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Central Opioidergic System Interplay with Histamine on Food Intake in Neonatal Chicks: Role of μ-Opioid and H1/H3 Receptors

■Author(s)

Jaefari-Anari M[I]
Zendehdel M[II]
Gilanpour H[I]
Asghari A[III]
Babapour V[II]

[I] Department of Basic Sciences, Faculty of Veterinary Medicine, Science and Research Branch, Islamic Azad University, Tehran, Iran.
[II] Department of Basic Sciences, Faculty of Veterinary Medicine, University of Tehran, 14155-6453, Tehran, Iran.
[III] Department of Clinical Science, Faculty of Veterinary Medicine, Science and Research Branch, Islamic Azad University, Tehran, Iran.

■Mail Address

Corresponding author e-mail address
Morteza Zendehdel
Department of Basic Sciences, Faculty of Veterinary Medicine, University of Tehran, 14155-6453, Tehran, Iran.
Phone: +98-21-61117186
Email: zendedel@ut.ac.ir

■Keywords

Central opioidergic, Histamine, Food intake, Broiler chicken.

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ABSTRACT

The present study was designed to examine the role of Opioidergic and Histaminergic systems on feeding behavior in 3-hour food deprived neonatal meat- type chicks. In experiment 1, chicks received intracerebroventricular (ICV) injection of (A) control solution, (B) α-FMH (alpha fluoromethyl histidine; 250 nmol), (C) DAMGO (μ-opioid receptor agonist, 125 pmol) and (D) α-FMH + DAMGO. Experiments 2-4 were similar to experiment 1, except chicken ICV injected with Chlorpheniramine (histamine H_1 receptors antagonist; 300 nmol), famotidine (histamine H_2 receptors antagonist; 82 nmol) and Thioperamide (histamine H_3 receptors antagonist; 300 nmol) instead of the α-FMH. In experiments 5-8, birds ICV injected with the same procedure as experiments 1-4, except they were injected with DPDPE (δ-opioid receptor agonist, 40 nmol) instead of DAMGO. Experiments 9-12 were similar to the experiments 1-4, except neonatal broilers ICV were injected with U-50488H (κ-opioid receptor agonist, 30 nmol) instead of DAMGO. Then the cumulative food intake was measured until 120 min post injection. According to the results, ICV injection of DAMGO, significantly decreased food intake ($p<0.05$) while DPDPE and U-50488H increased feeding behavior compared to the control group ($p<0.05$). Co-administration of the α-FMH and DAMGO significantly inhibited hypophagic effect of the DAMGO in neonatal broilers ($p<0.05$). Also, Chlorpheniramine significantly inhibited DAMGO-induced feeding behavior in neonatal chicks ($p<0.05$). In addition, co-administration of the Thioperamide + DAMGO significantly amplified the hypophagic effect of the DAMGO in neonatal chicks ($p<0.05$). However, famotidine had no effect on food intake induced by DAMGO ($p>0.05$). Also, the hyperphagic effect of DPDPE and U-50488 had no affect by α-FMH, Chlorpheniramine, famotidine and Thioperamide ($p>0.05$). These results suggested that an interconnection between central opioidergic and histaminergic systems on feeding behavior is mediated via μ-opioid and H_1/H_3 receptors in neonatal broilers.

INTRODUCTION

Feeding behavior is a very complex neurochemical pathway which is regulated hierarchically from the central nervous system (CNS) and the peripheral nervous system (PNS) (Jonaidi *et al.*, 2012). Complex physiological interaction exists on food intake and expenditure by afferent signals and efferent effectors between the CNS and gastrointestinal tract (Hassanpour *et al.*, 2015). In the CNS, this process is regulated by complex neurochemical mechanisms in the hypothalamic nuclei, striatum, amygdala and arcuate nucleus (ARC) (D'Addario *et al.*, 2014). Several neurotransmitters in the CNS have been identified where food intake is regulated (Ladepeche *et al.*, 2013).

Histamine is one of the main neurotransmitters which express in the paraventricular nucleus (PVN) and ventromedial hypothalamus (VMH) of the brain (Giannoni *et al.*, 2009; Blandina *et al.*, 2012). To date, 4 subtypes of histamine receptors have been identified including H_1, H_2, H_3 and H_4 in the several parts of CNS (Schneider *et al.*, 2014). The central histaminergic (HAergic) system has the key role in feeding behavior (Rozov *et al.*, 2014) where the ICV injection of histamine decreases food intake whereas ICV injection of alpha-fluoromethylhistidine (α-FMH, selective inhibitor of the histidine decarboxylase as histamine synthesizing enzyme) or chlorpheniramine (histamine H_1 receptor antagonist) increases food intake in rats (Morimoto *et al.*, 2001) and chicken (Kawakami *et al.*, 2000). It is well documented that appetite is regulated by the interaction of various neurotransmitters and complex network (Branch *et al.*, 2013).

Opioids are known as inhibitory neurotransmitters and 3 receptor subtypes are identified, mu (μ), delta (δ) and kappa (κ), belonging to the G protein-coupled receptors (GPCRs) (Filizola & Devi, 2013). Opioids are responsible in numerous physiologic functions such as pain modulation, respiratory, neuroendocrine and reward and food intake regulation (Kaneko *et al.*, 2012). The intracerebroventricular (ICV) injection of [D-Ala^2, NMe-Phe^4, Gly^5-ol]-enkephalin (DAMGO) and β-casomorphin (μ-opioid receptor agonists) induce hypophagia while [D-Pen^{2,5}]-enkephalin (DPDPE) (δ-opioid receptor agonist) exerts orexigenic effects in mammals (Kaneko *et al.*, 2012). The ICV injection of μ-opioid receptor agonists induces hypophagia while δ-opioid receptor agonist and U-50488H (κ-opioid receptor agonist) has a hyperphagic effect in neonatal layer and broiler chicks (Bungo *et al.*, 2004; Shiraishi *et al.*, 2008, Shojaei *et al.*, 2015; Zendehdel *et al.*, 2016a).

Based on the literature, an interconnection exists between central HAergic and opioidergic systems in some areas in the brain. Endomorphins have the highest affinity in the amygdala, PVN and dorsomedial hypothalamus with histaminergic neurons and might regulate arousal and sedative behaviors (Koneru *et al.*, 2009). It is reported that Naloxone-induced water intake decreased by blockade of H_1 and H_2 receptors in male rats (Oryan *et al.* 2004). The interaction of the histaminergic and opioidergic systems in the hippocampus mediates pain from originating (Mojtahedin *et al.*, 2008). Co-injection of the histamine H_1 receptor antagonists and morphine, increased analgesic activity in the acute trigeminal model of pain in rats (Khalilzadeh *et al.*, 2017). Despite the researches being done on interaction of the central HAergic and opioidergic systems, there is no report on interaction of these two systems on feeding behavior in mammals and poultry. It is known that central food intake regulation is dissimilar between mammals and birds (Zendehdel & Hassanpour, 2014). It is logical to assume the regulatory mechanisms governing these processes in birds (Hassanpour *et al.*, 2015). Therefore, the current study was designed for the first time to determine the possible interconnection of the central opioidergic and HAergic systems on feeding behavior in neonatal meat- type chicks.

MATERIALS AND METHODS

Animals

A total 528 male meat-type one-day-old chickens (Ross 308) were purchased from a local hatchery (Mahan Co. Iran). Birds were kept as flocks for 2 days then randomly transferred into individual cages at a temperature of 30 ± 1°C with 50 ± 2 percent humidity (Olanrewaju *et al.*, 2006). A commercial diet provided during the study containing 21% crude protein and 2850 kcal/kg of metabolizable energy (Chineh Co. Iran) (table). All birds had free access to food and fresh water during the study. Just 3 hours prior the

Table – Ingredient and nutrient analysis of experimental diet

Ingredient	(%)	Nutrient analysis	
Corn	52.85	ME, kcal/g	2850
Soybean meal, 48% CP	31.57	Crude protein (%)	21
Wheat	5	Linoleic acid (%)	1.69
Gluten meal, 61% CP	2.50	Crude fiber (%)	3.55
Wheat bran	2.47	Calcium (%)	1
Di-calcium phosphate	1.92	Available phosphorus (%)	0. 5
Oyster shell	1.23	Sodium (%)	0.15
Soybean oil	1.00	Potassium (%)	0.96
Mineral premix	0.25	Chlorine (%)	0.17
Vitamin premix	0.25	Choline (%)	1301.22
Sodium bicarbonate	0.21	Arginine (%)	1.14
Sodium chloride	0.20	Isoleucine (%)	0.73
Acidifier	0.15	Lysine (%)	1.21
DL-Methionine	0.10	Methionine (%)	0.49
Toxin binder	0.10	Methionine + cystine (%)	0.83
L-Lysine HCl	0.05	Threonine (%)	0.70
Vitamin D_3	0.1	Tryptophan (%)	0.20
Multi enzyme	0.05	Valine (%)	0.78

ME: metabolisable energy, CP: crude protein, per kg of diet, the mineral supplement contains 35.2 g manganese from MnSO4·H2O; 22 g iron from FeSO4·H2O; 35.2 g zinc from ZnO; 4.4 g copper from CuSO4·5H2O; 0.68 g iodine from ethylene diamine dihydroiodide; 0.12 g seleniumfrom Na2SeO3. The vitamin supplement contains 1.188 g of retinyl acetate, 0.033 g of dl-α-tocopheryl acetate, 8.84 g of tocopherol, 1.32 g of menadione, 0.88 g of thiamine, 2.64 g of riboflavin, 13.2 g of nicotinic acid, 4.4 g of pantothenic acid, 1.76 g of pyridoxin, 0.022 g of biotin, 0.36 g of folic acid, 1500 mg of choline chloride.

ICV injections, chicken were food deprived (FD_3) but had free access to water. The injections were applied to all birds at 5 days of age. Animal handling and experimental procedures were performed according to the Guide for the Care and Use of Laboratory animals by the National Institutes of Health (USA) and the current laws of the Iranian government for animal care.

Experimental Drugs

DAMGO (μ-opioid receptor agonist), DPDPE (δ-opioid receptor agonist), U-50488H (κ-opioid receptor agonist), α-FMH(alpha fluoromethyl histidine; histidine decarboxylase inhibitor), Chlorpheniramine (histamine H_1 receptors antagonist), famotidine (histamine H_2 receptors antagonist), Thioperamide (histamine H_3 receptors antagonist) and Evans blue were purchased from Sigma Co. (Sigma, USA) and Tocris Co. (UK). The drugs were first dissolved in absolute dimethyl sulfoxide (DMSO) then diluted with 0.85% saline containing Evans blue at a ratio of 1/250. DMSO with this ratio does not have cytotoxic effect (Blevins *et al.*, 2002; Qi *et al.*, 2008).

ICV injection procedures

The birds were randomly allocated into 12 experimental groups (each experiment includes 4 groups, n=11 in each group). Prior to each experiment, the chicks were weighed and based on their body weight, divided into experimental groups so the average weight between treatment groups was as uniform as possible. The ICV injection was applied using a microsyringe (Hamilton, Switzerland) without anesthesia according to the technique previously described by Davis *et al.*, (1979) and Furuse *et al.*, (1997) where the head of the birds was held with an acrylic device while the bill holder was 45° and calvarium parallel to the surface of table (Van Tienhoven & Juhasz, 1962). A hole was drilled in a plate where the skull overlaid immediately_over the right lateral ventricle. A microsyringe was inserted into the right ventricle via the hole and the tip of the needle penetrated 4 mm beneath the skin of the skull. It is revealed that, there is no injection-induced physiological stress using this method in neonatal chicks (Saito *et al.*, 2005). Each chick received an ICV injection (with vehicle or drug solution) in a volume of 10 μL (Furuse *et al.*, 1999). The control group received a control solution (DMSO/ saline mixture containing Evan's blue, 10 μL) (Furuse *et al.*, 1999). Right away after the injection, FD_3 the birds returned to their individual cages and supplied fresh water and food (pre-weighed). Cumulative food intake (gr) was measured at 30, 60 and 120 minutes post the injection. Food consumption was calculated as a percentage of body weight to minimize the impact of the body weight on the amount of food intake. Each bird was used just once in each experimental group. At the end of the experiments, the accuracy of the placement of the injection in the ventricle was verified by presence of Evans blue followed by slicing the frozen brain tissue. All experimental procedures were done from 8:00 A.M. until 3:30 P.M.

Feeding experiments

To investigate the interconnection of opioidergic and histaminergic systems on cumulative food intake in neonatal meat-type birds, 12 experiments designed (each experiment contains 4 groups (A-D) within 11 replicates in each group) were used. In experiment 1, FD_3 the chicks received a dose of the ICV injection of (A) control solution, (B) α-FMH (alpha fluoromethyl histidine; 250 nmol), (C) DAMGO (μ-opioid receptor agonist, 125 pmol) and (D) α-FMH + DAMGO. Experiments 2-4 were similar to experiment 1, except FD_3 chicks were ICV injected with chlorpheniramine (histamine H_1 receptors antagonist; 300 nmol), famotidine (histamine H_2 receptors antagonist; 82 nmol) and thioperamide (histamine H_3 receptors antagonist; 300 nmol) instead of α-FMH. In experiment 5, FD_3 chicken received a dose of the ICV injection of (A) control solution, (B) α-FMH (250 nmol), (C) DAMGO (μ-opioid receptor agonist, 125 pmol) and (D) α-FMH + DPDPE. Experiments 6-8 were similar to experiment 1, except FD_3 birds were ICV injected with chlorpheniramine (histamine H_1 receptors antagonist; 300 nmol), famotidine (histamine H_2 receptors antagonist; 82 nmol) and thioperamide (histamine H_3 receptors antagonist; 300 nmol) instead of α-FMH. In experiment 9, FD_3 chicken received a dose of the ICV injection of (A) control solution, (B) α-FMH (250 nmol), (C) U-50488H (κ-opioid receptor agonist; 30 nmol) and (D) α-FMH + U-50488H. Experiments 10-12 were similar to experiment 1, except FD_3 chicks received ICV injection of the chlorpheniramine (histamine H_1 receptors antagonist; 300 nmol), famotidine (histamine H_2 receptors antagonist; 82 nmol) and thioperamide (histamine H_3 receptors antagonist; 300 nmol) instead of α-FMH. Each bird was injected once only. These doses of drugs were calculated based on the previous studies (Bungo *et al.*, 2004, 2005; Taati *et al.*, 2009; Shojaei *et al.*, 2015; Zendehdel *et al.*, 2015, 2016a, b) and our pilot studies (un-published data). Right away after the injection, chickens were returned to their individual cages and provided *ad libitum* food (pre-weighed) and water. Cumulative food intake was recorded at 30, 60 and 120 minutes post injection.

Statistical analysis

Data is presented as mean ± SEM (standard error of the mean). Cumulative food intake (as percent of body weight) was analyzed by repeated measure two-way analysis of variance (ANOVA) using SPSS 16.0 for Windows (SPSS, Inc., Chicago, IL, USA). For treatment showing a main effect by ANOVA, means were compared by Tukey-Kramer test. $p<0.05$ was considered as significant differences between treatments.

RESULTS

Effects and interactions of central HAergic and opioidergic systems on cumulative food intake in FD_3 neonatal meat-type chicks are shown in figures 1-12. In this study to examine the possible interaction between these two systems, effective and sub-effective doses of pharmacological agents were administered to confront nullifying effects of the agents. In experiment 1, ICV injection of the DAMGO (μ opioid receptors agonist, 125 pmol) significantly decreased food intake until 120 min post injection compared to the control group ($p<0.05$). The ICV injection of_the sub effective dose of the α-FMH (alpha fluoromethyl histidine; 250 nmol) had no effect on cumulative food intake compared to the control group ($p>0.05$). Co-administration of the α-FMH and DAMGO significantly inhibited the hypophagic effect of the DAMGO in neonatal broilers [treatment effect: F (3, 80) = 162.1, $p<0.0001$; time effect: F (2, 80) = 541.3, $p<0.0001$; treatment and time interaction: F (6, 80) = 28.53; $p<0.0001$; Fig. 1].

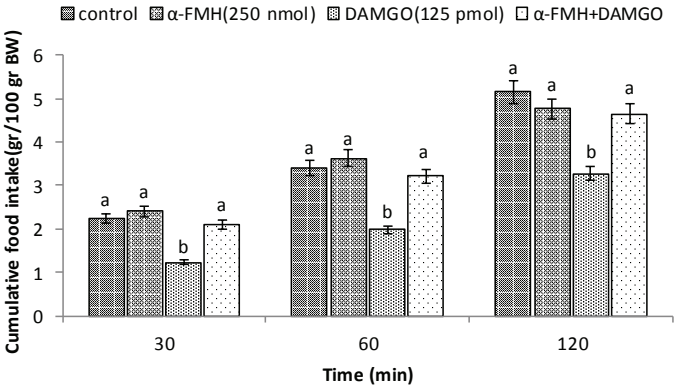

Figure 1 – Effects of intracerebroventricular injection of control solution, α-FMH (alpha fluoromethyl histidine; 250 nmol), DAMGO (μ-opioid receptor agonist, 125 pmol) and combination of α-FMH plus DAMGO on cumulative food intake (gr/100gr BW) in neonatal chicks. Data are expressed as mean ± SEM. Different letters (a and b) indicate significant differences between treatments at each time ($p<0.05$).

In experiment 2, hypophagia was observed after the ICV injection of DAMGO (125 pmol) in FD_3 neonatal chicken, compared to the control group ($p<0.05$). The ICV injection of the chlorpheniramine (histamine H_1 receptors antagonist; 300 nmol) had no effect on food intake in comparison to the control group ($p>0.05$). Co-injection of the chlorpheniramine + DAMGO significantly inhibited the hypophagic effect of the DAMGO in neonatal meat-type chicken [treatment effect: F (3, 80) = 416.2, $p<0.0001$; time effect: F (2, 80) = 985.13, $p<0.0001$; treatment and time interaction: F (6, 80) = 5.37; $p<0.0001$; Fig. 2].

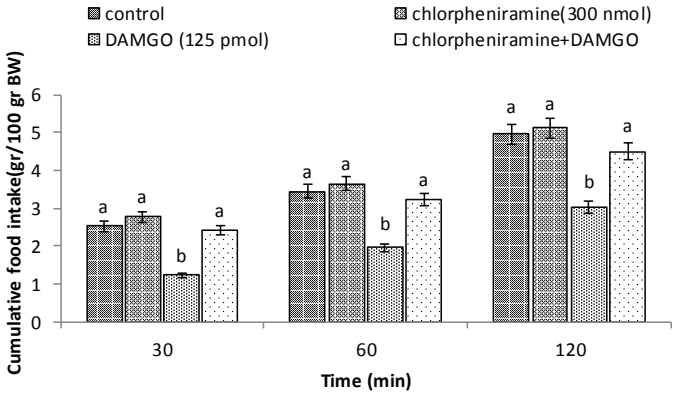

Figure 2 – Effects of intracerebroventricular injection of control solution, chlorpheniramine (histamine H1 receptors antagonist; 300 nmol), DAMGO (μ-opioid receptor agonist, 125 pmol) and combination of chlorpheniramine plus DAMGO on cumulative food intake (gr/100gr BW) in neonatal chicks. Data are expressed as mean ± SEM. Different letters (a and b) indicate significant differences between treatments at each time ($p<0.05$).

In experiment 3, significant decrease in food intake was observed after the ICV injection of DAMGO (125 pmol) in birds compared to the control group ($p<0.05$). The ICV injection of the famotidine (histamine H_2 receptors antagonist; 82 nmol) had no effect on food intake in comparison to the control group ($p>0.05$). Co-injection of the famotidine + DAMGO was not able to change DAMGO-induced hypophagia [treatment effect: F (3, 80) = 89.35, $p<0.0001$; time effect: F (2, 80) = 549.7, $p<0.0001$; treatment and time interaction: F (6, 80) = 9.17; $p<0.0001$; Fig. 3].

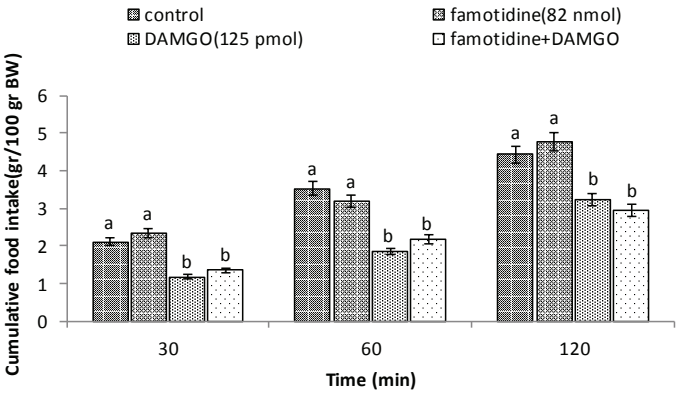

Figure 3 – Effects of intracerebroventricular injection of control solution, famotidine (histamine H2 receptors antagonist; 82 nmol), DAMGO (μ-opioid receptor agonist; 125 pmol) and combination of famotidine plus DAMGO on cumulative food intake (gr/100gr BW) in neonatal chicks. Data are expressed as mean ± SEM. Different letters (a and b) indicate significant differences between treatments at each time ($p<0.05$).

In experiment 4, the ICV injection of the DAMGO (125 pmol) significantly decreased food intake in comparison to the control group (p<0.05). No significant effect was observed on food intake by the ICV injection of thioperamide (histamine H_3 receptors antagonist; 300 nmol). Co-administration of the Thioperamide + DAMGO amplified hypophagic effect of the DAMGO in neonatal chicks [treatment effect: F (3, 80) = 119.61, p<0.0001; time effect: F (2, 80) = 859.14, p<0.0001; treatment and time interaction: F (6, 80) = 43.12; p<0.0001; Fig. 4].

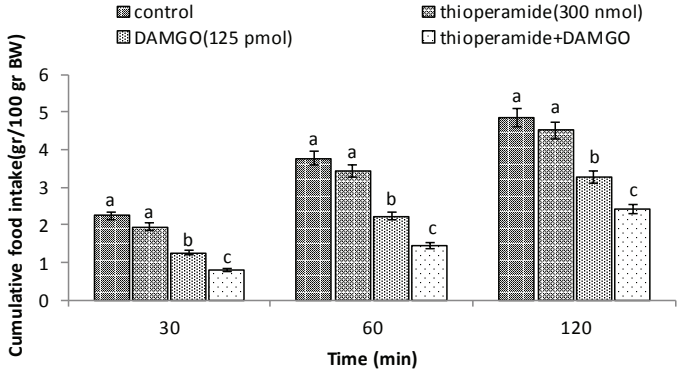

Figure 4 – Effects of intracerebroventricular injection of control solution, thioperamide (histamine H3 receptors antagonist; 300 nmol), DAMGO (μ-opioid receptor agonist; 125 pmol) and combination of thioperamide plus DAMGO on cumulative food intake (gr/100gr BW) in neonatal chicks. Data are expressed as mean ± SEM. Different letters (a, b and c) indicate significant differences between treatments at each time (p<0.05).

In experiment 5, the ICV injection of the α-FMH (250 nmol) had no significant effect on food intake (p>0.05). Hyperphagia was observed after the ICV injection of DPDPE (δ-opioid receptor agonist; 40 pmol) in FD_3 neonatal birds (p<0.05). Co-administration of the α-FMH + DPDPE had no significant effect on δ-opioid receptors agonist-induced hyperphagia in neonatal chicks [treatment effect: F (3, 80) = 74.46, p<0.0001; time effect: F (2, 80) = 750.71, p<0.0001; treatment and time interaction: F (6, 80) = 7.52; p<0.0001; Fig. 5].

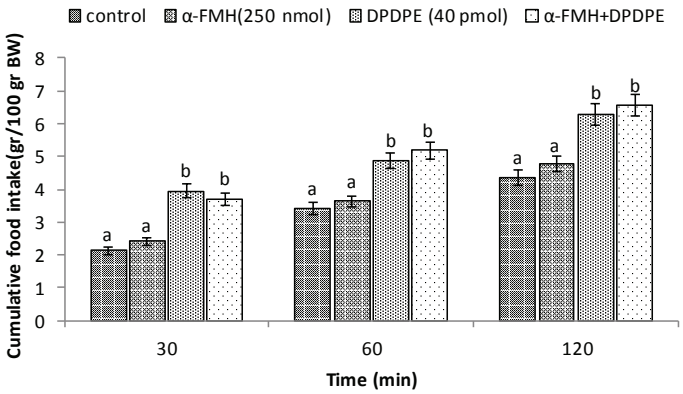

Figure 5 – Effects of intracerebroventricular injection of control solution, α-FMH (alpha fluoromethyl histidine; 250 nmol), DPDPE (δ-opioid receptor agonist; 40 pmol) and combination of α-FMH plus DPDPE on cumulative food intake (gr/100gr BW) in neonatal chicks. Data are expressed as mean ± SEM. Different letters (a and b) indicate significant differences between treatments at each time (p<0.05).

In experiment 6, no effect was observed after the ICV injection of the chlorpheniramine (300 nmol) in chicks. ICV injection of the DPDPE (40 pmol) significantly increased food intake in FD_3 neonatal birds compared to the control group (p<0.05). Co-injection of the Chlorpheniramine + DPDPE was not able to change hyperphagic effect of the DPDPE in neonatal birds [treatment effect: F (3, 80) = 31.83, p<0.0001; time effect: F (2, 80) = 518.96, p<0.0001; treatment and time interaction: F (6, 80) = 13.28; p<0.0001; Fig. 6].

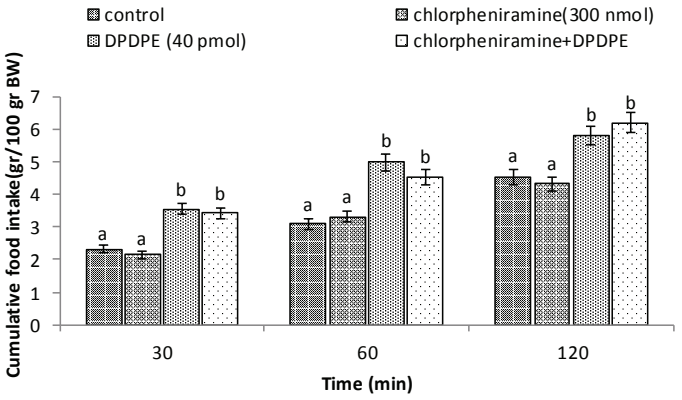

Figure 6 – Effects of intracerebroventricular injection of control solution, chlorpheniramine (histamine H1 receptors antagonist; 300 nmol), DPDPE (δ-opioid receptor agonist; 40 pmol) and combination of chlorpheniramine plus DPDPE on cumulative food intake (gr/100gr BW) in neonatal chicks. Data are expressed as mean ± SEM. Different letters (a and b) indicate significant differences between treatments at each time (p<0.05).

In experiment 7, hyperphagia was observed after the ICV injection of the DPDPE (40 pmol) in neonatal broilers compared to the control (p<0.05). Administration of the famotidine (82 nmol) had no effect on the food consumption in FD_3 neonatal birds (p>0.05). Co-injection of the DPDPE + famotidine had no effect on hyperphagic effect of the DPDPE in FD_3 neonatal birds [treatment effect: F (3, 80) = 83.19, p<0.0001; time effect: F (2, 80) = 472.21, p<0.0001; treatment and time interaction: F (6, 80) = 4.16; p<0.0001; Fig. 7].

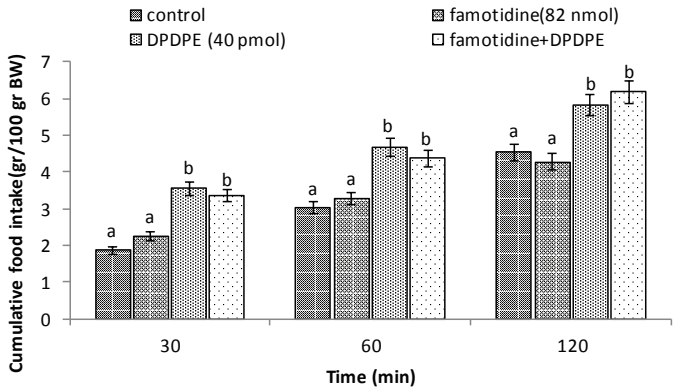

Figure 7 – Effects of intracerebroventricular injection of control solution, famotidine (histamine H2 receptors antagonist; 82 nmol), DPDPE (δ-opioid receptor agonist; 40 pmol) and combination of famotidine plus DPDPE on cumulative food intake (gr/100gr BW) in neonatal chicks. Data are expressed as mean ± SEM. Different letters (a and b) indicate significant differences between treatments at each time (p<0.05).

In experiment 8, no significant effect was observed on food intake after the ICV injection of the thioperamide (300 nmol) (p>0.05). ICV injection of the DPDPE (40 pmol) significantly increased food intake in FD_3 neonatal birds compared to the control group (p<0.05). While, the ICV injection of the DPDPE + famotidine was not able to affect hyperphagic effect of the DPDPE in FD_3 neonatal birds [treatment effect: F (3, 80) = 39.14, p<0.0001; time effect: F (2, 80) = 548.15, p<0.0001; treatment and time interaction: F (6, 80) = 5.17; p<0.001; Fig. 8].

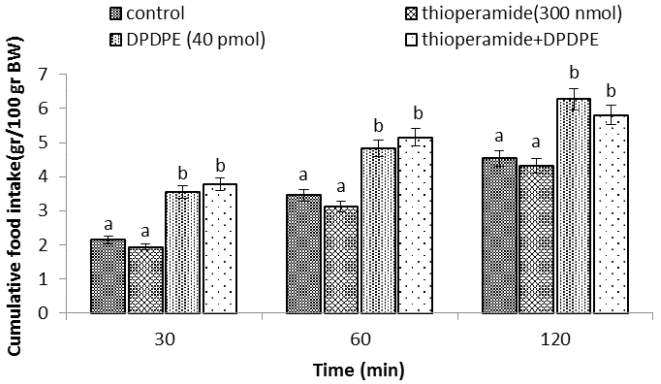

Figure 8 – Effects of intracerebroventricular injection of control solution, thioperamide (histamine H3 receptors antagonist; 300 nmol), DPDPE (δ-opioid receptor agonist; 40 pmol) and combination of thioperamide plus DPDPE on cumulative food intake (gr/100gr BW) in neonatal chicks. Data are expressed as mean ± SEM. Different letters (a and b) indicate significant differences between treatments at each time (p<0.05).

In experiment 9, ICV administration of the U-50488H (κ-opioid receptor agonist, 30 nmol) significantly increased food intake in FD_3 neonatal broilers compared to the control group (p<0.05). ICV injection of the α-FMH (250 nmol) had no effect on cumulative food intake compared to the control group (p>0.05). Also, Co-administration of the α-FMH and U-50488H had no effect on U-50488H-induced hyperphagia in neonatal broilers injection [treatment effect: F (3, 80) = 63.08, p<0.0001; time effect: F (2, 80) = 682.1, p<0.0001; treatment and time interaction: F (6, 80) = 4.53; p<0.0001; Fig. 9].

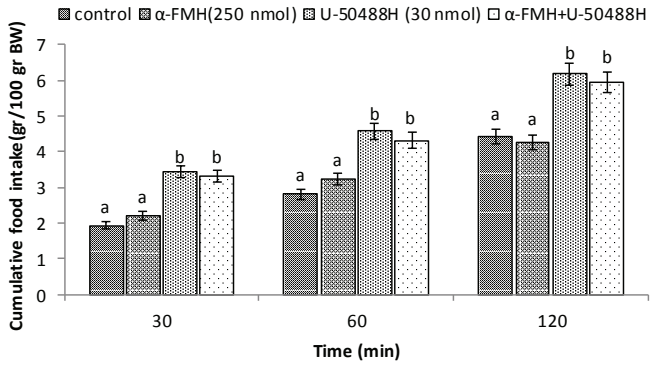

Figure 9 – Effects of intracerebroventricular injection of control solution, α-FMH (alpha fluoromethyl histidine; 250 nmol), U-50488H (κ-opioid receptor agonist; 30 nmol) and combination of α-FMH plus U-50488H on cumulative food intake (gr/100gr BW) in neonatal chicks. Data are expressed as mean ± SEM. Different letters (a and b) indicate significant differences between treatments at each time (p<0.05).

In experiment 10, the ICV injection of the chlorpheniramine (300 nmol) had no effect on cumulative food intake compared to the control group (p>0.05). ICV administration of the U-50488H (30 nmol) had hyperphagic effect compared to control group (p<0.05). Co-administration of the Chlorpheniramine + U-50488H had no effect on κ-opioid receptor agonist-induced hyperphagia in neonatal broilers [treatment effect: F (3, 80) = 117.39, p<0.0001; time effect: F (2, 80) = 450.8, p<0.0001; treatment and time interaction: F (6, 80) = 8.25; p<0.0001; Fig. 10].

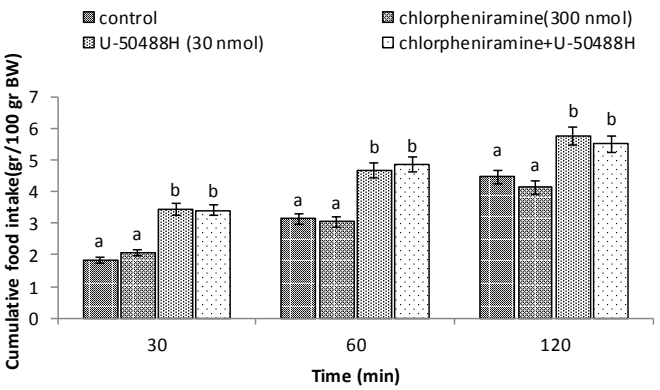

Figure 10 – Effects of intracerebroventricular injection of control solution, chlorpheniramine (histamine H1 receptors antagonist; 300 nmol), U-50488H (κ-opioid receptor agonist; 30 nmol) and combination of chlorpheniramine plus U-50488H on cumulative food intake (gr/100gr BW) in neonatal chicks. Data are expressed as mean ± SEM. Different letters (a and b) indicate significant differences between treatments at each time (p<0.05).

In experiment 11, ICV administration of the 82 nmol of the famotidine had no effect on feeding behavior compared to the control group (p>0.05). ICV administration of the 30 nmol of the U-50488H increased cumulative food intake compared to the control group (p<0.05). Co-administration of the famotidine + U-50488H had no effect on κ-opioid receptor agonist-induced hyperphagia in neonatal broilers [treatment effect: F (3, 80) = 82.06, p<0.0001; time effect: F (2, 80) = 246.37, p<0.0001; treatment and time interaction: F (6, 80) = 5.09; p<0.0001; Fig. 11].

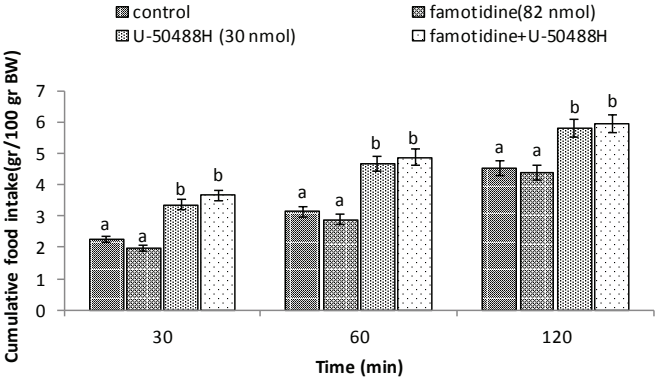

Figure 11 – Effects of intracerebroventricular injection of control solution, famotidine (histamine H2 receptors antagonist; 82 nmol), U-50488H (κ-opioid receptor agonist; 30 nmol) and combination of famotidine plus U-50488H on cumulative food intake (gr/100gr BW) in neonatal chicks. Data are expressed as mean ± SEM. Different letters (a and b) indicate significant differences between treatments at each time (p<0.05).

In experiment 12, the ICV injection of the 30 nmol U-50488H increased cumulative food intake compared to the control (p<0.05); while thioperamide (300 nmol) had no effect on feeding behavior compared to the control group (p>0.05). Injection of the Thioperamide + U-50488H had no effect on κ-opioid receptor agonist-induced hyperphagia in neonatal broilers [treatment effect: F (3, 80) = 58.94, p<0.0001; time effect: F (2, 80) = 639.25, p<0.0001; treatment and time interaction: F (6, 80) = 5.36; p<0.0001; Fig. 12].

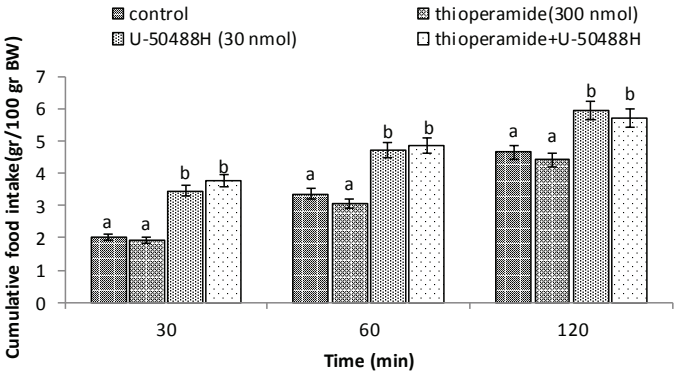

Figure 12 – Effects of intracerebroventricular injection of control solution, thioperamide (histamine H3 receptors antagonist; 300 nmol), U-50488H (κ-opioid receptor agonist; 30 nmol) and combination of thioperamide plus U-50488H on cumulative food intake (gr/100gr BW) in neonatal chicks. Data are expressed as mean ± SEM. Different letters (a and b) indicate significant differences between treatments at each time (p<0.05).

DISCUSSION

The present study was designed for the first time to investigate the possible interconnection of the opioidergic system with histamine on food intake in neonatal broiler chicks. To the best of our knowledge, this is the first report on the interaction of the central HAergic and opioidergic systems on appetite regulation in FD_3 neonatal broiler chicks. In this study we used sub effective doses of the HAergic antagonists and effective doses of the opioid receptors agonists to determine possible interconnection between HAergic and opioidergic systems on food intake in FD_3 broiler chicks. The results obtained imply that the ICV injection of DAMGO decreased food intake while DPDPE and U-50488H increased feeding behavior in FD_3 neonatal broilers. μ-opioid receptors act as orexigenic neurotransmitter on feeding behavior via nucleus accumbens (NAc) and nucleus tractus solitaries (NTS) in rodents (Zheng *et al.*, 2007). The central food intake regulation is also different among avian species. ICV injection of DAMGO inhibits food intake in neonatal broiler (Bungo *et al.*, 2004; 2005) while Khan *et al.*, (2009) reported μ-opioid receptors have an orexigenic role in broilers. Perhaps genetic selection for growth in broilers and layers for egg production altered their central appetite regulation mechanisms (Denbow, 1994).

H_1 receptors are known as hypophagic receptors in rats (Morimoto *et al.*, 2001) and broiler chickens (Taati *et al.*, 2010). Anorexic effects reported for H_2 receptors in broilers (Meade and Denbow, 2001) and thioperamide decreases cumulative food intake in broilers (Taati *et al.*, 2010). In poultry, histamine mediates its effect via H_1 receptors (Zendehdel *et al.*, 2015) but controversial reports exists for H_3 receptors. Taati *et al.*, (2009) reported that ICV injection of the thioperamide(300 and 600 nmol) decreased food intake in food-deprived broilers (Taati *et al.*, 2009). Scarce informtion exists about expression of the H_4 receptors in poultry brain (Zendehdel *et al.*, 2015). The ICV injection of thioperamide had no effect on feeding behavior in fasted or non-deprived rats in the lighting period (Passani *et al.*, 2011) while decreased appetite in the dark period when central histamine is at low levels. Perhaps, it affects when histaminergic system activity is low (Passani *et al.*, 2011). Blockade of the H_3 receptors decreases food intake in rats (Chiba *et al.*, 2009) and injection of the H_1 receptor antagonists attenuated effects of the H_3 antagonists in rats (Hancock & Brune, 2005).

As observed, α-FMH and chlorpheniramine inhibited hypophagic effect of the DAMGO in neonatal broilers. Additionally, co-administration of the histamine H_3 receptors antagonist (Thioperamide) with DAMGO significantly amplified hypophagic effect of the DAMGO in neonatal chicks. It is reported that Thioperamide induced anti-nociception mediates via the endogenous opioid system (Khalilzadeh *et al.*, 2010). ICV injection of thioperamide increased the nociceptive threshold at supraspinal level in a rat (Mobarakeh *et al.*, 2009). Also, Hough *et al.*, (1997) reported that the ICV injection of the thioperamide had no analgesic activities in nociception tests in rats while analgesic and hyperalgesic effects reported by ICV administration of the thioperamide and R-α-methylhistamine in rats (Malmberg-Aiello *et al.*, 1994). The H_3 receptors, exerted inhibitory effects on the morphine-induced anti-nociception at the spinal level (Mobarakeh *et al.*, 2009). The anti-nociceptive effect of the histamine was reversed by the ICV injection of the naloxone into periaqueductal gray (Khalilzadeh *et al.*, 2010). A close relationship reported between H_1 receptor and μ-opioid receptor in scratching behavior in mice, where co-injection of the histamine and morphine caused scratching and simultaneous

administration of morphine and histamine had an additive effect. Naloxone and chlorpheniramine reserved histamine-induced scratching behavior (Nakasone *et al.*, 2016). Anticonvulsant action observed by activation of the H_1 receptors whereas inhibition of H_1 receptors induced proconvulsant effects (Amini-Khoei *et al.*, 2015). Co-injection of morphine with H_1 and H_3 agonists/antagonists reversed their effects on PTZ-induced seizure (Amini-Khoei *et al.*, 2015). Pretreatment with H_1 antagonist decreased the amisulpride-induced seizures in mice (Rehni *et al.*, 2011). Co-injection of chlorpheniramine with morphine potentiates the anti-nociceptive activity of morphine in the acetic acid-induced visceral pain - in rats (Zanboori *et al.*, 2008).

Based on the literature, the histaminergic system mediates some of the central effects of morphine. However, there is no report on their interaction on feeding behavior. Histamine impresses its effect via agoutirelated protein (AgRP), neuropeptide Y (NPY), cocaine and amphetamine regulated transcript neurons (Zendehdel *et al.*, 2015). Also, the interconnection exists between opioidergic system, NPY and AgRP neurons in the ARC (Zendehdel *et al.*, 2015). However, the neural pathway between opioidergic system and NPY is not identified in poultry's hypothalamus (Dodo *et al.*, 2005). ICV injection of DAMGO increased μ-opioid receptor mRNA expression in ARC of rats (Zheng *et al.*, 2007). Perhaps the interaction of these systems on food intake regulation happens in these nuclei of the hypothalamous. However, neuroanatomic and pharmacological researches needed to determine their possible neural interconnection.

In conclusion, the new findings of the current study suggested ICV injection of the α-FMH + DAMGO or chlorpheniramine + DAMGO decreased DAMGO-induced hypophagia in neonatal chicks. It seems that the interaction exists among central opioidergic and HAergic systems on feeding behavior mediates via μ-opioid and H_1/H_3 receptors in neonatal broilers. There was no previous study on the role of central opioidergic and HAergic systems on food intake in poultry. Most research on central food intake regulation was done with rat models. So, authors were not able to compare their results with it. This information can be used as base data on central feeding behavior in poultry. It is suggested that further investigation needs to be done to determine direct cellular and molecular signaling pathways of the HAergic and opioidergic systems with other receptors in physiology of food intake regulation in domestic fowls.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

INFORMED CONSENT

This manuscript does not contain any studies with human subjects performed by any of the authors.

HUMAN AND ANIMAL RIGHTS

All experiments were executed according to the Guide for the Care and Use of Laboratory Animals and were approved by the institutional animal ethics committee.

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