Journal of Poultry Sciences and Avian Diseases

Journal homepage: www.jpsad.com

NPY1 and MC3/MC4 receptors mediate BDNF-induced hypophagia in 5-day-old chickens

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A r t i c l e I n f o

Article type:
Original Research

How to cite this article:
Zarei, H., Kiaee, G., & Zendehdel, M. (2025). NPY1 and MC3/MC4 receptors mediate BDNF-induced hypophagia in 5-day-old chickens. *Journal of Poultry Sciences and Avian Diseases*, *3*(1), 74-83.
http://dx.doi.org/10.61838/kman.jpsad.3.1.7

A B S T R A C T

Distinguishing the variables that control craving and examining the interaction between them can improve the efficiency of livestock breeding, genetic modification, and drug treatments of obesity-related complications. Hence, in the current study, we investigated the interaction between neuropeptide Y and melanocortinergic systems with brain-derived neurotrophic factor (BDNF) in regulating broilers' feed intake. The present study was conducted on 264 broiler chickens in 6 experiments. In experiment 1, chickens received intracerebroventricular (ICV) infusion of BDNF (7.5, 15, and 30 µg) after 3 h of food deprivation. BIBP-3226 (NPY1 receptor antagonist, 1.25 nmol), BDNF (30 µg), and BDNF + BIBP-3226 were administrated in the second treatment. Experiments 3-6 were similar to treatment 2, except birds were infused with BIIE 0246 (NPY2 receptor antagonist, 1.25 nmol), CGP71683A (NPY5 receptor antagonist, 1.25 nmol), SHU9119 (MC3/MC4 receptor antagonist, 0.5 nmol) and MCL0020 (MC4 receptor antagonist, 0.5 nmol) instead of BIBP-3226. Then, cumulative meal intake was recorded for 2 hours. Based on observations, BDNF injection (15 and 30 µg) caused significant hypophagia at all test times (p<0.05). The co-infusion of NPY2 and NPY5 receptor antagonists with BDNF had no effect on BDNF-induced hypophagia (p>0.05), while the infusion of NPY1 receptor antagonist + BDNF caused a significant strengthening of this effect (p<0.05). Also, despite the lack of significant effect of MC4 receptor antagonist + BDNF administration on the appetite-reducing effect of BDNF (p>0.05), simultaneous infusion of MC3/MC4 receptor antagonist and BDNF suppressed hypophagia (p<0.05). Finally, it appears that MC3/MC4 and NPY1 receptors mediate BDNF-induced hypophagia in 5-day-old broiler chickens.

Keywords: *Appetite, Brain-derived neurotrophic factor, Melanocortin, Neuropeptide Y, Chickens*

Article history:
Received 17 July 2024
Revised 27 September 2024
Accepted 04 October 2024
Published online 01 January 2025

1 Introduction

Undoubtedly, meeting the biological needs of humans and animals to ensure survival and proper growth requires the efficient functioning of the food intake processes. The regulation of food consumption depends on several factors, including the ambiance, energy reserves, different hormones secretion, and their feedback in the neural circuits of the brain (1, 2). Most importantly, imbalances in energy expenditure and feed intake lead to physical complications related to metabolism and weight, including type II diabetes and obesity. A detailed understanding of the processes involved in feeding regulation through the integration of central nervous system (CNS) circuits and peripheral signals may lead to the identification of new therapeutic approaches for these disorders (3). Until today, extensive research works have been conducted to identify the pathways and regulatory variables of food intake in mammals and more limited in birds, the result of which was the introduction of several neural mediators and appetite-regulating hormones and the interactions between them (4). However, the extent and complexity of the mechanisms involved in the feed intake process remind us of the need to conduct more research in this field.

Brain-derived neurotrophic factor (BDNF) is one of the neurogenic factors that show a protective effect under adverse conditions such as neurotoxicity, hypoglycemia, and cerebral ischemia (5). Also, this factor plays an important role in neural flexibility, which is indispensable for memory and learning. BDNF also stimulates the growth of new neurons from stem cells (6). The receptor of this factor is called TrkB (tyrosine kinase B) and by binding to BDNF, it activates signaling cascades (IRS1/2, PI3K, Akt) (7). Anatomical studies have proven the presence of this factor in the central nervous system (CNS), intestine, and some other tissues, and specifically its mRNA in areas such as the cerebral cortex, hippocampus, olfactory bulb, mesencephalon, brain stem, hypothalamus, and spinal cord (8). Since this factor supports the survival, differentiation and maturation of neurons, the synthesis and secretion of BDNF is reduced in many neurological diseases (9). In addition, BDNF plays a key role in energy homeostasis, and its peripheral or central administration reduces body weight and suppresses energy expenditure (10).

Melanocortins, including melanocyte-stimulating hormones (α-, β-, and γ-) and adrenocorticotropin hormone (ACTH), are peptide hormones derived from proepimelanocortin (POMC). Melanocortins are often released from the arcuate nucleus neurons (ARC) (11). These peptides can act on five different melanocortin receptor subtypes (MC1 to MC5) that are distributed throughout the body (11). The expression of MC3 and MC4 receptors has been proven in the mammalian brain (12). MC3 appears to regulate energy expenditure, while MC4 is involved in feeding regulation. The presence of subtype 3 and 4 receptors in the brain of birds has also been confirmed (13), and based on research, appetite-reducing effects caused by the function of these receptors have also been observed in chickens (14). It seems that MC3 receptor agonists reduce food intake in mice and intracerebroventricular (ICV) infusion of α-MSH reduces meal consumption in fasted meat-type chickens (15).

Neuropeptide Y (NPY) with a sequence of 36 amino acids, is one of the most abundant peptides expressed in the CNS and is considered one of the strongest stimulants of meal consumption in both birds and mammals (16). NPY receptors are classified into six groups: Y1, Y2, Y4, Y5, Y6, and Y7 (17). Based on research results, it has been determined that two receptors, NPY1 and NPY5, are responsible for stimulating food consumption, and the NPY2 receptor also affects meal intake in animals after food deprivation (18). In addition, based on the findings of an experiment, the GABAA receptor antagonist seems to be able to reduce the response to NPY (19). Little is known about the hypothalamic mechanisms underlying the appetite-related actions of NPY in birds. Based on the documentation of NPY gene expression in the hypothalamus of birds, similar to mammals, it increases in fasting and food restriction conditions (20). In Japanese quail, ICV injection of NPY was appetitive, but this effect occurred only during the light phase (21).

In this study, while knowing the effects of central infusion of BDNF on the appetite of broiler chickens, we will investigate the interaction between this peptide and the two main systems involved in the feed ingestion process (the melanocortinergic and NPY systems). The findings of this research can be useful in the field of livestock breeding, genetic modification, and the development of new drugs for diseases related to overweight.

2 Materials and Methods

2.1 Animals

To conduct the present experiments, a total of 264 meat-type chickens (Ross-308) were purchased from Mahan Company (Tehran, Iran). Then birds were divided into 24 experimental groups to perform 6 separate experiments (each experiment includes 4 experimental groups). During the

study, the birds were kept in standard environmental conditions (temperature (32 °C ± 1), lighting (23:1 lighting/dark period), and humidity (45–55%)) and had free access to water and food containing 2850 kcal/kg of energy and 21% crude protein (Co. for Animal Science Research). At the beginning, they were placed in individual cages for two days and then in group cages for three days. All procedures were approved by the Islamic Azad University Institutional Animal Care and Use Committee and performed based on US guidelines (Publication No. 23-85, revised 1996).

2.2 *Drugs & Experimental Groups*

The drugs required for the experiments were obtained from Sigma Aldrich, USA which include: BDNF, BIBP-3226 (NPY1 receptor antagonist), BIIE 0246 (NPY2 receptor antagonist), CGP71683A (NPY5 receptor antagonist), SHU9119 (MC3/MC4 receptor antagonist), MCL0020 (MC4 receptor antagonist), and Evans Blue. The drugs were diluted using 0.85 % saline which contained Evans blue at a ratio of 1/250. The saline mixture containing Evans blue was utilized for the control group. The classification of experimental groups and drugs injected into each group are presented in Table 1.

Table 1. Drugs injected into experimental groups

Groups	Exp.1	Exp.2	Exp.3	Exp.4	Exp.5	Exp.5
A	Control solution	Control solution	Control solution	Control solution	Control solution	Control solution
B	BDNF (7.5 µg)	BIBP-3226 (NPY1 receptor antagonist, 1.25 nmol)	BIIE 0246 (NPY2 receptor antagonist, 1.25 nmol)	CGP71683A (NPY5 receptor antagonist, 1.25 nmol)	SHU9119 (MC3/MC4 receptor antagonist, 0.5 nmol)	MCL0020 (MC4 receptor antagonist, 0.5 nmol)
C	BDNF (15 µg)	BDNF (30 µg)	BDNF (30 µg)	BDNF (30 µg)	BDNF (30 µg)	BDNF (30 µg)
D	BDNF (30 µg)	BIBP-3226 + BDNF (1.25 nmol) + (30 µg)	BIIE 0246 + BDNF (1.25 nmol) + (30 µg)	CGP71683A + BDNF (1.25 nmol) + (30 µg)	SHU9119 + BDNF (0.5 nmol)+ (30 µg)	MCL0020+ BDNF (0.5 nmol)+ (30 µg)

2.3 *Injection Procedure*

To conduct the present study, Ross-308 (meat) chickens were prepared as an animal model, and 11 chickens were placed in each experimental group. On the day of injection, food deprivation was applied for three hours. Then, to perform the injection, the chicken's head was immobilized through an acrylic tool so that the surface of the chicken's skull was placed parallel to the table's surface. A perforated mold was placed on the head of chickens in the desired area for injection. Then the injection was done using a Hamilton syringe and through the same port (22). It has been proven that this injection method does not cause physiological stress in birds (23). Broilers were returned to their boxes after injection and had free access to food and water. Then the amount of meal consumption was recorded at 30, 60, and 120 minutes after infusion. It should be noted that to minimize the effect of weight on the amount of feed consumed, the measured values were calculated as a percentage of body weight. At the end, the chickens were killed by neck twisting and the injection area was checked by Evans Blue control. The infusion volume in all test groups was 10 µl, and the dose of drugs was determined based on previous studies (24, 25).

2.4 *Statistical Analysis*

The data of this research was analyzed using SPSS software. The significant differences between study groups were also investigated by two-way analysis of variance (ANOVA) and Tukey's post hoc test. Finally, graphs were drawn using Sigma Plot software. $p \leq 0.05$ was considered as a significant level of difference.

3 Results

As shown in Figure 1, central injection of 7.5 µg of BDNF did not remarkably alter the meal ingestion of chicks ($p > 0.05$),

while a significant hypophagia compared to the control group was observed following administration of doses of 15 and 30 µg. BDNF (p<0.05).

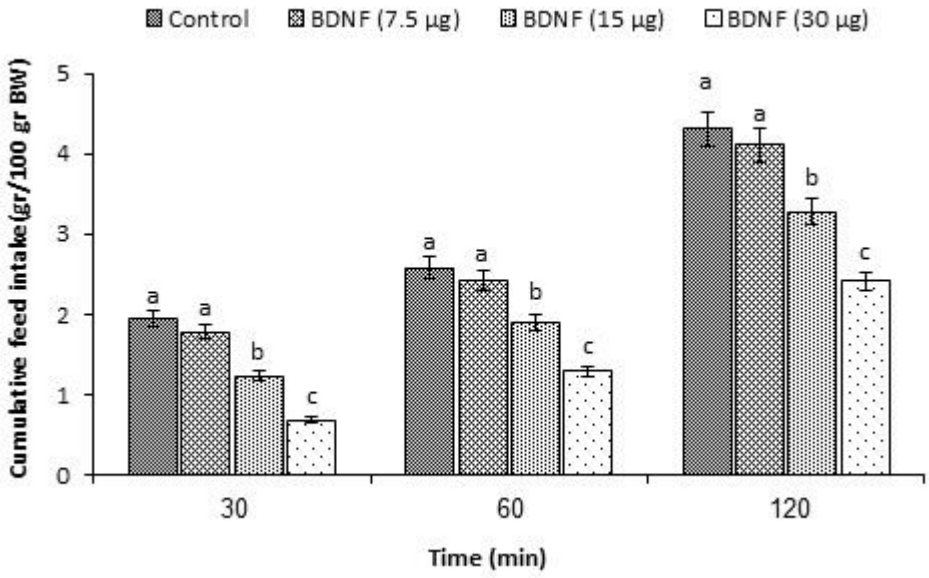

Figure 1. Effect of ICV injection of BDNF (7.5, 15 and 30 µg) on cumulative food intake in neonatal chicken (n=44). Data are expressed as Mean ± SEM. Different letters (a, b, and c) indicate significant differences between treatments (p < 0.05).

In the second test, although the infusion of a sub-effective dose of BIBP-3226 did not affect the amount of meal ingestion (p≥0.05), administration of BIBP-3226 + BDNF significantly strengthened the BDNF-induced hypophagia (p<0.05) (Figure 2).

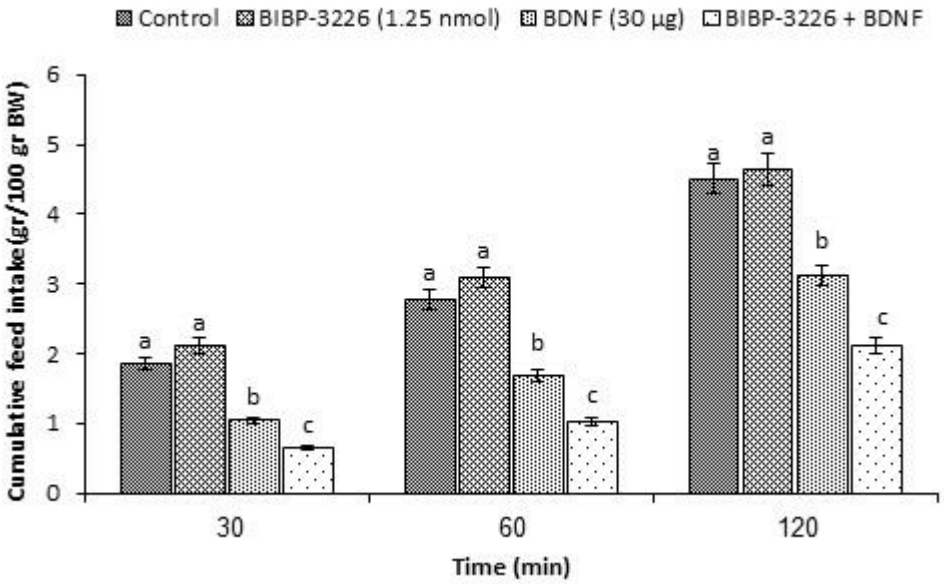

Figure 2. Effect of ICV injection of BIBP-3226 (1.25 nmol), BDNF (30 µg), and their combination on cumulative food intake in neonatal chicken (n=44). BIBP-3226: NPY1 receptor antagonist. Data are expressed as Mean ± SEM. Heterogenous letters (a, b and c) indicate significant differences between treatments (p < 0.05).

According to Figure 3 and Figure 4, central infusion of of sub-effective dose of BIIE 0246 and CGP71683A in combination with BDNF did not remarkably change the decreased appetite caused by BDNF (p>0.05).

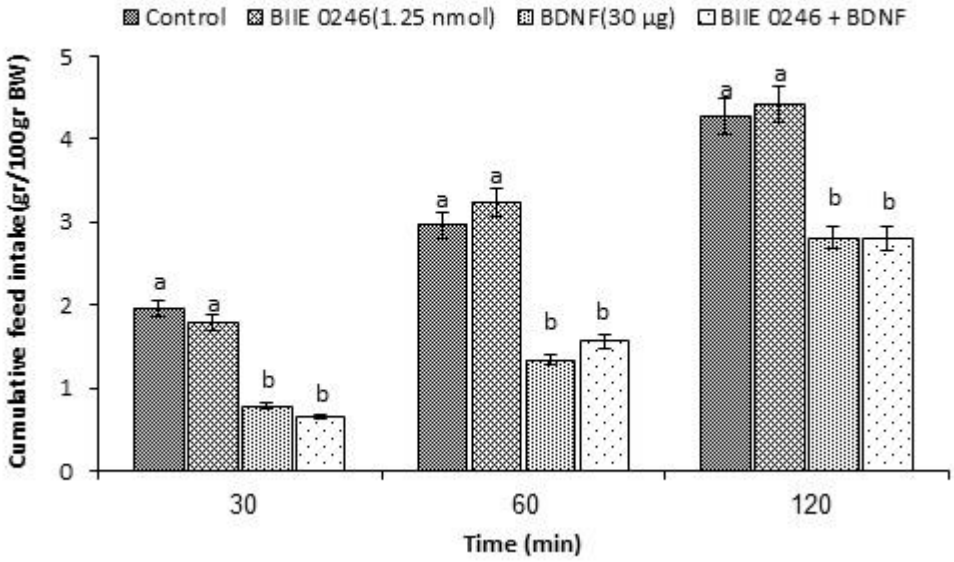

Figure 3. Effect of ICV injection of BIIE 0246 (1.25 nmol), BDNF (30 µg), and their combination on cumulative food intake in neonatal chicken (n=44). BIIE 0246: NPY2 receptor antagonist. Data are expressed as Mean ± SEM. Heterogenous letters (a, and b) indicate significant differences between treatments (p < 0.05).

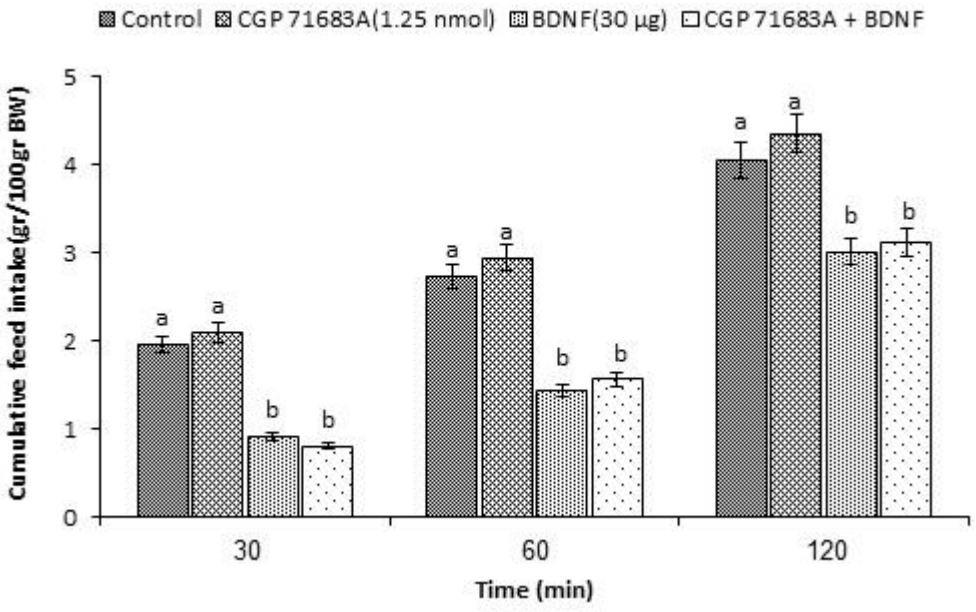

Figure 4. Effect of ICV injection of CGP71683A (1.25 nmol), BDNF (30 µg), and their combination on cumulative food intake in neonatal chicken (n=44). CGP71683A: NPY5 receptor antagonist. Data are expressed as Mean ± SEM. Heterogenous letters (a, and b) indicate significant differences between treatments (p < 0.05).

In the fifth test, the infusion of SHU9119 did not change the feed ingestion of broilers compared to the control treatment (p>0.05), but the simultaneous administration of SHU9119 + BDNF suppressed BDNF-induced hypophagia (p<0.05) (Figure 5).

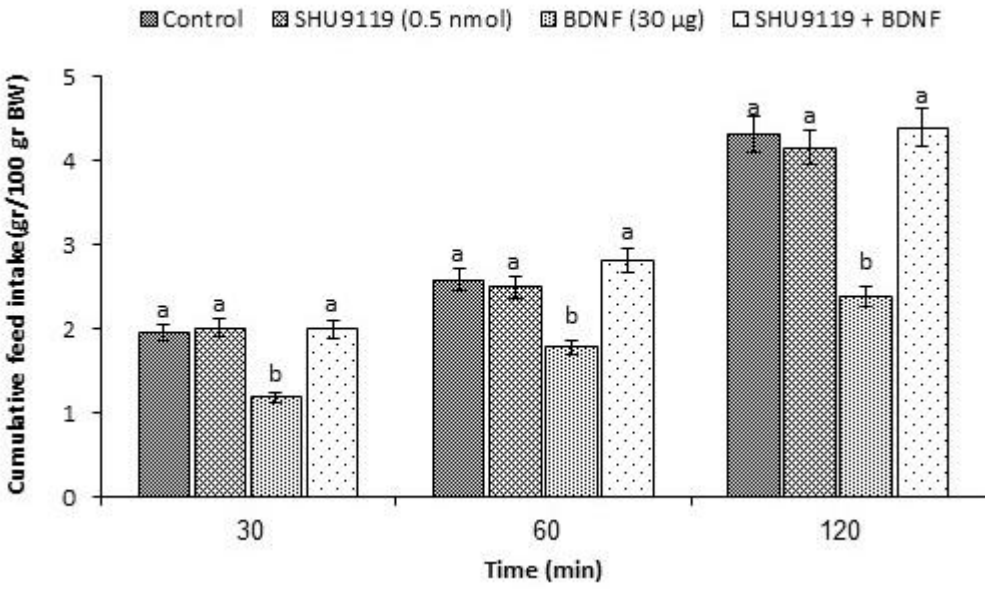

Figure 5. Effect of ICV injection of SHU9119 (0.5 nmol), BDNF (30 µg), and their combination on cumulative food intake in neonatal chicken (n=44). SHU9119: MC3/MC4 receptor antagonist. Data are expressed as Mean ± SEM. Heterogenous letters (a, and b) indicate significant differences between treatments (p < 0.05).

In the last test, the administration of MCL0020 alone could not significantly change the food intake of five-day-old chickens (p>0.05), and its combined administration with BDNF did not have a remarkable effect on induced hypophagia (p>0.05) (Figure 6).

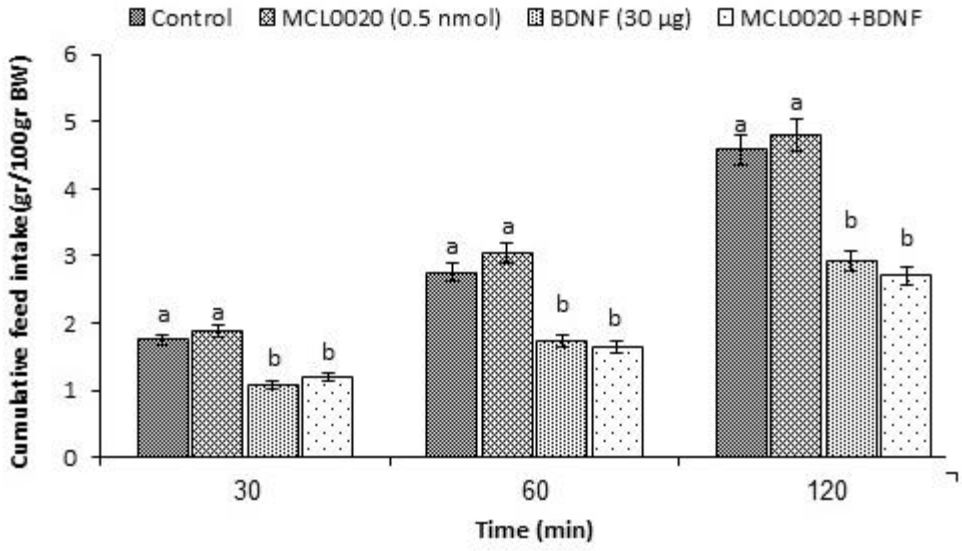

Figure 6. Effect of ICV injection of MCL0020 (0.5 nmol), BDNF (30 µg), and their combination on cumulative food intake in neonatal chicken (n=44). MCL0020: MC4 receptor antagonist. Data are expressed as Mean ± SEM. Heterogenous letters (a, and b) indicate significant differences between treatments (p < 0.05).

4 Discussion and Conclusion

Since the beginning of the 1950s, there have been extensive studies on the function of the CNS in energy homeostasis. Depending on the location, lesions created in different regions of the brain stimulate or inhibit feed ingestion and subsequently change body weight (26). The hypothalamic nuclei and specifically the arcuate nucleus play a considerable role in processing peripheral and central messages related to food intake (27). To date, several experiments have been conducted in this field, focusing more on mammalian models. Also, more than 40 neural mediators participating in birds' appetite regulation have been identified. Nevertheless, a comprehensive and accurate understanding of the mechanisms involved in avian feeding regulation requires more studies in this area (28).

In this study, to observe and confirm the hypophagic role of BDNF in chickens, different doses of it were injected into 5-day-old broiler chickens based on studies conducted on mammals. According to the obtained results, central injection of BDNF (15 and 30 µg) significantly reduced feed consumption in chickens. Undoubtedly, one of the most important members of the neutrophin family is BDNF, which is very similar to the nerve growth factor in terms of its amino acid sequence (29). Numerous studies have indicated the appetite-decreasing and blood sugar-lowering effects of BDNF, which indicates the therapeutic role of this mediator in complications such as diabetes and overweight (30). On the other hand, researchers found that receiving BDNF stimulates energy consumption so it prevents the decrease in body temperature caused by cold or not receiving a meal (31, 32). Based on the experiments, BDNF has a positive correlation with all types of lipids (33). Administering this factor in diabetic animals causes a decrease in blood glucose levels, types of fats, and liver weight along with an increase in beta-oxidation (34). Stimulation of TrkB (the main BDNF receptor) is necessary to regulate energy homeostasis and feed ingestion. Since the receptors of this factor are expressed in the brain areas that influence the amount of food received and body weight, the effect of BDNF on appetite is likely done through hypothalamic pathways (35). According to the findings of a study, peripheral and central injection of BDNF caused the weakening of food intake in different strains of mice. Also, its chronic intake reduced food intake in overweight rats (25). Based on these documents, the findings of the current study are in line with the previous research and indicate the hypophagic effect of BDNF on the appetite of broiler chickens.

The melanocortinergic system is also one of the most important systems involved in regulating the amount of meal consumption and body weight (11). Based on the studies done so far, five groups of melanocortin receptors have been identified in birds and mammals (13). Researchers showed that type three and four receptors of this system play a momentous role in appetite regulation and the presence of these receptors in different hypothalamic nuclei has been proven (11). It should be noted that administration of melanocortin type 3 receptor agonists suppresses meal consumption. It has been observed that the central infusion of α-MSH reduces feed consumption in food-deprived chickens (15). Subsequent studies have indicated the suppressive role of β-MSH on food and water intake in birds (36). Also, γ-MSH showed a weaker reducing effect than the previous two agonists on the amount of food intake (37). On the other hand, NPY with a sequence of 36 amino acids has been one of the most important appetite-stimulating factors (38). Numerous and diverse experiments on animal models have shown the presence of this neuropeptide and its receptors in the hypothalamus as the most important appetite-regulating center (39). However subsequent research has shown the spread of its neuronal branches in other brain areas as well (40). The appetite-enhancing role of NPY is often exerted by its type 1 and 5 receptors (41). In a study on birds, it was found that the condition of food deprivation increases the mRNA expression of this neuropeptide one and a half times (42). Also, increased activity of hypothalamic nuclei has been observed after central administration of NPY. In addition, the findings of a research showed that the combined administration of NPY and α-MSH weakens food intake (43).Despite proving the effect of the melanocortinergic and NPY systems on the food consumption of birds, considering that in this study, the sub-effective doses of antagonists were used, their administration alone did not have a meaningful effect on the birds' appetite.

Based on the studies conducted, the distribution of BDNF and its receptors in the hypothalamic nuclei has been proven, which can indicate the possibility of its effect interfering with other systems present in these areas, including the melanocortin system and NPY (44). Among the hypothalamic nuclei, the highest level of BDNF has been observed in the ventromedial hypothalamus (VMH) (45). Previous research works have proven that the central administration of BDNF can partially suppress overweight caused by defective melanocortin type 4 receptor signaling in rats. It has also been

found that in wild mice with food deprivation, the expression of BDNF in the hypothalamic nuclei is weakened, and the injection of melanocortin receptor agonists inhibits this effect (46). It has been proven that NPY can balance the hypophagic signaling of other neuropeptides, especially BDNF (41). The results of the study by Wang et al (2007) proved that the activity of NPY inhibits the hypophagic signals formed in the ventral nucleus of the hypothalamus, which also indicates the interaction between NPY-BDNF (47). The findings of a mammalian study demonstrated that central administration of BDNF significantly suppresses NPY-induced hyperphagia (48). Researchers also showed that systemic administration of NPY reduces BDNF production in the mammalian brain (49). In our study, although co-administration of BDNF + NPY2, NPY5, or MC4 receptor antagonists did not cause remarkable changes in induced hypophagia, but administration of NPY1 and MC3/MC4 antagonists + BDNF enhanced and weakened this effect, respectively, which is consistent with previous research. Therefore, it seems that the hypophagic effect caused by BDNF in broilers is mediated by NPY1 and MC3/MC4 receptors.

Acknowledgements

The authors would like to extend their gratitude to the central laboratory (Dr. Rastegar Lab.) of the Faculty of Veterinary Medicine, the University of Tehran for their cooperation.

Conflict of Interest

The authors declared no conflicts of interest.

Author Contributions

Authors equally contributed to this study.

Data Availability Statement

Data are available from the corresponding author upon reasonable request.

Ethical Considerations

None.

Funding

This work was supported by the research grant of Islamic Azad University, Garmsar Branch.

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