Iranian Journal of Veterinary Science and Technology

Received: 2021- Dec- 23
Accepted after revision: 2021- Mar- 05
Published online: 2022- Apr- 01

RESEARCH ARTICLE

DOI: 10.22067/ijvst.2022.72134.1071

Role of central opioid receptors on serotonin-Induced hypophagia in the neonatal broilers

Behrouz Rahmani[a], Kimia Mahdavi[a], Morteza Zendehdel[a], Mina Khodadadi[a], Maryam Keshavarz[a], Ali Baghbanzadeh[a], Majid Shahabi[b]

[a] Department of Basic Sciences, Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran.
[b] Department of Clinical Sciences, Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran.

ABSTRACT

Serotonin (5-HT) plays an underpinning role in appetite regulation and the opioid system has a role in the modulation of the ingestion behavior in birds. The current survey was aimed to evaluate the effect of opioid receptors on serotonin-induced hypophagia in neonatal broilers. During experiments, food-deprived chickens received intracerebroventricular (ICV) injection and thereafter, the cumulative food intake was measured after 30, 60, and 120 minutes. In experiment 1, to determine the effective dose of serotonin, the control solution and the various doses of serotonin (2.5, 5, and 10 µg) were administered to birds. In the second experiment, groups received not only the control solution, but also an effective dose of serotonin (10 µg), µ-opioid receptor antagonist (β_FNA, 5 µg), and a co-injection of β_FNA (5 µg) and serotonin (10 µg), respectively. The next experiments were similar to the second experiment, however, in place of β_FNA, the antagonist of κ- opioid receptor (nor_BNI, 5 µg), the δ- opioid receptor antagonist (NTI, 5 µg), and the agonist of µ opioid receptor (DAMGO, 62.25 pmol) were used in experiments 3, 4, and 5, respectively. The results showed a dose-dependent hypophagic impact of serotonin. This effect was attenuated by β_FNA; however, nor_BNI and NTI had no effect. Furthermore, the diminishing effect of serotonin on food consumption in chickens was strengthened following DAMGO administration ($p < 0.05$). According to the results, the hypophagic effect of serotonin is possibly mediated through µ opioid receptors in neonatal broilers.

Keywords

Serotonin; central opioid receptors; food intake; anorexigenic effects; broilers

Number of Figures: 5
Number of Tables: 2
Number of References:: 57
Number of Pages: 11

Abbreviations

5-HT: 5-hydroxytryptamine
ICV: intracerebroventricular
β_FNA: beta-funaltrexamine
NTI: naltrindole
nor_BNI: norbinaltorphimine
DAMGO: [D-Ala, N-MePhe, Gly-ol]-enkephalin

Corresponding author: *Mina Khodadadi*
Email: : *mina.khodadadi@alumni.ut.ac.ir*
Tel: *+98 (21)6111-7081*

Introduction

The appetite regulation is one of the interesting topics for research in physiology and nutrition sciences nowadays. Ingestion habits are modulated via external factors such as environmental and dietary alterations as well as the internal ones, those are in relevance with the gastrointestinal, hormonal, and brain elements [1]. In this respect, central control of appetite is related to the function of various neurotransmitters and related neuronal pathways in the central nervous system (CNS) [2]. Serotonin (5-hydroxytryptamine, 5-HT) is a monoamine neurotransmitter with some roles in physiologic functions such as sleep, circadian rhythm, motor control, pain perception, and behaviors such as mood, anxiety, aggressiveness, depression, and so on [3-5]. The serotonergic neurons are primarily located in the raphe nuclei, central grey and reticular formation in the CNS, and seven main classes of 5-HT receptors called 5-HT1–5-HT7, have been discovered and categorized as G protein-coupled receptors (GPCRs) [6]. It has been revealed that the central serotonergic system has a key role in the modulation of the ingestion behavior in different species. Based on the former studies, the ICV injection of 5-HT decreased food intake in chickens [7-10].

It has been demonstrated that opioids are a kind of inhibitory neurotransmitters in the brain. The opioid receptors are categorized into three main types containing mu (μ), delta (δ), and kappa (κ) [11]. Opioid receptors exist within the vast regions of the CNS especially septo-hypothalamic one [12]. A myriad of studies has illustrated the effect of the central opioidergic system on pain perception, respiration control, and immune system response [13]. Recently, the interest to study the effect of central opiates in the regulation of food intake has increased [14]. But it seems that the involvement of endogenous opiates in food intake has been assigned controversial results. For example, in mammals, the ICV injection of μ- and δ-, receptors' agonist increased food intake while κ-opioid one had no same effect [15,16]. However, in avian species, the ICV injection of μ-opioid receptors agonist could decrease food consumption, and the administration of δ- and κ-opioid receptors agonists enhanced it [17]. Based on the literature, similar to mammals, 6 opioid peptides encrypted by proenkephalin (PENK), pro-opiomelanocortin (POMC), prodynorphin (PDYN), and 4 opioid receptors were considered as highly-preserved ones in chickens. Also, it has been suggested that the ligand-receptor pairs of the chicken opioidergic system are similar to those of mammals, while it is not identical [18]. By taking into consideration of revealed differences among species, several studies showed that the feeding behavior was stimulated by μ-opioid receptor activation in broilers [19,20]. Presumably, food intake behavior is controlled via neuroendocrine and the balance of energy is a complex process in which a whole host of overlapping integrated pathways have potential roles. In this view, the possibility of the interaction between endogenous opioids and other neurotransmitters has been suggested by different research studies [21-23]. To exemplify, in some previous studies, the interaction of the central opioidergic system with oxytocin, histaminergic, and dopaminergic systems have been demonstrated [24-26].

In terms of the interplay between the opioidergic and serotonergic systems at the level of the CNS, several studies, such as those on nociception, have detected an interaction between these two systems [27]. However, there is no report available concerning the evaluation of possible interconnection between these two systems in food intake behavior, especially in avian species. Since different opioid receptor subtypes were found in raphe nuclei in which 5-HT are the major neurotransmitter [28], and in consideration of the effects of both opioidergic and serotonergic systems on appetite, we designed and performed this study to investigate the possible effect of the central opioid system on feeding behavior related to serotonin in broilers.

Results

In the first experiment, the ICV injection of 2.5 μg serotonin had no important effect on food consumption in comparison with the control in none of the time points ($p \geq 0.05$), while the ICV administration of 5 and 10 μg of serotonin noticeably and dose-dependently declined the consumption of food compared with the control group at all the time-points ($p < 0.05$). The results suggested a dose-dependent hypophagic impact of serotonin on the eating habit of neonatal meat-type chicken (Fig. 1).

Regarding experiment 2, the hypophagic effect of serotonin was remarkably attenuated by β_FNA pretreatment in chickens compared to the control group at all the time points ($p < 0.05$). In addition, β_FNA alone did not affect food intake. The data suggested that the hypophagic effect of serotonin was mediated through the central receptors of μ opioid in broilers (Fig. 2).

In the next experiment neither ICV administration of 5 μg nor_BNI nor ICV co-injection of 5 μg nor_BNI plus 10 μg serotonin altered the hypophagic impact of serotonin at different time points compared with the control group ($p \geq 0.05$). These results suggested that the hypophagic effect of serotonin was not

mediated via the central kappa opioid receptors in chickens (Fig. 3).

In the fourth experiment, administration of 5 µg NTI made no major change in cumulative food consumption compared to the control group at all the time points. The hypophagic effect of serotonin was not altered by the addition of 5 µg NTI and 10 µg serotonin rather than the control group at all times ($p \geq 0.05$). This information suggested that, regarding the hypophagic effect of serotonin, delta-opioid receptors do not have a mediatory role (Fig. 4).

In experiment 5, the hypophagic effect of serotonin was noticeably increased by administration of 62.25 pmol DAMGO in FD3 chicks than the control group at all the time points after injection ($p < 0.05$), while 62.25 pmol DAMGO alone had no impact on food intake in comparison with the control group. This suggests the hypophagic effect of serotonin in broilers is possibly mediated via µ opioid receptors (Fig. 5).

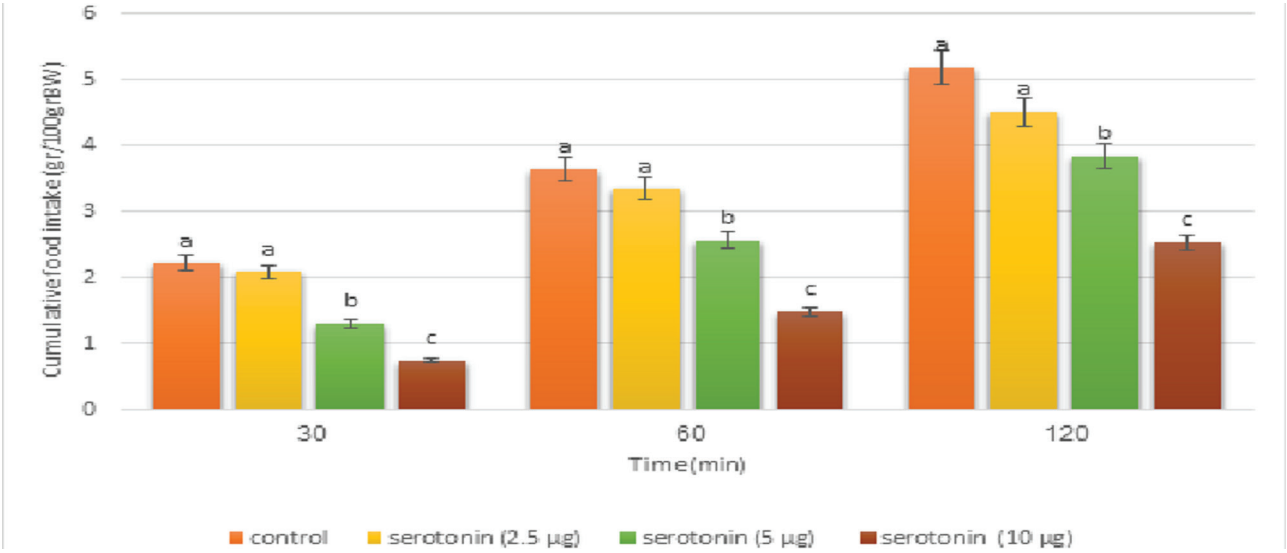

Figure 1.
Effects of ICV injection of different doses of serotonin (2.5, 5 and 10 µg) on cumulative food intake (gr/100gr BW) in neonatal chicks (n=44). Data are expressed as mean ± SEM. Different letters (a, b and c) indicate significant differences between treatments at each time ($P < 0.05$).

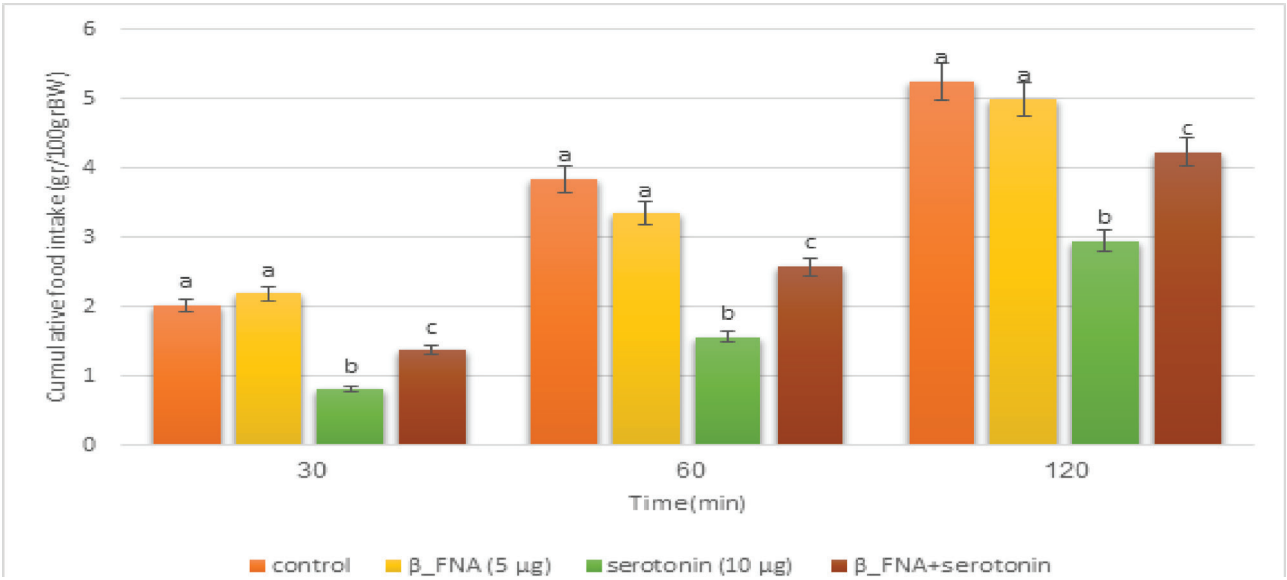

Figure 2.
Effects of intracerebroventricular injection of control solution, serotonin (10 µg), β–FNA (5 µg) and a combination of serotonin plus β–FNA on cumulative food intake (gr/100gr BW) in neonatal chicks (n=44). β–FNA: µ receptor antagonist. Data are expressed as mean ± SEM. Different letters (a, b, and c) indicate significant differences between treatments at each time ($p < 0.05$).

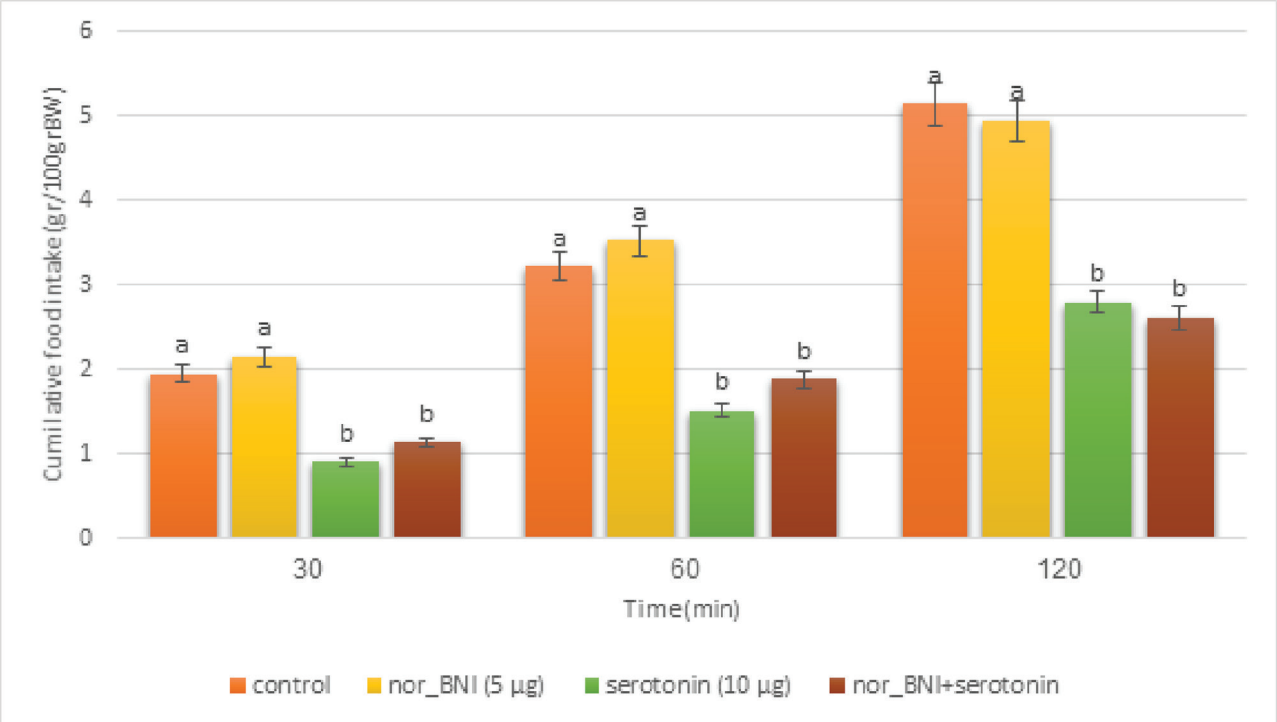

Figure 3.
Effects of intracerebroventricular injection of control solution, serotonin (10 µg), nor-BNI (5 µg) and a combination of serotonin plus nor-BNI on cumulative food intake (gr/100gr BW) in neonatal chicks (n=44). nor-BNI: Kappa receptor antagonist. Data are expressed as mean ± SEM. Different letters (a and b) indicate significant differences between treatments at each time ($p < 0.05$).

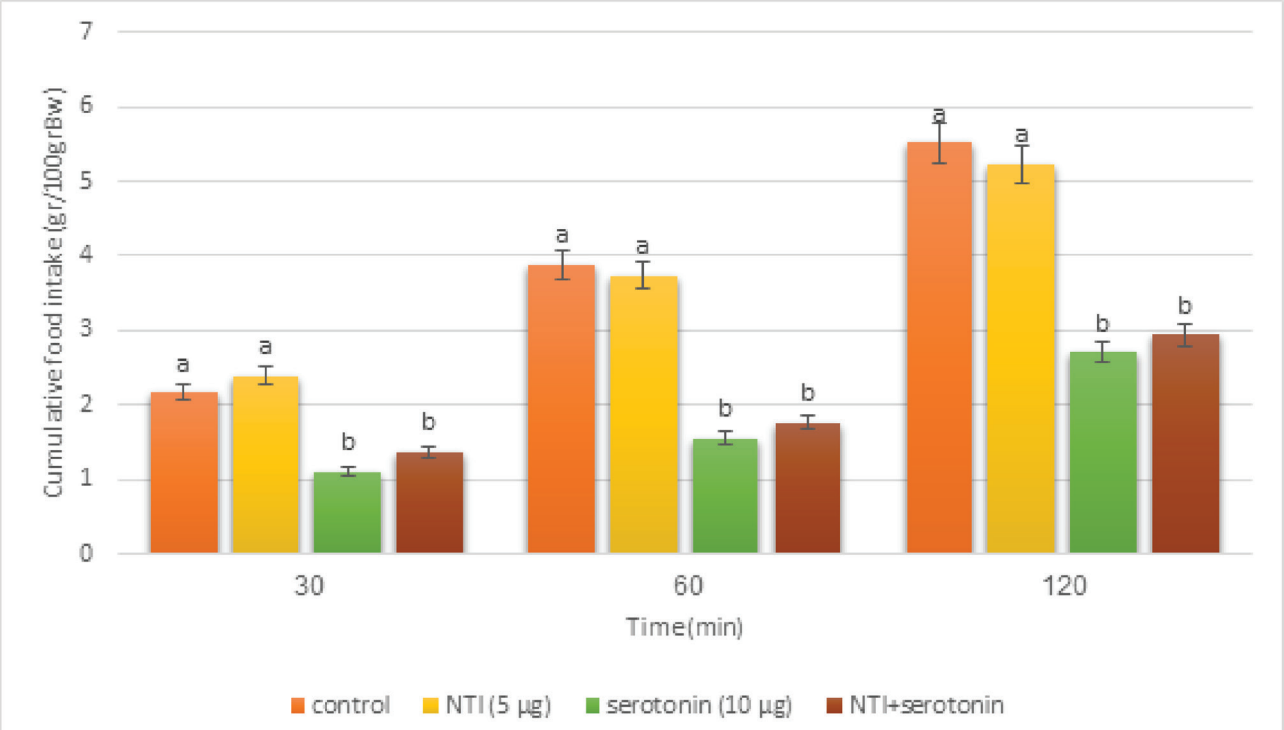

Figure 4.
Effects of intracerebroventricular injection of control solution, serotonin (10 µg), NTI (5 µg) and a combination of serotonin plus NTI on cumulative food intake (gr/100gr BW) in neonatal chicks (n=44). NTI: Delta receptor antagonist. Data are expressed as mean ± SEM. Different letters (a and b) indicate significant differences between treatments at each time ($p < 0.05$).

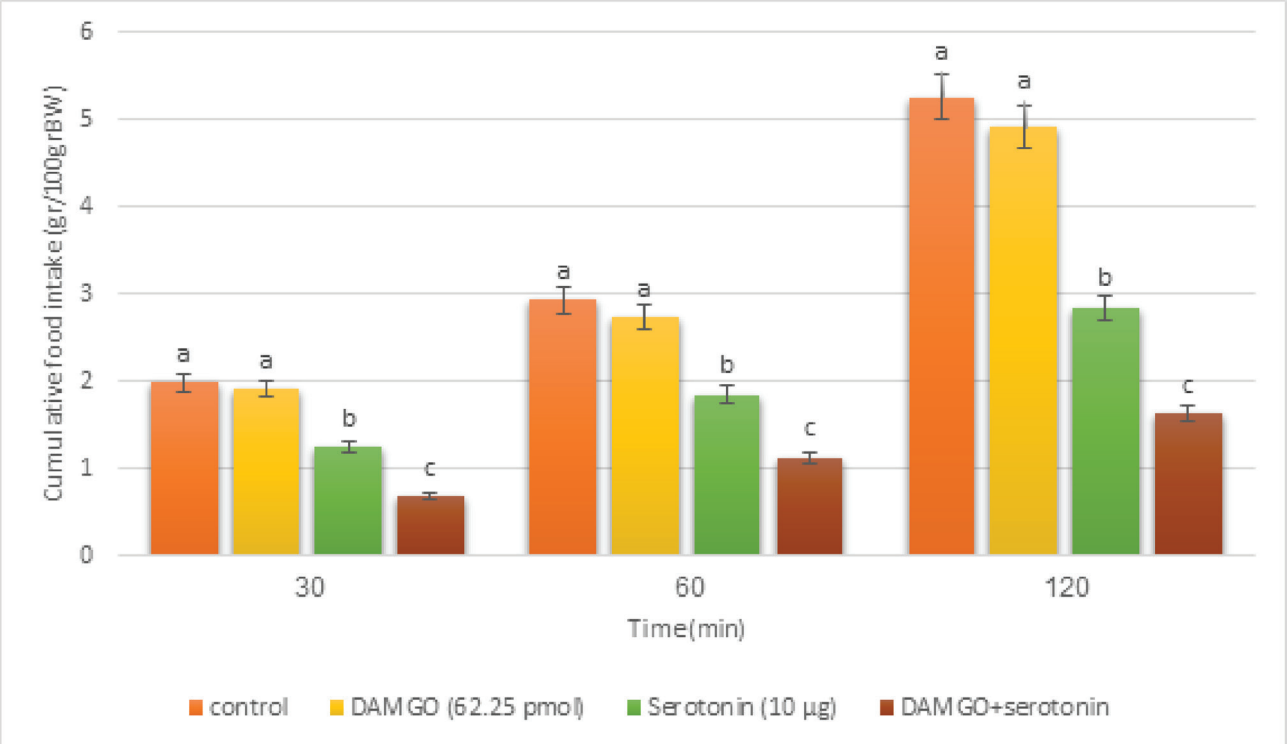

Figure 5.
Effects of intracerebroventricular injection of control solution, serotonin (10 µg), DAMGO (62.25 pmol) and a combination of serotonin plus DAMGO on cumulative food intake (gr/100gr BW) in neonatal chicks (n=44). DAMGO: µ receptor agonist. Data are expressed as mean ± SEM. Different letters (a, b, and c) indicate significant differences between treatments at each time ($p < 0.05$).

Discussion

This report is the first one concerning the interplay of opioidergic receptors in hypophagic behavior which is induced by serotonin in broilers. In the current study, serotonin decreased food intake in neonatal broilers, which agreed with former surveys in some birds' breeds besides mammals [29-32]. In consideration of the receptor's subtype, serotonergic receptors have different effects on appetite and food consumption. It seems that in mammals the appetite is attenuated via 5-HT2c receptors while 5-HT1A receptors do not affect that [9,10]. Although in one study done on adult rats, the 5-HT1A receptor showed a pivotal effect on water consumption [33]. Although the mechanism of appetite regulation varies between mammals and birds, a large amount of 5-HT receptors has been found in different regions of the CNS in both species such as the hypothalamus and the prefrontal cortex and its homologous the pallial part of the birds' brain [34]. Also, pharmacological studies in mammals showed that 5-HT receptors have a decreasing effect on food intake; in this regard, 5-HT2c receptors located in POMC neurons might have a contributing role in appetite regulation. This latter has highlighted that the serotonergic system modulates the ingestion behavior through the melanocortin pathway [3,7]. Likewise, the 5HT2c receptors can regulate appetite through several other neurotransmitters, such as dopamine and ghrelin [9,10]. Since lack of similar molecular investigation in the birds' brain, this pathway might be similar to those in mammals at least at the level of septo-hypothalamic regions, which is more conservative in avian species than the mammalian ones. Moreover, in consideration of the function of the opioid receptor in ingestion behavior, the role of various kinds of receptors has been illustrated. For instance, one research on rodents has depicted that the ICV administration of the agonists of µ and δ-, but not κ-, could induce the orexigenic behavior [15,16]. Interestingly, the research on poultry has revealed the hypophagic effect induced by µ-opioid receptor activation and the orexigenic function of δ- and κ-opioid receptors, during ICV injection of opioid agonists [17].

In terms of the interplay between two central systems in chickens' brains, it sounds like the serotonin signaling is only mediated by µ opioid receptors. In our study, the co-administration of β_FNA, the antagonist of µ opioid receptor, with serotonin significantly blocked hypophagia which is induced by serotonin in neonatal broilers. In addition, the hypophagic effect induced by serotonin was remarkably increased by administration of DAMGO, the agonist of µ opioid receptor, however nor_BNI and NTI, κ- and δ- receptors antagonists, had no impact on hypophagia induced by serotonin.

The feeding behavior can be modulated within

many regions of the brain such as the striatum, hypothalamus, amygdala, etc. While the arcuate nucleus of the hypothalamus (ARC) has a prominent role among all, it has a lot of neurotransmitters with complicated interactions with one another to regulate appetite in mammals and birds. Finally, the net output of all these interactions can regulate energy expenditure in living creatures [20]. In mammals, it has been shown that at the site of ARC appetite is mainly regulated by releasing different neuropeptides and proteins from higher-order neurons located in this nucleus [36]. In addition, it is suggested that in the ARC, the μ-opioid receptors are contributed to the hyperphagic properties of neuropeptide Y (NPY) and agouti-related protein (AgRP) neurons [12]. The conspicuous role of ARC in food intake regulation has been demonstrated within avian species [35,36]. Although it seems that there are similar pathways in the hypothalamus, more complementary molecular investigations are needed in the future.

Furthermore, the interaction between the μ-opioid receptors and the serotonergic system has been demonstrated in the previous research on the different properties of opioids in mammals. For instance, the co-administration of the agonists of the μ-opioid receptors and the 5-HT receptor agonists has shown the postulated antinociceptive effects [27]. According to several research studies, a wide distribution of opioid receptors has been indicated in different brain regions with a regulatory function in the feeding behavior such as ARC, NAc, amygdala, and NTS [37]. The 5-HT containing neurons originated from the raphe nuclei innervate different parts of the brain such as the ARC and NAc [9, 38]. Under the administration of serotonin or its reuptake inhibitor, the *in vivo* microdialysis assessment in rats has shown the increasing levels of beta-endorphins within ARC and NAc [39]. This, in turn, has postulated an interplay between serotonin and opioid receptors in these nuclei. By taking into account the effect of different brain regions such as ARC and NAc nuclei in feeding behavior and the detected interaction between the serotonergic and opioidergic systems in the mentioned nuclei, it is proposed that this interaction may be one of the mechanisms in which the food intake can be regulated. In terms of the observation of the interplay between serotonin and opioid receptors, this finding can be in line with our obtained results, which showed a mediatory effect of opioid receptors in the serotonin-induced behavior and inverse. However, the exact mechanism remains to be experimentally determined in birds.

From a different aspect of view, anatomical studies have illustrated that μ, δ, and κ opioid receptors are expressed in raphe nuclei. Owing to the existence of various subtypes of receptors in both systems, the explanation of the opioid-5-HT interaction is to some extent difficult. In this relation, researchers have presented that the μ- and δ-opioid receptors stimulation increased the levels of serotonin in raphe nuclei, even though the activation of κ-opioidergic receptors diminished it [28]. In addition, a significant role of 5-HT in opioid biosynthesis has been mentioned [40]. Nevertheless, the exact process of the interaction between μ-opioid and 5-HT receptors needs more investigation [28]. The evidence revealed that the post-synaptic 5-HT2c receptor is located in different neuronal systems such as GABAergic, with a high level of heterogeneity in the rat and human CNS cells [10]. In this respect, previous research referred to the possibility of an indirect act of the μ-opioid receptors on the 5-HT2C receptors by inhibiting local GABAergic neurons. As we know this GABAergic neurons synapse on serotonergic neurons in the raphe nuclei [28].

In terms of the determination of the underlying mechanisms for opioid- 5-HT interaction, the involvement of other neurotransmitters and neuropeptides should be considered. For instance, it seems that the opioidergic and serotonergic systems might be regulated via other peptides in the CNS [41], the functional assessment of this neuropeptide in the modulation of the opioid- 5-HT interaction, is a notable subject that needs to be determined in the future research studies. Similar to the opioid receptors, the serotonin receptor couples to Gi/o. Consequently, extracellular signal-regulated kinases 1 and 2 (ERK1/2) mitogen-activated protein kinase (MAPK) signaling pathways will be active by activation of 5-HT1A [42]. Furthermore, different signaling pathways such as activation of p38 and ERK1/2 MAPK are indicated by opioid's effect [43]. Related to the mediatory effect of the 5-HT2C receptor on μ-opioid receptors, the major role of the dopaminergic system is already seen in mammals, which is in agreement with our findings [44]. To sum, the role of the μ-opioid receptors in terms of regulation in food intake and its direct and/or indirect interplay with the serotonin is a complicated matter which needs more investigation. The new findings showed herein could be a starting spot for more investigation in this field on broiler-type chicken. Undoubtedly, in this respect, future surveys are needed to explain the direct and/or indirect relevant neurological pathway(s).

Materials & Methods

Animals

220 male neonatal one-day hatched chicks (Ross 308) were prepared (from Mahan Company nearby Tehran, Iran). At first,

all birds were placed in a group and followed for 2 days. Then they were put in individual cages. In this study, the electrically heated cages with a stabilized temperature of 32 °C ± 1 were employed. The relative humidity of the housing room was set at 40–50%, and the 23:1 lighting/dark period was determined [45]. Chickens had access without any limitation to a diet of the commercial starter (Table 1). On the 5th day of age, the ICV injections were performed on birds. Three hours before ICV injections, all birds were deprived of food, while they freely access water. All the experimental procedures were performed based on the US Guide (publication No. 85-23, revised 1996) and were approved by the Institutional Animal Ethics Committee of Faculty of Veterinary Medicine, University of Tehran.

Drugs

Drugs consisted of serotonin, β_FNA (antagonist of μ opioid receptor), nor_BNI (antagonist of the kappa-opioid receptor), NTI (antagonist of the delta-opioid receptor), DAMGO (an agonist of μ opioid receptor), and color as Evans Blue (Sigma, USA). Drugs were prepared in a solution of absolute dimethyl sulfoxide (DMSO) which were diluted with 0.85% NaCl 0.9% plus color at the proportion of 1:250. The using DMSO has no cytotoxic effects [46,47]. The mixture of DMSO/ Saline containing color was used as a control solution.

ICV

Chickens were divided into 5 experiments (n=44) in such a way that every experiment involved 4 groups (n = 11). Before performing the experiments, the birds were accurately weighed and distributed into different groups. Averagely, body weight (BW) between understudied groups was uniform. In each experiment, the ICV injection was performed by a microsyringe (Hamilton, Switzerland) without the need for anesthesia (1979) and Furse et al. (1997) methods [48,49]. In brief, by using an acrylic device consisting of a holder of a bill at 45 degrees, the calvarium of the chicken head was being placed parallel to the table surface, as was stated previously [50]. Immediately after the head positioning, a hole was made over the right lateral ventricle of the brain. Via the orifice, the tip of the needle penetrated 4 mm below the skull [51]. All drugs were administered in the volume of 10 μL via the ICV route [52] and the control group merely received the solution of control (10 μL). It should be mentioned that the procedure made no physiological stress in newly hatched birds [53]. In the end, the chicken was decapitated (according to AVMA Guidelines for the Euthanasia of Animals 'No: M3.6, cervical dislocation), and the preciseness of the injection site was evaluated based on the method published in our previous publications.

Food intake measurement

The experiment procedure and all the details are described in Supplementary file 1. Also, the design of the experiments is shown in Table 2. Following performing the ICV injections, birds were returned to their cages with available food which was pre-weighed and freshwater. 30, 60, and 120 minutes after injections, and the cumulative food intake was measured. To adjust the diversity among the weights, all measurements were calculated as %BW. The dosage of the drugs was determined based on the pilot and previous research studies [54-57].

Statistical Analysis

As mentioned before, cumulative food intake was applied to analysis as extracted data. The statistical analysis was done by using repeated measure two-way analysis of variance (ANOVA) and the outcomes were raised as mean ± SEM. The analytical procedure was the same as previous publications [54-57].

Table 1.
Ingredient and nutrient analysis of experimental diet

Ingredients	%	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 (%)	1.30
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 D3	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 $MnSo_4 \cdot H_2O$; 22 g iron from $FeSO_4 \cdot H_2O$; 35.2 g zinc from ZnO; 4.4 g copper from $CuSO_4 \cdot 5H_2O$; 0.68 g iodine from ethylene diamine dihydroiodide; 0.12 g seleniumfrom Na_2SeO_3. 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

Table 2.
Intracerebroventricular injections in experiments

Groups	Exp. 1	Exp. 2	Exp. 3	Exp. 4	Exp. 5
A	CS[a]	CS	CS	CS	CS
B	Serotonin (2.5 µg)	β_FNA[b] (5 µg)	nor_BNI[c] (5 µg)	NTI[d] (5 µg)	DAMGO[e] (62.25 pmol)
C	Serotonin (5 µg)	Serotonin (10 µg)	Serotonin (10 µg)	Serotonin (10 µg)	Serotonin (10 µg)
D	Serotonin (10 µg)	β_FNA+serotonin (5 µg)+(10 µg)	nor_BNI+serotonin (5 µg)+(10 µg)	NTI+serotonin (5 µg)+(10 µg)	DAMGO+serotonin (62.25 pmol)+(10 µg)

[a] Control solution
[b] µ opioid receptor antagonist
[c] kappa opioid receptor antagonist
[d] delta opioid receptor antagonist
[e] µ opioid receptor agonist

Authors' Contributions

M.Z. conceived and planned the experiments. K.M. carried out the experiments. M.Z. and M.KH. contributed to the interpretation of the results. M.KH took the lead in writing the manuscript. All authors provided critical feedback and helped shape the research, analysis, and the manuscript.

Acknowledgements

This study was assisted by the authors' self-fund.

Conflict of interest

The authors declare that there is no conflict of interest.

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How to cite this article
Rahmani B, Mahdavi K, Zendehdel M, Khodadadi M, Keshavarz M, Baghban Zadeh A,Shahabi M. Role of central opioid receptors on serotonin-Induced hypophagia in the neonatal broilers. Iran J Vet Sci Technol. 2022;14(1): 9-19.
DOI: https://doi.org/10.22067/ijvst.2022.72134.1071
URL: https://ijvst.um.ac.ir/article_41006.html