due to the disturbance of neuronal histamine.

Recently, the CLOCK genes regulate circadian nutrient homeostasis in mice [70].The neuronal circadian clock located within the hypothalamic SCN regulates the cycles in the physiological rhythm including food intake [70]. CLOCK mutant mice have an attenuated diurnal feeding rhythm, are hyperphagic and obese, and develop a metabolic syndrome of hyperlipidemia and hyperglycemia [70]. These results suggest that the circadian CLOCK gene network play an important role in food intake, glucose and lipid metabolism.

Taken together, the diurnal rhythm of food intake can be an independently and crucial factor for regulation of obesity.

CONCLUDING REMARKS

The activation of histamine neurons suppressed food intake and body weight through histamine H_1-R and H_3-R in the brain. The signals of histamine neurons to regulate food intake and obesity were observed as down stream of adipocytokine leptin. It is indicated that energy homeostasis is tightly maintained through the formation of a loop bridged between histamine neuron, its receptors and leptin.

Taken together, histamine neuron, H_1-R and H_3-R activation implicate possible maintenance of food intake and obesity in rodents. In the future, therapeutic application of activating of histamine neuron, H_1-R and H_3-R might be effective and promising therapy to reduce food intake and obesity.

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