

## The role of central endogenous histamine and H<sub>1</sub>, H<sub>2</sub> and H<sub>3</sub> receptors on food intake in broiler chickens

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### Summary

The role of endogenous histamine and H<sub>1</sub>, H<sub>2</sub> and H<sub>3</sub> central receptors on food intake in broiler chickens was investigated. For this purpose, a probe was used to manipulate the concentration of endogenous histamine by intracerebroventricular (ICV) injection of thioperamide, an H<sub>3</sub> receptor antagonist, and R- $\alpha$ -methylhistamine, an H<sub>3</sub> receptor agonist and subsequently the effects of brain histaminergic system on food intake was assessed. Moreover, to determine the receptors involved in histamine-induced feeding behaviour changes, H<sub>1</sub> and H<sub>2</sub> blockers were administered to thioperamide-treated chickens. Injection of thioperamide (600 and 300 nmol) decreased food intake dose-dependently ( $P < 0.05$ ). On the contrary, ICV injection of R- $\alpha$ -methylhistamine (400 and 200 nmol) increased food intake ( $P < 0.05$ ). Chlorpheniramine (128 and 256 nmol), a H<sub>1</sub> receptor antagonist, increased food intake ( $P < 0.05$ ). Famotidine, a H<sub>2</sub> receptor antagonist at 74 or 148 nmol had no effect on food intake but at 296 nmol significantly decreased food intake ( $P < 0.05$ ). Pretreatment with chlorpheniramine (256 nmol) significantly attenuated thioperamide effects (600 nmol) on food intake ( $P < 0.05$ ). In conclusion, the results of the present study demonstrated that histamine exerts anorexigenic effects through H<sub>1</sub> but not H<sub>2</sub> receptors in broiler chickens. Furthermore, it was shown that thioperamide through stimulation of synthesis and release of endogenous neuronal histamine can decrease food intake in broiler chickens.

**Key words:** Histaminergic neurons, Food intake, Chicken, Thioperamide

### Introduction

In the CNS, histamine (HA) is a putative neurotransmitter that is heterogeneously distributed in the brain and synthesized from the amino acid precursor histidine, which is then decarboxylated to HA via histidine decarboxylase (Panula *et al.*, 1990). Peripheral HA does not cross the blood-brain barrier (Mercer *et al.*, 1994). Histamine in the brain can be found most prominently in a restricted population of neurons originating from the tuberomammillary nucleus (TM) of the posterior hypothalamus (Panula *et al.*, 1990). Histaminergic neurons project diffusely from TM to several brain areas and

consistent with this widespread projection, the three subtypes of histamine receptors (H<sub>1</sub>, H<sub>2</sub> and H<sub>3</sub>) are distributed in almost all parts of the brain (Schwartz *et al.*, 1991). The central HA receptors and histaminergic neurons have been implicated in physiological processes such as circadian rhythms, cardiovascular and neuroendocrine and sleep-wakefulness control (Schwartz *et al.*, 1991; Onodera *et al.*, 1994). Several lines of evidence also suggest that central HA may be involved in the regulation of feeding behaviour. Intracerebroventricular injection of HA suppresses food intake in rats (Sakata *et al.*, 1988a, b; Ookuma *et al.*, 1989; Machidori *et al.*, 1992), cats (Machidori *et al.*, 1992), goats (Tuomisto

and Erikson, 1979) and chickens (Meade and Denbow, 2001).

Central infusion of  $H_1$  and  $H_2$  receptor antagonists in chickens (Meade and Denbow, 2001) and  $H_1$  receptor antagonists in mammals (Sakata *et al.*, 1988a; Fukagawa *et al.*, 1989; Ookuma *et al.*, 1989; Doi *et al.*, 1994) has affected the feeding response. The autoreceptor  $H_3$  modulates the release and synthesis of histamine (Arrang *et al.*, 1983). R- $\alpha$ -methylhistamine (RAMH), a selective  $H_3$  receptor agonist, inhibits the release of endogenous brain histamine from histaminergic neurons (Oishi *et al.*, 1989; Itoh *et al.*, 1992), while, thioperamide, a selective  $H_3$  receptor antagonist, enhances histamine release (Itoh *et al.*, 1991; Mochizuki *et al.*, 1991). A better understanding of food intake regulation in poultry will provide new strategies for managing birds to increase food consumption as an important issue in broiler production (Meade and Denbow, 2001).

Exogenous HA has been shown to decrease food intake when injected into the brain of broiler chickens (Kawakami *et al.*, 2000; Meade and Denbow, 2001). A critical drawback of previous reports is that the function of brain HA was estimated from results of exogenous application (Sakata *et al.*, 1997). Exogenous histamine does not mimic the physiological role of endogenous histamine, because this amine induces variable modification of synaptic transmission and autoinhibition of its endogenous release via the histamine  $H_3$  receptor (Arrang *et al.*, 1983). Exogenous HA does neither distinguish between the effects of neuronal and extraneuronal HA on brain functions nor detect the effects on  $H_1$  and  $H_2$  receptors (Sakata *et al.*, 1997). Therefore, the present study was conducted to determine the effects of endogenous HA and its central receptors on feeding behaviour in broiler chickens.

## Materials and Methods

### Animals and drugs

All experiments were carried out by using male Ross broiler chickens from Iran-Germany Poultry Breeding Company. Twelve-day-old chickens were housed in heated batteries with continuous lighting.

The housing temperature was 37°C during the first week, which was decreased 3°C weekly until week 4 of age. Birds were fed a mash diet (21% crude protein and 2900 kcal/kg metabolizable energy, Aminabad Animal Research Center, Tehran) and had free access to tap water. All drugs were purchased from Sigma Aldrich (St. Louis, USA), unless otherwise indicated. Famotidine was purchased from Merck (Germany). The drugs were dissolved in physiological saline except for famotidine which was dissolved in 10% aqueous lactic acid and diluted with distilled water. Drugs were prepared so that the necessary dose could be injected in 10  $\mu$ l using a microsyringe. All investigations were conducted in accordance with the guiding principles for the care and use of research animals of Faculty of Veterinary Medicine in University of Tehran.

### Experimental procedure

At week 3 of age and weight of 750 g, broilers were anaesthetized intravenously using sodium pentobarbital (25 mg/kg BW, Rhone Merieux, Belgium) and a 23-gauge thin-walled stainless steel guide cannula was stereotactically implanted into the right lateral cerebral ventricle according to the method of Davis *et al.* (1979). The cannula was secured with three stainless steel screws placed in the calvaria surrounding each guide cannula, and acrylic dental cement (Aqua Cem, Dentsply) was applied to the screws and guide cannula. Placement of the cannula into the ventricle was verified by presence of cerebrospinal fluid (CSF). Birds were allowed a minimum of 5 days recovery prior to injection.

Drugs were injected using a 27-gauge stainless steel injection cannula connected to a 10- $\mu$ l Hamilton syringe with a 20-cm long polyethylene tube. Food intake was monitored at 15-min intervals up to 1 h, and at 30 min intervals until 3 h after injection of drugs. In experiment 1, after being deprived from food for 12 h, the birds were injected ICV with 0, 150, 300 and 600 nmol of thioperamide in a volume of 10  $\mu$ l. In experiment 2, chlorpheniramine was administered at the doses of 0, 64, 128 and 256 nmol/10  $\mu$ l. In experiment 3, chlorpheniramine (256 nmol) was infused

into the lateral ventricle followed by thioperamide (600 nmol) 5 min later. These doses were chosen on the basis of the preliminary stages. Each bird was given two 5- $\mu$ l injections 5 min apart as described in Table 1. Experiment 4 evaluated the effect of ICV administration of  $H_3$  receptor agonist, R- $\alpha$ -methylhistamine (RAMH), on food intake, which was injected at the doses of 0, 100, 200 and 400 nmol/10  $\mu$ l. Normal saline was administered to the control birds in experiment 1 to 4. In experiment 5, famotidine was administered at the doses of 74, 148 and 256 nmol in a volume of 10  $\mu$ l and 1% lactic acid was used as control. Experiments 1, 2, 4 and 5 were carried out for determining the effective dose of thioperamide, chlorpheniramine, RAMH and famotidine on the chicken food intake, respectively. Experiment 3 was also achieved to determine the effect of thioperamide on food intake in chickens which have been preinjected with the effective dose of chlorpheniramine. Each experiment consisted of 12 chickens which were arranged in four groups and each group per day received one of the A, B, C, or D treatments (in experiments 1, 2, 4, and 5 different drug doses and in experiment 3 a combination of chlorpheniramine and thioperamide with saline). Drugs were injected for 4 days every other day, in which on days 1, 3, 5 and 7 after beginning of the experiments, each group of chickens received non-repetitive treatment. Accordingly, in the last day of injections, each group had received all of the treatments. Injection of drugs on day 1 in the experiment 3 is presented in Table 1. By

days 3, 5 and 7 after beginning of the experiment, chickens received the treatments with another arrangement.

### Statistical analysis

All results were analyzed using SPSS/PC program. Experimental procedure and data analysis were carried out according to the method which previously described by Jonaidi *et al.* (2002) as well as Meade and Denbow (2001). Briefly, five series of experiment were designed in a replicated 4  $\times$  4 latin square (as mentioned above) in which birds and days were the blocking factors. In all experiments, cumulative food intake (g) was subjected to analysis of variance at each time period, and *Tukey* test as a post hoc was used for determination of difference among groups. The level of significant value was set at  $p < 0.05$ .

**Table 1: Procedure of receiving treatments by chickens in experiment 3 with a replicated latin square design (day 1)**

Groups	Treatments	Injections
I (n=3)	A	saline+saline
II (n=3)	B	saline+thioperamide
III (n=3)	C	chlorpheniramine+saline
IV (n=3)	D	chlorpheniramine+thioperamide

### Results

The results of food intake responses to ICV injection of thioperamide in chickens are summarized in Table 2. Food intake was significantly decreased by thioperamide ( $P < 0.05$ ) in the birds which were food-deprived for 12 h before injection. At the dose of 300 and 600 nmol, the effect was

**Table 2: Cumulative food intake (g) in the control and thioperamide-treated chickens at different times after injection (means  $\pm$  SEM)**

Dose (nmol)	Postinjection times (min)							
	15	30	45	60	90	120	150	180
Control	13.58 $\pm 0.62^a$	22.16 $\pm 0.87^a$	30.08 $\pm 1.38^a$	35.33 $\pm 1.28^a$	39.50 $\pm 1.29^a$	44.75 $\pm 1.40^a$	49.0 $\pm 1.38^a$	54.0 $\pm 1.35^a$
150	11.58 $\pm 0.67^a$	21.0 $\pm 0.68^a$	28.66 $\pm 0.68^a$	33.58 $\pm 0.85^a$	37.08 $\pm 0.89^a$	43.66 $\pm 0.91^{ab}$	46.58 $\pm 0.62^a$	52.25 $\pm 0.78^a$
300	6.75 $\pm 0.87^b$	12.66 $\pm 0.82^b$	14.75 $\pm 0.78^a$	22.41 $\pm 1.20^b$	28.25 $\pm 0.76^b$	40.16 $\pm 0.66^b$	45.66 $\pm 0.98^a$	52.66 $\pm 1.16^a$
600	5.66 $\pm 0.83^b$	7.41 $\pm 0.91^c$	9.75 $\pm 1.08^c$	13.75 $\pm 0.75^c$	22.91 $\pm 0.70^c$	28.33 $\pm 0.79^c$	34.41 $\pm 0.79^b$	41.08 $\pm 0.78^b$

Means with different superscripts (a, b, c) within each column are significantly different ( $P < 0.05$ )

dose-dependent. Food intake in the chickens treated with 150 nmol of thioperamide was similar to the control group during infusion. Injection of chlorpheniramine increased food intake at doses of 128 and 256 nmol ( $P<0.05$ ), while 64 nmol did not significantly influence food consumption (Table 3). When birds were pretreated with chlorpheniramine followed by thioperamide,

the suppressive effects of thioperamide on the food intake was significantly attenuated ( $P<0.05$ ; Table 4). Activation of brain  $H_3$  receptors by ICV administration of RAMH at the doses of 200 and 400 nmol, markedly increased feeding as compared with saline-treated group ( $P<0.05$ ; Table 5), although the lower dose was more effective on food intake, 100 nmol RAMH had no effect on

**Table 3: Cumulative food intake (g) in the control and chlorpheniramine-treated chickens at different times after injection (means  $\pm$  SEM)**

Dose (nmol)	Postinjection times (min)							
	15	30	45	60	90	120	150	180
Control	12.25 $\pm 0.78^a$	17.50 $\pm 0.79^a$	20.9 $\pm 10.82^a$	24.08 $\pm 0.99^a$	29.75 $\pm 0.98^a$	36.33 $\pm 0.95^a$	39.16 $\pm 0.79^a$	44.50 $\pm 1.05^a$
64	14.58 $\pm 0.57^a$	22.66 $\pm 4.57^{ab}$	22.83 $\pm 0.66^a$	25.00 $\pm 0.76^a$	30.83 $\pm 1.006^a$	34.33 $\pm 0.76^a$	39.25 $\pm 0.72^a$	42.83 $\pm 0.63^a$
128	17.75 $\pm 0.92^b$	25.41 $\pm 1.02^{ab}$	32.83 $\pm 1.17^b$	35.33 $\pm 1.01^b$	39.50 $\pm 1.01^b$	42.25 $\pm 0.94^b$	44.91 $\pm 0.84^b$	50.08 $\pm 0.82^b$
256	22.91 $\pm 0.77^c$	31.75 $\pm 1.27^b$	38.08 $\pm 0.97^c$	43.08 $\pm 1.46^c$	48.91 $\pm 0.73^c$	54.50 $\pm 0.98^c$	57.00 $\pm 1.10^c$	63.58 $\pm 0.85^c$

Means with different superscripts (a, b, c) within each column are significantly different ( $P<0.05$ )

**Table 4: Cumulative food intake (g) in the control and chlorpheniramine (256 nmol) + thioperamide-treated (600 nmol) chickens at different times after injection (means  $\pm$  SEM)**

Treatment	Postinjection times (min)							
	15	30	45	60	90	120	150	180
Saline + saline	17.73 $\pm 1.07^a$	28.58 $\pm 0.98^a$	31.75 $\pm 0.94^a$	34.83 $\pm 0.99^a$	36.50 $\pm 0.84^a$	40.91 $\pm 0.52^a$	44.50 $\pm 0.95^a$	51.75 $\pm 0.80^a$
Chlorpheniramine + thioperamide	12.25 $\pm 1.03^d$	18.66 $\pm 0.68^d$	21.75 $\pm 0.57^d$	24.75 $\pm 0.52^d$	27.25 $\pm 0.70^d$	31.33 $\pm 0.81^d$	36.16 $\pm 0.91^d$	40.75 $\pm 0.80^d$
Chlorpheniramine + saline	33.25 $\pm 0.88^c$	37.75 $\pm 0.76^c$	42.25 $\pm 0.73^c$	45.41 $\pm 0.76^c$	46.75 $\pm 0.81^c$	52.16 $\pm 0.58^c$	55.41 $\pm 0.58^c$	59.50 $\pm 0.58^c$
Saline + thioperamide	7.91 $\pm 0.94^b$	11.16 $\pm 0.66^b$	14.75 $\pm 0.6^b$	16.58 $\pm 0.58^b$	19.83 $\pm 0.79^b$	27.33 $\pm 1.2^b$	30.00 $\pm 1.06^b$	34.66 $\pm 0.83^b$

Means with different superscripts (a, b, c, d) within each column are significantly different ( $P<0.05$ )

**Table 5: Cumulative food intake (g) in the control and R- $\alpha$ -methylhistamine-treated chickens at different times after injection (means  $\pm$  SEM)**

Dose (nmol)	Postinjection times (min)							
	15	30	45	60	90	120	150	180
Control	11.16 $\pm 0.74^a$	15.58 $\pm 0.91^a$	21.66 $\pm 0.80^a$	27.16 $\pm 0.96^a$	30.41 $\pm 0.97^a$	35.83 $\pm 0.74^a$	39.33 $\pm 0.81^a$	42.83 $\pm 0.91^a$
100	10.58 $\pm 0.67^a$	13.41 $\pm 0.69^a$	21.83 $\pm 0.75^a$	26.91 $\pm 0.70^a$	32.33 $\pm 1.28^a$	34.16 $\pm 2.50^a$	41.66 $\pm 0.83^a$	43.66 $\pm 0.98^a$
200	19.66 $\pm 0.89^b$	26.33 $\pm 0.80^b$	35.66 $\pm 1.27^b$	42.75 $\pm 1.08^b$	46.66 $\pm 0.65^b$	50.25 $\pm 0.77^b$	55.75 $\pm 1.33^b$	59.50 $\pm 1.29^b$
400	14.58 $\pm 0.62^c$	22.58 $\pm 1.05^c$	29.33 $\pm 0.83^c$	33.41 $\pm 0.82^c$	38.91 $\pm 0.96^c$	44.75 $\pm 1.08^c$	47.66 $\pm 0.65^c$	51.25 $\pm 0.77^c$

Means with different superscripts (a, b, c) within each column are significantly different ( $P<0.05$ )

**Table 6: Cumulative food intake (g) in the control and famotidine-treated chickens at different times after injection (means  $\pm$  SEM)**

Dose (nmol)	Postinjection times (min)							
	15	30	45	60	90	120	150	180
Control	7.50 $\pm 2.80^{ab}$	14.33 $\pm 2.20^a$	20.00 $\pm 5.34^{ab}$	25.00 $\pm 5.34^a$	26.83 $\pm 4.82^a$	29.50 $\pm 5.01^a$	35.66 $\pm 6.17^a$	37.16 $\pm 5.70^a$
74	15.25 $\pm 2.70^a$	20.08 $\pm 2.62^a$	22.41 $\pm 2.49^a$	24.41 $\pm 2.26^a$	27.16 $\pm 2.45^a$	29.50 $\pm 2.62^a$	31.66 $\pm 2.27^a$	35.75 $\pm 1.72^a$
148	7.33 $\pm 2.80^{ab}$	11.33 $\pm 3.10^{ab}$	11.16 $\pm 3.07^{bc}$	12.33 $\pm 2.98^{ab}$	18.16 $\pm 3.78^{ab}$	21.66 $\pm 4.20^{ab}$	24.83 $\pm 3.60^{ab}$	27.50 $\pm 3.47^{ab}$
296	1.50 $\pm 0.67^b$	2.00 $\pm 1.00^b$	2.66 $\pm 1.58^c$	5.16 $\pm 1.40^b$	7.83 $\pm 2.35^b$	12.50 $\pm 3.21^b$	14.66 $\pm 3.39^b$	16.66 $\pm 3.78^b$

Means with different superscripts (a, b, c) within each column are significantly different ( $P < 0.05$ )

food consumption. In the experiment 5, ICV administration of famotidine, an  $H_2$  receptor antagonist, had a considerable anorexigenic effect on feeding at 296 nmol ( $P < 0.05$ ), whereas at the doses of 74 and 148 nmol, there were no significant differences in the food consumption in comparison with lactic acid-treated group (Table 6).

## Discussion

The reduction in food intake due to thioperamide was dose-dependent, with the greatest decrease at 600 nmol. Our data on the effect of thioperamide on feeding are not consistent with those of Kawakami *et al.* (2000) who found no inhibitory effect on feeding under fasting condition in broiler chickens. Thioperamide appears to have a specific inhibitory effect on feeding, while, during the light period, it had no inhibitory effect on feeding behaviour in fasted and nonfasted rats (Itoh *et al.*, 1992). Circadian rhythm of histamine concentration in the rat hypothalamus is well known, with the peak in the early light phase and the nadir in the early dark (Orr and Quay, 1975). Activation rate of histaminergic neurons during the dark period gradually increases with maximum rate at the light beginning and inversely decreases during the light period. Endogenous histamine modulates physiological feeding in an inhibitory fashion through stimulation of histamine  $H_3$  receptors in the ventromedial nucleus (Sakata *et al.*, 1991, 1997). Therefore, a difference in experimental conditions (i.e., early light phase or during the light period) seems to be an important factor. Since

thioperamide has been shown to suppress feeding by increasing histaminergic neurons activity via blocking of histamine inhibitory feedback pathway (Arrang *et al.*, 1983), it would be effective only when the activity of histaminergic neurons is low during the light period and early dark phase. This has been reported with histidine decarboxylase inhibitor alpha-fluoromethylhistidine (FMH, Itoh *et al.*, 1999). Intracerebroventricular administration of FMH stimulates feeding in the early light phase, when the histamine synthesis is in peak, however, it does not affect feeding behaviour in early darkness, in which histamine synthesis is at minimum (Ookuma *et al.*, 1993). In our experiment, histaminergic neuronal activity during the infusion was probably low which caused thioperamide to act in a dose-dependent manner for food intake decline; infusion of thioperamide in our study was started at 09:00, 3 h after the beginning of the light period. Further research is necessary to determine the central histaminergic activities in birds that undergo photoperiodic changes.

In our investigation, ICV injection of chlorpheniramine dose-dependently enhanced the food intake. This result is consistent with other reports. Injection of other  $H_1$  antagonists into the ventromedial and paraventricular nuclei had similar effect on the appetite. Metoprine increases the brain histamine through inhibition of main histamine catabolism pathway and  $H_1$  receptor antagonists ameliorate the metoprine effect. Several studies demonstrated that endogenous brain histamine in mammals decreased the appetite via  $H_1$  receptors. Our study showed

the role of central H<sub>1</sub> receptors on appetite regulation in birds (Doi *et al.*, 1994; Lecklin *et al.*, 1998; Lecklin and Tuomisto, 1998; Morimoto *et al.*, 2001; Meade and Denbow, 2001). Preinjection of chlorpheniramine inhibited the appetite decrease induced by thioperamide which is in agreement with studies in rats (Schliker *et al.*, 1994; Sakata *et al.*, 1997).

R- $\alpha$  methylhistamine, as a specific H<sub>3</sub> receptor agonist, inhibited the release of brain neuronal histamine (Clark and Hill, 1996). In our investigation RAMH enhanced the appetite, however, its ICV injection had no effect on the rat appetite (Lecklin *et al.*, 1998). In that experiment infusion was performed without regard to the circadian rhythm of neuronal histaminergic system activity in rats and the agent was applied during the lowest activity of this system. The results of the present study suggested that RAMH can decrease the neuronal histaminergic activity in broiler chickens. The effect of RAMH confirms the results of thioperamide in the present study. Because, histaminergic neuronal activity at 09:00 is not likely at maximum, RAMH could activate inhibitory H<sub>3</sub> receptors and consequently inhibit histamine release and induce food intake increment. Using famotidine as a potent and specific H<sub>2</sub> receptor antagonist (Cooper *et al.*, 1991) at low dose had no effect on appetite which is in agreement with other reports (Mercer, 1997; Kjaer *et al.*, 1998; Sindelar *et al.*, 2004), whereas at high dose, not only decreased appetite but also excitement, restlessness and occasionally shock were noticed. Similar signs were reported in the guinea pigs (Koutsoviti-Papadopoulos and Nikolaidis, 2003). This effect can not be related to the food intake center in brain. Rather, it may be due to anxiety as a result of famotidine at high dose and inhibition of central GABAergic system (Koutsoviti-Papadopoulos and Nikolaidis, 2003). Injection of other H<sub>2</sub> receptor antagonists into the ventromedial and paraventricular nuclei of hypothalamus (Sakata *et al.*, 1997) and third ventricle (Lecklin and Tuomisto, 1998) did not affect the food intake in rats. Similarly in broiler chickens, endogenous histamine decreased the appetite via H<sub>1</sub> receptors, however the nuclei that regulate

the birds feeding behaviour have not yet been determined.

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