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The effect of brain-derived neurotrophic factor (BDNF) on food consumption of broilers: Role of serotonergic receptor

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A B S T R A C T

Previously, the effects of brain-derived neurotrophic factor (BDNF) on feed intake of mammals were studied. However, its role in avian feeding regulation remains unclear. The aim of this study was to investigate the possible effects of BDNF on the food consumption of broilers and its interaction with the serotonergic system. For this purpose, five experiments were conducted on 220 broiler chickens. In the first treatment, broilers received intracerebroventricular (ICV) infusion of BDNF (7.5, 15, and 30 µg). BDNF (30 µg), Fluoxetine (10 µg), a serotonin reuptake inhibitor, and BDNF + Fluoxetine were injected in the second treatment. In subsequent treatments, instead of Fluoxetine, PCPA (serotonin synthesis inhibitor, 1.25 µg), SB242084 (antagonist of 5-HT2C receptor, 1.5 µg), and 8-OH-DPAT (agonist of 5-HT1A receptor, 15.25 nmol) were applied. Then, cumulative food intake was recorded for 2 hours. Based on the results, BDNF injection (15 and 30 µg) caused a significant decrease in the food intake of broilers compared to the control group ($p<0.05$). Simultaneous administration of PCPA and SB242084 with BDNF suppressed BDNF-induced hypophagia ($p<0.05$), while the injection of Fluoxetine + BDNF strengthened this hypophagic effect ($p<0.05$). The decrease in feed intake caused by BDNF was not significantly changed by simultaneous injection of BDNF + 8-OH-DPAT ($p>0.05$). According to the findings, BDNF reduces broilers' food consumption, and this effect is probably mediated via 5-HT2C receptors.

Keywords: *BDNF; Serotonergic receptors; Food consumption; Broilers*

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1 Introduction

Food consumption regulation includes physiological mechanisms with different regulatory levels involving various sites of the central nervous system (CNS) and regions outside this system. Many factors such as hormones, neurotransmitters, and peptides, play a role in meal intake regulation. For this reason, dozens of hypotheses have been proposed to understand the mechanisms involved in appetite control (1). Despite the many research studies that have been carried out in this field in the last few decades, there are still many unknowns about how voluntary food intake is regulated. Most studies about the central mechanisms involved in appetite control have been conducted on mammals. Considering the genetic differences between mammals and birds, it seems necessary to carry out specific studies on the appetite regulation mechanisms of birds (2). According to the findings, avian food intake is also controlled by different neural and hormonal mediators (3); therefore, identifying these factors and carefully examining their effect on the feeding process will be a pivotal step in understanding food consumption.

Brain-derived neurotrophic factor (BDNF) is a neurogenic factor that supports the maturation, survival, and differentiation of neurons and demonstrates a neuroprotective effect in adverse conditions such as hypoglycemia, neurotoxicity, and cerebral ischemia (4, 5). Also, this factor plays a key role in neural flexibility, which is important for memory and learning. BDNF also regulates the growth of new neurons from stem cells. This factor binds to the TrkB (tyrosine kinase B) receptor with high affinity and activates signaling cascades (IRS1/2, PI3K, Akt) (6). Past studies have shown the distribution of BDNF in the CNS and its mRNA in regions such as the spinal cord, hippocampus, cortex, hypothalamus, hippocampus mesencephalon, and brainstem (7). BDNF levels decrease in many neurological disorders such as multiple sclerosis, Alzheimer's, Huntington's, and Parkinson's (8). In addition to its neuroprotective effect, BDNF plays an important role in regulating energy expenditure. Based on research, peripheral or intracerebroventricular (ICV) administration of BDNF in mammals suppresses energy consumption and decreases body weight (BW) (9).

Serotonin (5HT) is a neurotransmitter that affects several biological functions such as sleep and wakefulness, circadian rhythm, anxiety, aggression, depression, pain sensation, movement control, and the immune system (10, 11). Serotonergic neurons are scattered in clusters in the raphe nucleus, reticular formation, and periaqueductal gray. Seven main groups of serotonin receptors ($5HT_1$-$5HT_7$) have been identified in the CNS, which are among the receptors belonging to the G protein family (12). Recent studies show that strengthening or disrupting the function of serotonergic neurons effectively improves rodent food intake (13). Stimulation of serotonergic receptors can cause hypophagia or hyperphagia, depending on the receptor type. Among various serotonergic receptors, the effects of 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors in appetite regulation in mammals have been proven (14-16). Regarding the bird animal model, it has been observed that the central administration of serotonin causes a decrease in meal consumption. Also, the mediating role of serotonergic receptors in the feeding regulation caused by a number of neurotransmitters has been investigated. (11).

According to the authors' search, no previous study has been conducted on the role of BDNF in avian appetite regulation. Therefore, the present research investigates the possible effects of BDNF on broilers' food consumption and its interaction with the serotonergic system. Finally, we hope that the findings of this research will be an effective step toward a comprehensive understanding of the appetite regulation process as one of the most important physiological functions.

2 Materials and Methods

2.1 Animals: broiler chickens

In order to conduct the present study, five experiments, each including four treatment groups, were determined. According to the division of chicks into groups of 11, 220 male broilers were procured from Mahan Company (Tehran, Iran). After arrival, the broiler chickens were kept in common cages for two days and then in individual cages until five days old. Their keeping environment was in standard conditions in terms of temperature (32± 1°C), humidity (45–55%), and lighting (23:1 lighting/dark period) in all stages of the tests (17). Finally, on the day of injection (broilers were five days old), they were feed-deprived for three hours, and then the drugs were injected intracerebroventricularly. All procedures were performed based on US guidelines (Publication No. 23-85, revised 1996) and approved by the Islamic Azad University Institutional Animal Care and Use Committee.

2.2 Drugs

The main drug used in this study was BDNF, and to check the interaction of its effect with the serotonergic system, Fluoxetine (serotonin reuptake inhibitor), SB242084 (antagonist of 5-HT_{2C} receptor), p-chlorophenylalanine (PCPA) (Serotonin synthesis inhibitor), and 8-OH-DPAT (agonist of 5-HT_{1A} receptor) were used. Evans Blue was also purchased as an indicator along with other drugs from Sigma Aldrich, USA. All compounds were dissolved in a dimethyl sulfoxide (DMSO) solution, which was diluted with 0.85% saline plus Evans blue at a ratio of 1:250. Past experiments have proven that DMSO does not have cytotoxic impacts at the level used in the current study (18).

2.3 Injection Protocol & Feed Intake Measurement

In the present research, broilers were divided into different treatment groups based on BW to equalize the average weight of each group. The first experiment was conducted to determine the effective dose of BDNF, and then the effect of its interaction with the serotonergic system was evaluated in subsequent experiments. The prescribed doses were based on previous research (11, 19). The order of drug administration was as follows:

The first experiment: (A) Control solution, (B) BDNF (7.5 µg), (C) BDNF (15 µg), and (D) BDNF (30 µg)

The second experiment: (A) Control solution, (B) Fluoxetine (10 µg), (C) BDNF (30 µg), and (D) Fluoxetine (10 µg) + BDNF (30 µg)

The third experiment: (A) Control solution, (B) PCPA (1.25 µg), (C) BDNF (30 µg), and (D) PCPA (1.25 µg) + BDNF (30 µg)

The fourth experiment: (A) Control solution, (B) SB242084 (1.5 µg), (C) BDNF (30 µg), and (D) SB242084 (1.5 µg) + BDNF (30 µg)

The fifth experiment: (A) Control solution, (B) 8-OH-DPAT (15.25 nmol), (C) BDNF (30 µg), and (D) 8-OH-DPAT (15.25 nmol) + BDNF (30 µg)

Without anesthesia and surgery, drugs were injected using a micro syringe (Hamilton, Switzerland). During the injection, the head of the bird was placed parallel to the working surface using an acrylic device, and a cavity was created in the right lateral ventricle of the brain. In this injection method, the tip of the needle was inserted 4 mm into the skull, and all the mentioned drugs were injected in a volume of 10 microliters. It is important to mention that based on past experiments, this drug infusion method does not cause any physiological stress in chickens (20). After administration, chickens were returned to separate boxes with free feed and drinking water access. Total feed consumption was recorded 30, 60, and 120 minutes after infusion, respectively. In order to minimize the effect of chicken weight on meal consumption, cumulative feed intake was calculated as a %BW. At the end of the experiment, the broilers were ethically euthanized. After separating each chicken's brains, the injection's correctness was confirmed by observing the dye in the desired region.

2.4 Statistical Analysis

The findings of this study were presented as mean ± SEM. The repeated measure two-way analysis of variance (ANOVA) method was used to measure the amount of cumulative meal consumption, and the Tukey-Kramer test was used to compare the means. Also, $p \leq 0.05$ was statistically considered significant.

3 Results

In the first treatment, the central infusion of BDNF (7.5 µg) had no significant effect on feed consumption ($p>0.05$), while the administration of 15 and 30 µg of BDNF significantly attenuated feeding ($p<0.05$) (Figure 1).

In treatment 2, Fluoxetine administration alone did not affect meal consumption ($p> 0.05$). Whereas the infusion of Fluoxetine + BDNF significantly enhanced the BDNF-induced decrease in feed intake ($p<0.05$) (Figure 2).

Regarding treatment 3, an injection of 1.25 µg PCPA made no significant change in meal intake ($p>0.05$). However, BDNF-induced hypophagia was attenuated by co-administration of BDNF and PCPA ($p<0.05$) (Figure 3).

In the fourth treatment, central administration of SB242084 (1.5 µg) didn't change total meal consumption significantly ($p>0.05$). However, the reducing effect of BDNF on meal consumption was decreased by the administration of BDNF + SB242084 ($p<0.05$) (Figure 4).

In treatment 5, the administration of 8-OH-DPAT (15.25 nmol) had no significant effect on the feeding behavior of chickens ($p>0.05$). Also, infusion of 8-OH-DPAT + BDNF did not cause significant changes in BDNF-induced hypophagia ($p>0.05$) (Figure 5).

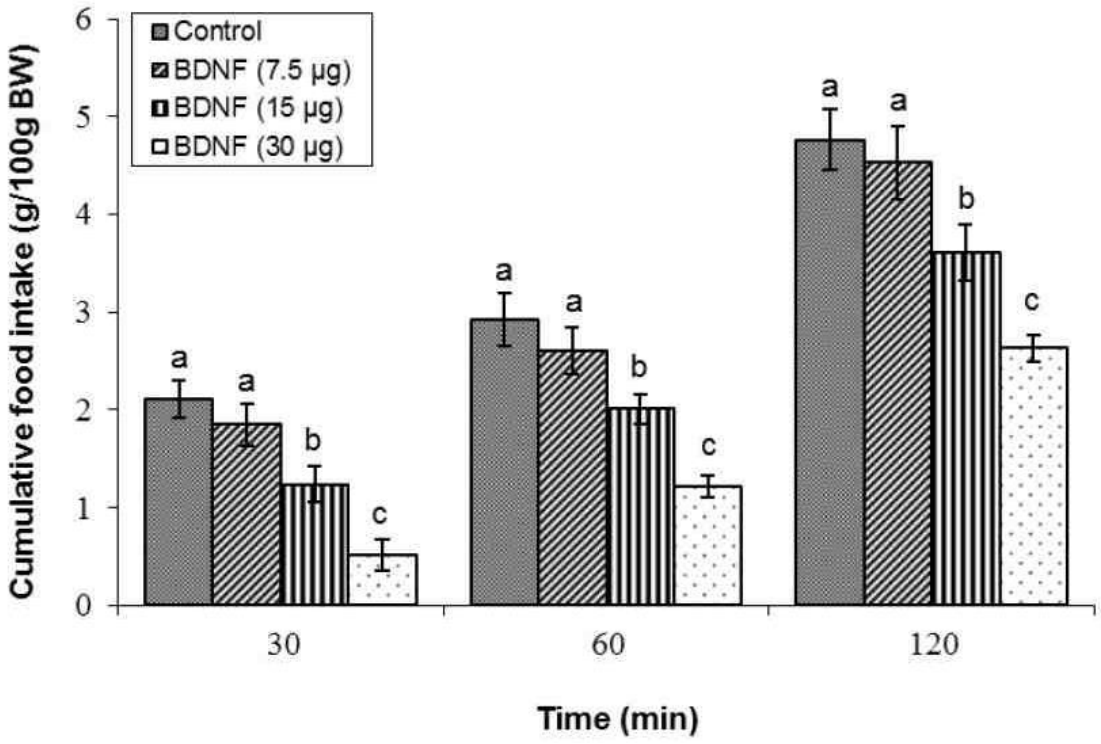

Figure 1. Effect of ICV injection of BDNF (7.5, 15 and 30 µg) on cumulative food intake in neonatal chicken (n=44). Data are expressed as mean±SEM. Heterogenous letters (a, b and c) indicate significant differences between treatments (***p***<0.05).

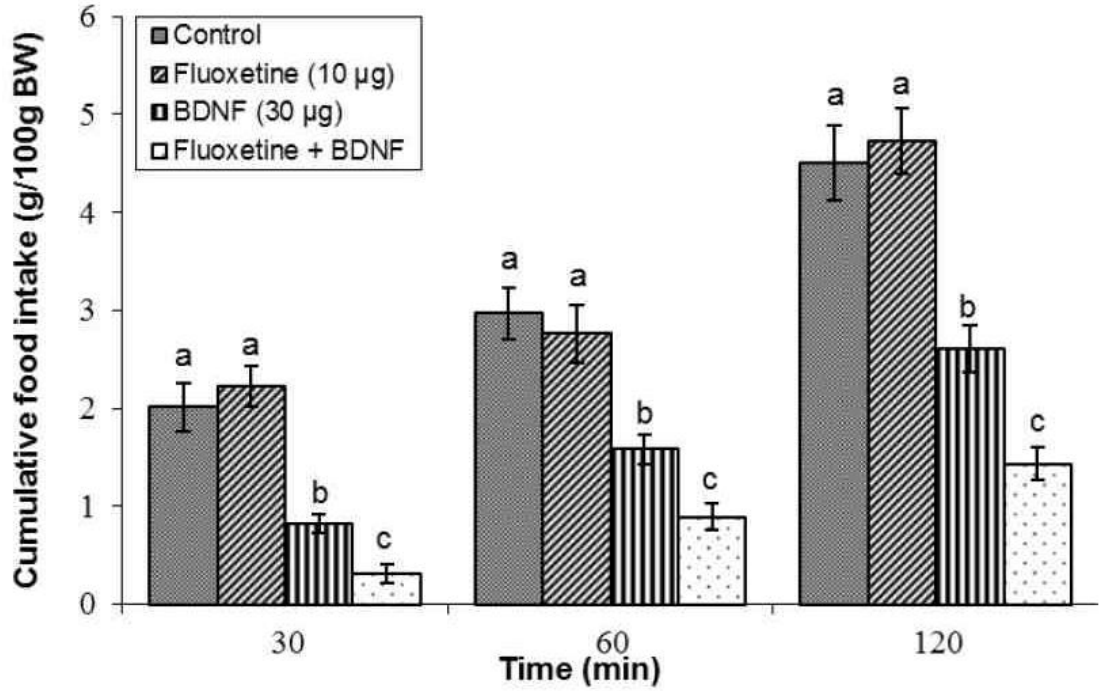

Figure 2. Effect of ICV injection of Fluoxetine (10 µg), BDNF (30 µg) and their combination on cumulative food intake in neonatal chicken (n=44). Fluoxetine: Serotonin reuptake inhibitor. Data are expressed as mean±SEM. Heterogenous letters (a, b and c) indicate significant differences between treatments (*p*<0.05).

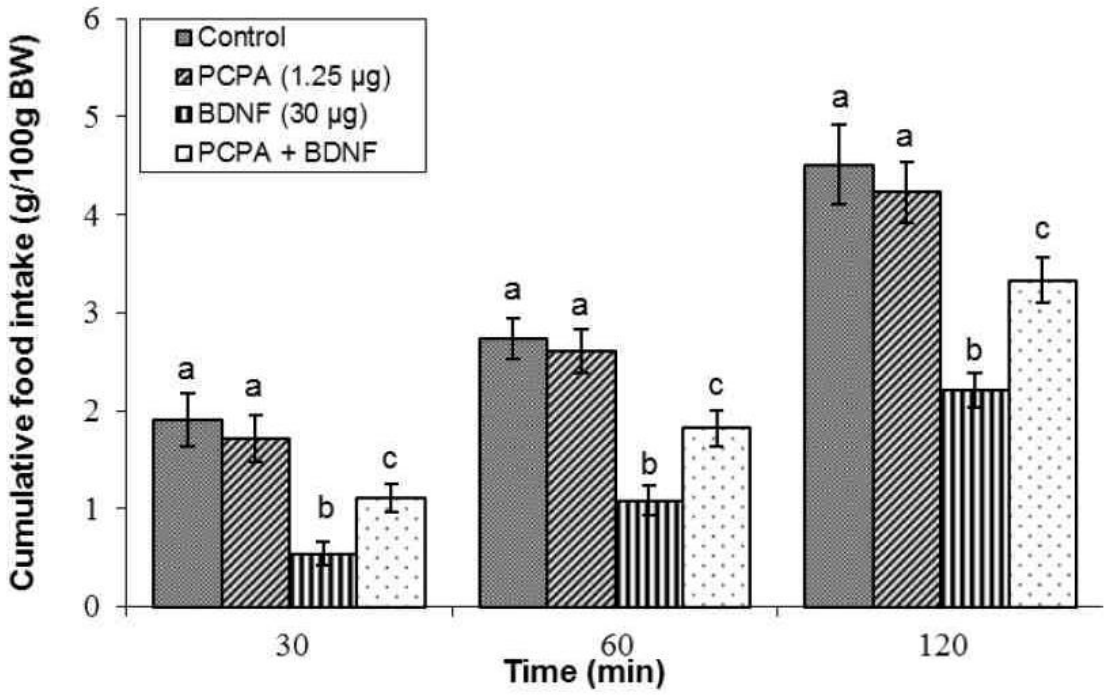

Figure 3. Effect of ICV injection of PCPA (1.25 µg), BDNF (30 µg) and their combination on cumulative food intake in neonatal chicken (n=44). PCPA: Serotonin synthesis inhibitor. Data are expressed as mean ±SEM. Heterogenous letters (a, b and c) indicate significant differences between treatments (p <0.05).

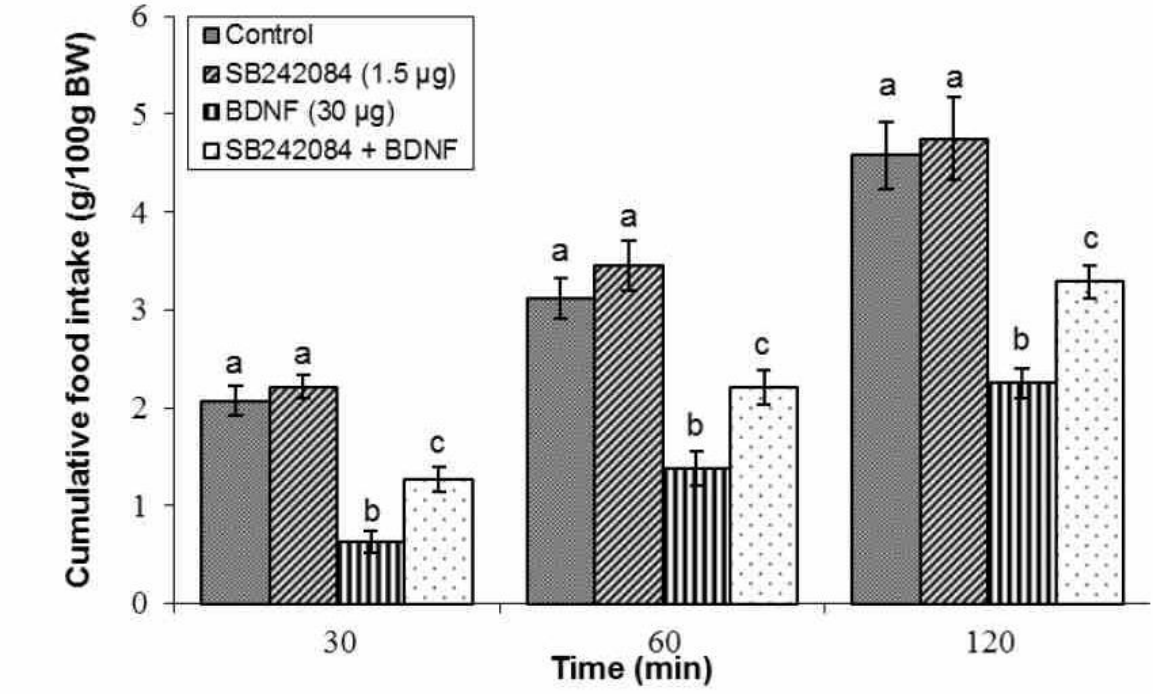

Figure 4. Effect of ICV injection of SB242084 (1.5 µg), BDNF (30 µg) and their combination on cumulative food intake in neonatal chicken (n=44). SB242084: 5-HT2c receptor antagonist. Data are expressed as mean±SEM. Heterogenous letters (a, b and c) indicate significant differences between treatments (p< 0.05).

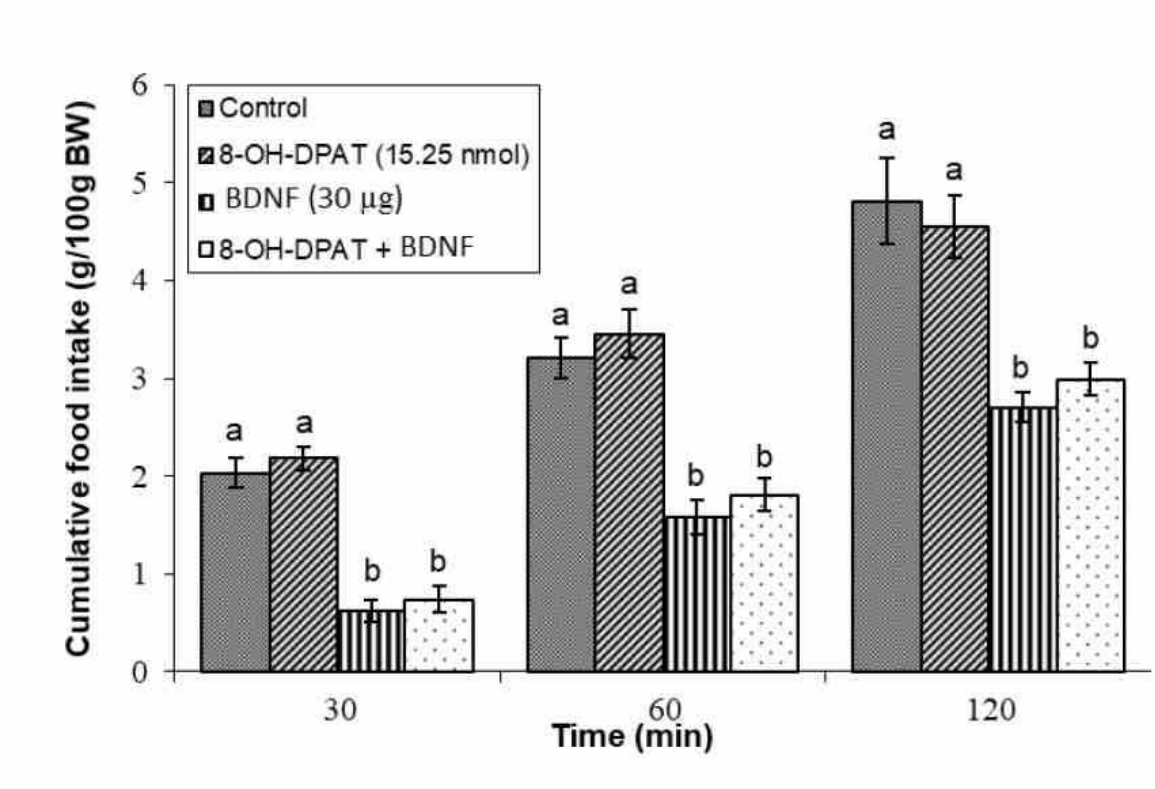

Figure 5. Effect of ICV injection of 8-OH-DPAT (15.25 nmol), BDNF (30 µg) and their combination on cumulative food intake in neonatal chicken (n=44). 8-OH-DPAT: 5-HT1A receptor agonist. Data are expressed as mean±SEM. Heterogenous letters (a and b) indicate significant differences between treatments (p<0.05).

4 Discussion

In recent years, along with conducting extensive studies on mammalian models, remarkable progress has been made in research on the regulatory mechanisms of birds' food intake, which has led to the identification of dozens of factors involved in this physiological process. However, there are still many unknowns in this field. In this regard, the effect of BDNF on the feed consumption of chickens was investigated in the current study. According to the findings, the administration of BDNF with the lowest dose (7.5 µg) did not have a signifaicant effect on the appetite of chickens (p>0.05). In comparison, the infusion of 15 and 30 µg of BDNF remarkably suppressed the meal intake of broilers (p<0.05). BDNF is a member of the neurotrophin family and plays a pivotal role in the differentiation and survival of some types of neurons (21). BDNF has a close structural similarity with nerve growth factor (NGF), and about half of its amino acid content is identical to NGF, neurotrophin-3 (NT-3), and neurotrophin-4/5 (NT-4/5) (22). Researchers have demonstrated that peripheral administration of BDNF induces hypoglycemic and hypophagic in hyperglycemic obese animals (23, 24). They also found that the administration of BDNF prevented decreased body temperature during food deprivation or cold exposure (25). This factor positively correlates with triglycerides, low-density lipoprotein (LDL), and cholesterol (26). BDNF treatment in diabetic animals leads to a decrease in liver weight and plasma non-esterified fat, phospholipids, and glucose, along with an increase in peroxisome proliferator receptor (PPAR-α) activation, β-oxidation, and fibroblast growth factor concentrations (27). Activation of TrkB, as the main BDNF receptor, is essential for energy homeostasis and appetite regulation. Scientists have shown that omega-3 fatty acids regulate BDNF expression, improve learning ability, and inhibit oxidative damage (28). Since TrkB is expressed in the hypothalamus, the effects of BDNF on appetite are probably carried out through the hypothalamic mechanism (29). Based on the results of a study, intraperitoneal (IP) infusion of BDNF decreased cumulative meal consumption in two different strains of mice. Also, repeated subcutaneous (SC) infusion of BDNF inhibited feed consumption in diet-induced obese rats (19). According to the above, the findings of our study are in accordance with

previous experiments on mammalian models and report the hypophagic role of BDNF in birds for the first time.

The design and implementation of various research on the role of the serotonergic receptors in feed intake regulation have shown that hypophagia caused by central injection of serotonin is often mediated through 5-HT_{1A} and 5-HT_{2C} receptors (30). It has been reported that central administration of serotonin causes hypophagia in pigeons, turkeys, and chickens with free access or deprived of food (31). Also, although the central administration of 5-HT had no significant effect on the appetite of broilers with food deprivation, it led to the suppression of feeding in chickens with free access to the diet (2). Furthermore, central infusion of 8-OH-DPAT in chicks with feed deprivation increased the time interval of feed intake, while having no meaningful effect on feed consumption (32). In the present study, due to the fact that serotonin receptor antagonists and serotonin reuptake and synthesis inhibitors were injected in sub-effective doses, no meaningful effect was observed on the amount of feed consumption of broilers ($p>0.05$).

Regarding the interaction between BDNF and the serotonergic system, the anatomical distribution of BDNF, serotonin, and their receptors in the hypothalamic nuclei has been reported as one of the key areas of appetite regulation (33). Studies have proven that the ICV infusion of BDNF increases the ratio of 5-hydroxyindoleacetic acid/serotonin in the hypothalamus of rats, which is accompanied by severe loss of appetite and weight (26). In addition, it has been found that deletion of the BDNF encoding gene causes abnormalities in serotonergic neurons located in the frontal cortex, hippocampus, and hypothalamus, which play an important role in serotonin-induced meal consumption and satiety regulation (34-36). In the current study, in accordance with previous research, the interaction between the serotonergic system and BDNF was observed. According to the findings, the simultaneous injection of Fluoxetine with BDNF strengthened its hypophagic effect ($p<0.05$). On the other hand, BDNF-induced decrease in feed intake was attenuated via PCPA + BDNF and SB242084 + BDNF injections ($p<0.05$). At the same time, 8-OH-DPAT + BDNF administration did not cause a remarkable change in BDNF-induced hypophagia ($p>0.05$). Finally, 5-HT_{2C} receptors appear to mediate BDNF-induced hypophagia in broiler chickens.

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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

This study was approved by the local ethics committee for animal experiments of Islamic Azad University, Garmsar.

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