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RESEARCH ARTICLE

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Evidence for an interaction between cannabinoidergic and dopaminergic systems with melanocortin MC3/MC4 receptors in regulating food intake of neonatal chick

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ABSTRACT

The current study aimed to see how the central dopaminergic and cannabinoidergic mechanisms affect melanocortin-induced food intake in neonatal layer chickens. In this regard, 9 experiments were designed. In experiment 1, chicks were injected with a control solution, MTII (2.5, 5, and 10 ng). In experiment 2, control solution, L-DOPA (125 nmol), MTII (10 ng), and L-DOPA + MTII were applied to the birds. Experiments 3-9 were similar to experiment 2, except birds injected with 6-OHDA (150 nmol), SCH23390 (5 nmol), AMI-193 (5 nmol), NGB2904 (6.4 nmol), L-741,742 (6 nmol), SR141716A (6.25 µg), and AM630 (5 µg) instead of L-DOPA. Then, cumulative food intake was recorded at 30, 60, and 120 min following injection. According to the results, in comparison with the control group, dose-dependent hypophagia was observed in 3-h food-deprived neonatal layer chickens following ICV injection of MTII (2.5, 5, and 10 ng) ($p < 0.05$). ICV injection of L-DOPA and SR141716A increased hypophagia induced by MTII in chickens ($p < 0.05$), while 6-OHDA greatly suppressed MTII- induced hypophagia ($p < 0.05$). In addition, SCH23390 and AMI-193 greatly weakened the MTII-induced hypophagia in neonatal layer chickens ($p < 0.05$). However, NGB2904, L-741742, and AM630 had no role in hypophagia induced by MTII ($p > 0.05$). These results demonstrated that melanocortin-induced hypophagia in the neonatal layer chickens is likely mediated by D1, D2, and CB1 receptors.

Keywords

Dopamine, Cannabinoid, Melanocortin, Food intake, Layer chicken

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Abbreviations

ICV: Intracerebroventricular
CNS: Central nervous system
CB: Endocannabinoids receptors
GPCRs: G protein-coupled receptor subtypes
DA: Dopamine
ARC: Arcuate nucleus
VMH: Ventromedial hypothalamus
PVN: Periventricular nucleus

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Introduction

One of the most complicated aspects of animals is appetite regulation that modulates a large number of parts in the brain for cooperating with signals received from the peripheral organs [1]. The appetite is regulated by various neurotransmitters through complex neurological pathways in the central nervous system (CNS) [2]. Endocannabinoids and their receptors (CB1 and CB2) belong to the G protein-coupled receptor subtypes (GPCRs) with a role in several physiological functions in the brain, including locomotion nociception, learning and memory, food intake, and energetic metabolism [3,4]. Besides, it has a regulatory role in immune regulation, endocrine processes, cardiovascular system, emesis, and brain development [5]. The CB1 receptors are expressed in the presynaptic terminals of the brain, and CB2 receptors were previously found on immune system cells and organs in the peripheral nervous system (PNS), but they are also expressed in CNS [6]. Moreover, both CB1 and CB2 receptors have a role in food intake regulation in rats [7]. However, little is known about the contribution of endocannabinoids to feeding behavior in domestic fowl. Some studies claim that just the CB1 receptors have a regulatory role in appetite in broilers [8, 9]. Recently, a number of studies revealed that both CB1 and CB2 receptors have hyperphagic effects in the neonatal layer chickens [4, 10, 48, 49]

Dopamine is the main catecholamine neurotransmitter expressed in several nuclei of the brain, such as the hypothalamus, substantia nigra, and ventral tegmental area. At least five different dopamine receptor subtypes have been discovered so far (D1-D5) [11]. At least five distinct GPCRs of dopamine affect its mediatory effects [11]. The receptors D1 and D2 are found frequently than others in the brain. The dopaminergic system is involved in a variety of physiological functions, including appetite regulation, locomotor activity, emotion, and cognition [12]. Food intake reduces through D1 and D2 receptors in rats [13]. Besides, in meat-type chickens, hypophagia induced by dopamine is mediated by D1 receptors, while others (D2-D4) may have no role in appetite regulation [1, 14]. Thus, it is evident that no single neuropeptide regulates central feeding behavior and that there are interactions between a broad distributed neural network and other neurotransmitters to assess feeding status [15, 49].

The melanocortin is a neurotransmitter for which five subtypes (MC1R-MC5R) have been identified to date [16]. It has a prominent role in physiologic functions, including grooming, thermoregulation, learning, and energy balance regulation [17]. The melanocortin receptors have been identified in the bird's brain. Only the melanocortin-3 (MC3R) and melanocortin-4 (MC4R) subtypes of melanocortin receptors are responsible for the central regulation of food intake [17]. The MC3R and MC4R are mainly found in the arcuate nucleus (ARC), ventromedial hypothalamus (VMH), and periventricular nucleus (PVN) regions of the hypothalamus. According to the related published studies, the ICV injection of the MC3 and MC4 receptors reduces the food intake in rats [18].

Dopaminergic neurons interact with the actions of cannabinoids in the CNS. Dopaminergic neuronal cell bodies are located in the substantia nigra and ventral tegmental area (VTA) and projected to the caudate-putamen (CP) and nucleus accumbens (NA). The effector neurons in these structures are regulated by dopaminergic and cannabinoidergic mechanisms [3]. Motor effects of CB1 agonists are linked to intracellular responses elicited by D1 and D2 receptors in the striatal projection neurons [19]. The melanocortin and dopamine mechanisms have interactions by which several significant physiological functions are regulated [20]. In the ventral tegmental area, the MC3R, and MC4R are located in dopaminergic neurons innervated by proopiomelanocortin (POMC) neurons in the arcuate nucleus [21]. MC4R plays a critical role in regulating D1 and D2 receptors in the nucleus accumbens [20]. Activation of the dopaminergic neurons in the ventral tegmental area by melanocortin and the dopamine-mediated effects of reward and reinforcement associated with the food intake is suppressed by the dopamine D1 and D2 receptors in the nucleus accumbens [21]. Studies reveal that cannabinoids, dopamine, and melanocortin are interconnected in CNS; however, there is little data on how their interactions affect the regulation of food intake in poultry. Therefore, the current work aimed to see how the central dopaminergic and cannabinoidergic mechanisms affect melanocortin-induced food intake in neonatal layer chickens.

Abbreviations-Cont'd

VTA: Ventral-tegmental area
POMC: Proopiomelanocortin
FD3: 3-h food-deprived
BW: Body weight
ACTH: Adrenocorticotropic hormone
α-MSH: α-Melanocyte-stimulating hormone
NPY: Neuropeptide Y

Results

In experiment No.1, a dose-dependent hypophagia was observed following the MTII (2.5, 5, and 10 ng) ICV injection in the 3-h food-deprived neonatal layer chickens 120 min following the injection in comparison with the control group ($p < 0.05$) (Fig. 1).

In experiment No.2, the MTII (10 ng) ICV injection reduces food intake considerably in the 3-h food-deprived layer chickens ($p < 0.05$), whereas in comparison with the control group ($p > 0.05$), the L-DOPA (125 nmol) ICV injection has no significant effects on the cumulative food intake. Furthermore, the MTII+L-DOPA co-injection greatly increased hypophagia induced by MTII in the chickens ($p < 0.05$) (Fig. 2).

In experiment No.3, hypophagia was observed following the MTII (10 ng) ICV injection in the 3-h food-deprived layer chickens ($p < 0.05$). On the other hand, in comparison with the control group ($p > 0.05$), the 6-OHDA (150 nmol) ICV injection has no significant effects on the cumulative food intake. Also, the MTII+6-OHDA co-injection greatly reduced hypophagia induced by MTII in 3-h food-deprived layer chickens at 30, 60, and 120 min following the injection ($p < 0.05$) (Fig. 3).

As shown in Figure 4, the MTII (10 ng) ICV injection greatly reduces cumulative food intake in the 3-h food-deprived layer chickens ($p < 0.05$). In comparison with the control group ($p > 0.05$), the SCH23390 (5 nmol) ICV injection has no significant effects on the cumulative food intake. The MTII+SCH23390 co-injection greatly weakened hypophagia induced by

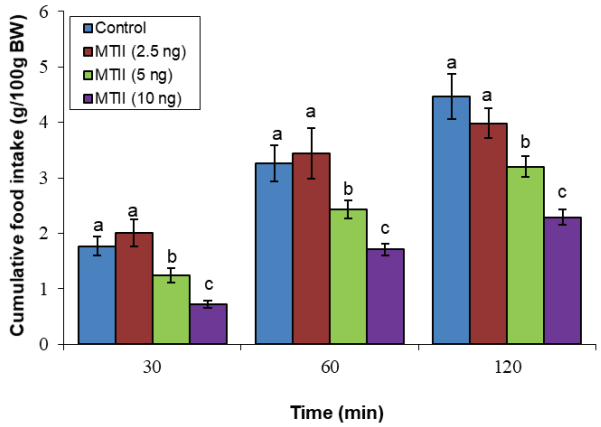

Figure 1.
Effect of intracerebroventricular injection of the MTII (MC3/MC4 receptors agonist) on food intake in the neonatal layer chickens. Data are expressed as mean ± SEM. Different letters (a, b, and c) indicate significant differences between treatments at each time ($p < 0.05$).

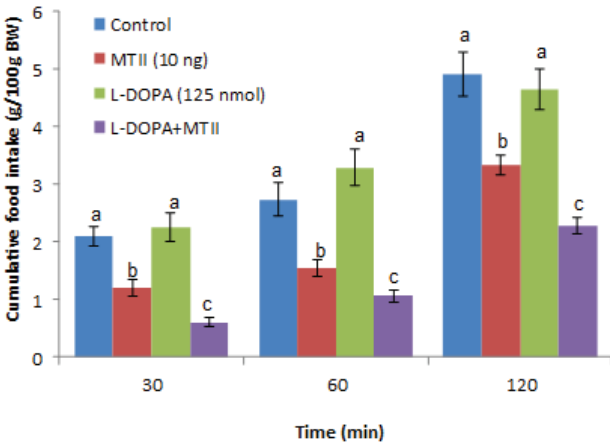

Figure 2.
Effect of intracerebroventricular injection of L-DOPA (dopamine precursor) on hypophagia-induced by MTII (MC3/MC4 receptors agonist) in the neonatal layer chickens. Data are expressed as mean ± SEM. Different letters (a, b, and c) indicate significant differences between treatments at each time($p < 0.05$).

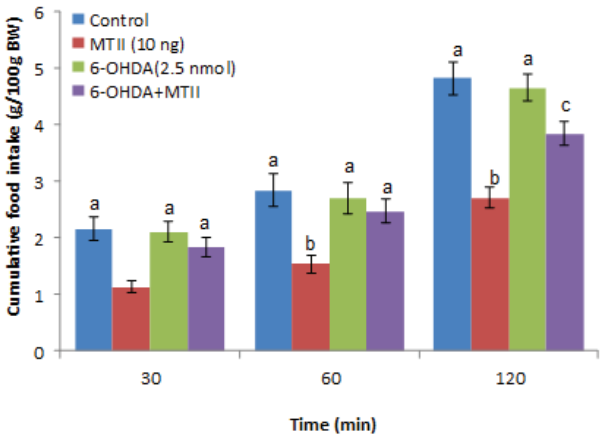

Figure 3.
Effect of intracerebroventricular injection of 6-OHDA (a dopamine depletion) on hypophagia-induced by MTII (MC3/MC4 receptors agonist) in the neonatal layer chickens. Data are expressed as mean ± SEM. Different letters (a, b, and c) indicate significant differences between treatments at each time($p < 0.05$).

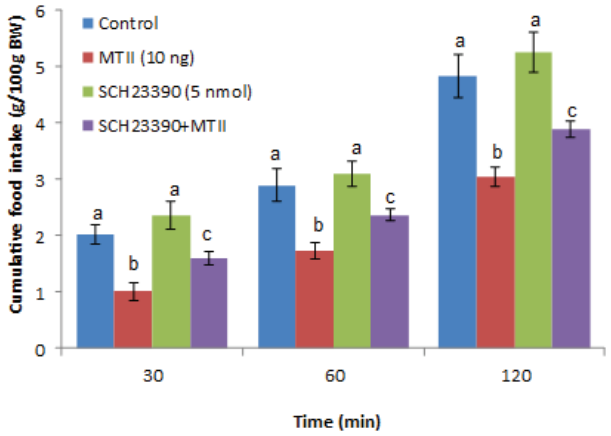

Figure 4.
Effect of intracerebroventricular injection of SCH23390 (D1 receptor antagonist) on hypophagia-induced by MTII (MC3/MC4 receptors agonist) in the neonatal layer chickens. Data are expressed as mean ± SEM. Different letters (a, b, and c) indicate significant differences between treatments at each time($p < 0.05$).

MTII in the chickens at 30, 60, and 120 min following the injection ($p < 0.05$) (Fig. 4).

In experiment No. 5, in comparison with the control group ($p > 0.05$), the MTII (10 ng) ICV injection greatly reduced food intake ($p < 0.05$), whereas the AMI-193 (5 nmol) ICV injection alone has no significant effects on the cumulative food intake. The MTII + AMI-193 co-injection greatly suppressed hypophagia induced by MTII in comparison with the control group ($p < 0.05$) (Fig. 5).

In experiment No. 6, in comparison with the control group ($p > 0.05$), the MTII (10 ng) ICV injection greatly reduced food intake ($p < 0.05$), whereas the NGB2904 (6.4 nmol) ICV injection has no significant effects on the cumulative food intake. Furthermore, the MTII + NGB2904 co-injection did not significantly affect hypophagia induced by MTII in the chickens ($p > 0.05$) (Fig. 6).

In experiment No.7, in comparison with the control group ($p > 0.05$), the MTII (10 ng) ICV injection greatly reduced food intake in the 3-h food-deprived layer chickens ($p < 0.05$), whereas the L-741,742 (6 nmol) ICV injection has no significant effects on the cumulative food intake. Furthermore, the

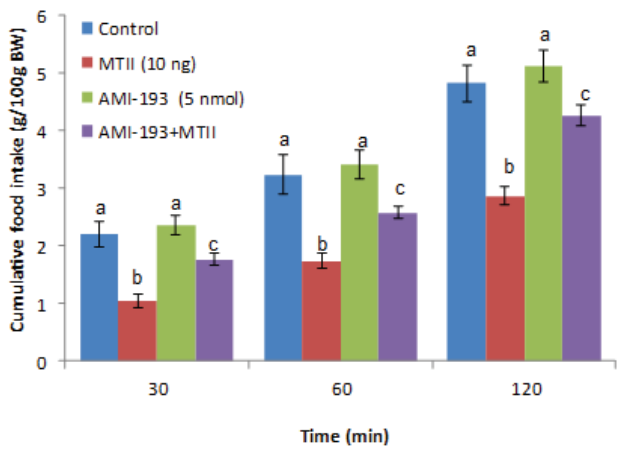

Figure 5.
Effect of intracerebroventricular injection of AMI-193 (D2 receptor antagonist) on hypophagia-induced by MTII (MC3/MC4 receptors agonist) in the neonatal layer chickens. Data are expressed as mean ± SEM. Different letters (a, b, and c) indicate significant differences between treatments at each time($p < 0.05$).

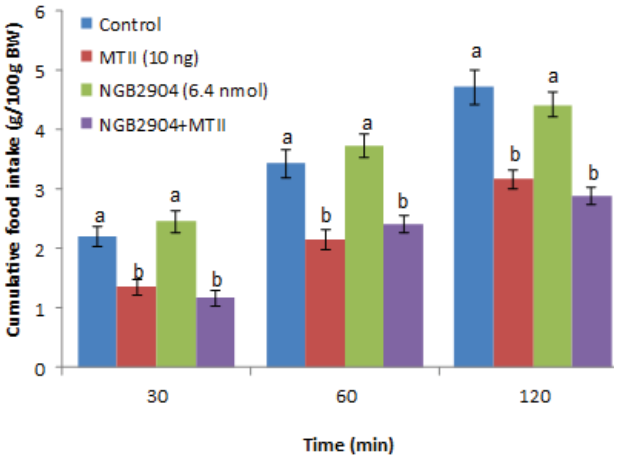

Figure 6.
Effect of intracerebroventricular injection of NGB2904 (D3 receptor antagonist) on hypophagia-induced by MTII (MC3/MC4 receptors agonist) in the neonatal layer chickens. Data are expressed as mean ± SEM. Different letters (a and b) indicate significant differences between treatments at each time($p < 0.05$).

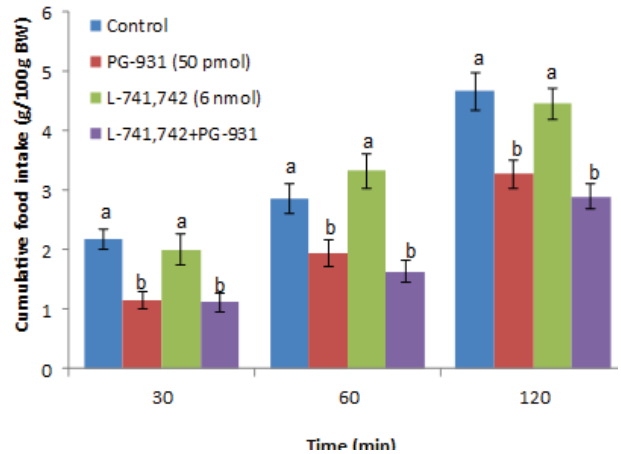

Figure 7.
Effect of intracerebroventricular injection of L-741,742 (D4 receptor antagonist) on hypophagia-induced by MTII (MC3/MC4 receptors agonist) in the neonatal layer chickens. Data are expressed as mean ± SEM. Different letters (a, b, and c) indicate significant differences between treatments at each time($p < 0.05$).

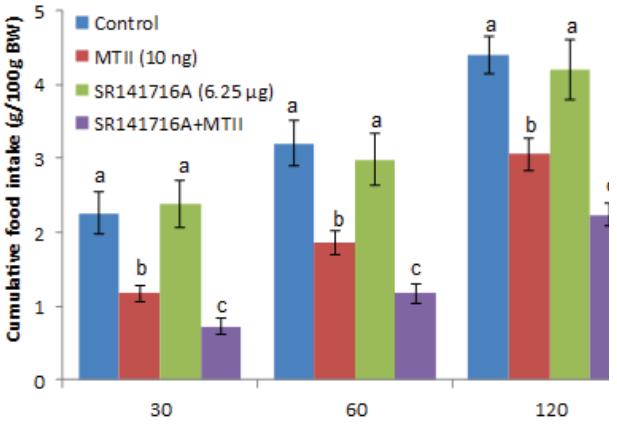

Figure 8.
Effect of intracerebroventricular injection of SR141716A (CB1 receptor antagonist) on hypophagia-induced by MTII (MC3/MC4 receptors agonist) in the neonatal layer chickens. Data are expressed as mean ± SEM. Different letters (a, b, and c) indicate significant differences between treatments at each time($p < 0.05$).

MTII+L-741,742 co-injection did not significantly affect MTII induced hypophagia in the neonatal layer chickens ($p > 0.05$) (Fig. 7).

As shown in Figure 8 (experiment No.8), in comparison with the control group ($p > 0.05$), the MTII (10 ng) ICV injection greatly reduces food intake ($p < 0.05$), whereas the SR141716A (6.25 µg) ICV injection has no significant effects on the cumulative food intake. In addition, the MTII+SR141716A co-injection greatly increased hypophagia-induced by MTII in comparison with the control group ($p < 0.05$) (Fig. 8).

In experiment No.9, in comparison with the control group ($p > 0.05$), MTII (10 ng) ICV injection greatly reduced food intake ($p < 0.05$). Also, the AM630 (5 µg) ICV injection has no significant effects on the cumulative food intake. Furthermore, the MTII + AM630 co-injection did not significantly affect hypophagia induced by MTII in 3-h food-deprived neonatal layer chickens ($p > 0.05$) (Fig. 9).

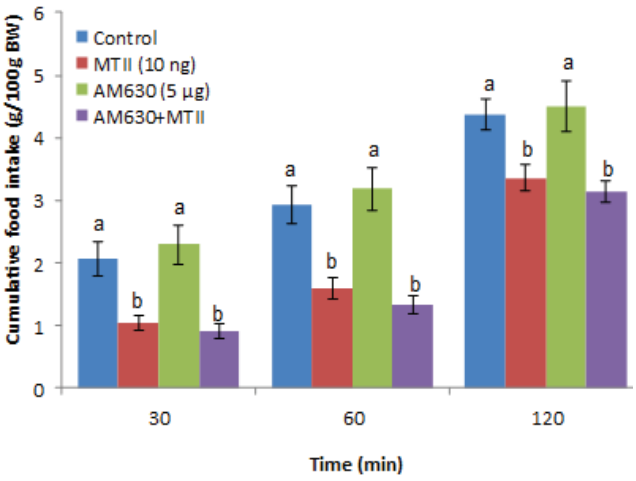

Figure 9.
Effect of intracerebroventricular injection of AM630 (CB2 receptor antagonist) on hypophagia-induced by MTII (MC3/MC4 receptors agonist) in the neonatal layer chickens. Data are expressed as mean ± SEM. Different letters (a and b) indicate significant differences between treatments at each time ($p < 0.05$).

Discussion

This research aimed to see how the melanocortin interacts with the dopaminergic and cannabinoidergic mechanisms to affect food intake in the neonatal layer chickens. As far as we know, this is the first study conducted to show how central melanocortin-induced hypophagia interconnect with these mechanisms in layer chickens. The results demonstrated dose-dependent hypophagia following the MTII (2.5, 5, and 10 ng) ICV injection in the 3-h food-deprived neonatal layer chickens. According to Ahmadi et al. [29, 30], the MTII (2.5, 5, and 10 ng) ICV injection reduces feeding behaviors in neonatal meat-type chickens in a dose-dependent manner. The MC3/4R activation reduces feeding behavior in rodents, while the MC3/4R antagonist ICV injection increases food intake [31]. Although both MC3R and MC4R are expressed in the rat brain, only MC4R appears to be found in the bird's brain [32]. A group of peptides known as melanocortin includes adrenocorticotropic hormone (ACTH) and various types of POMC-derived α-MSH in the pituitary gland.

[33]. POMC and α-MSH contribute to food intake regulation, of which; the latter is a key endogenous ligand for MC3R and MC4R in the arcuate nucleus [34, 35]. Also, the agouti-related protein (AgRP) is a natural antagonist of MC3R and MC4R, which is often co-expressed with neuropeptide Y(NPY), and the α-MSH effects can be suppressed by their co-injection [18]. Despite the identification of melanocortin-related signaling pathways regulating mammals' central food intake, little is known about melanocortin in birds [36]. According to the literature, hypophagia induced by MTII seems to be weakened with a protein kinase A (PKA) inhibitor [37].

The MTII+L-DOPA co-injection increased hypophagia induced by MTII in the chickens. The MTII+6-OHDA co-injection greatly suppressed hypophagia induced by MTII in the chickens. Also, co-injection of MTII+D1 receptors antagonist greatly suppressed hypophagia induced by MTII in the chickens. The co-injection of MTII+D2 receptors antagonist greatly suppressed hypophagia induced by MTII. Food intake reduces through D1 and D2 receptors in rats [13]. Besides, the D1 receptors mediate hypophagia induced by dopamine in the chickens, whereas others (D2-D4) may not be involved in appetite regulation of meat-type chickens [1]. Melanocortin acts through MC4R on mesolimbic dopamine pathways on feeding behavior and motivation to food intake suppressed in rats by the MCR agonist ICV injection into the ventral tegmental area containing dopaminergic neurons [38]. However, this effect is reversed by the SHU9119 (MCR antagonist) ICV injection [38]. The anorexigenic and orexigenic effects of α-MSH and AgRP were blocked completely, respectively, by the nonselective α-flupenthixol (dopamine antagonist), reflecting dopamine signaling pathways are involved in the regulating melanocortin peptides and AgRP effects [39]. The process includes dopaminergic neurons in the ventral tegmental area, responsible for the effects of reward and reinforcement, and MC4R expressing neurons in the nucleus accumbens [39]. MC4R regulates D1 and D2 neurons in the nucleus accumbens and is elicited to consume sweet foods [20]. Activation of dopaminergic neurons in the ventral tegmental area by melanocortin and D1

and D2 neurons of the nucleus accumbens suppresses the dopamine-mediated feeding behavior [21]. In the ventral tegmental area, both MC3R and MC4R are expressed in dopaminergic neurons innervated by POMC-expressing neurons in the arcuate nucleus [21]. Data on the colocalization of dopamine and MCR in neurons for their regulatory role in appetite regulation and food intake support the melanocortin-dopamine interactions [40]. In this regard, Yoon and Baik [41] reported that MC4R and D2 receptors in the hypothalamic area are responsible for food intake and control of energy homeostasis.

Based on the results, co-injection of MTII + CB1 receptors antagonist increased hypophagia induced by MTII while CB2 receptors had little effect on hypophagia induced by MTII in the neonatal layer chickens. Food intake increases through both CB1 and CB2 receptors in the layer chickens, similar to mammals [7, 41, 43], but not in broilers where only the CB2 receptors interact on feeding [8, 9]. The SR141716SA or AM251 ICV injection reduced food intake in normal mice but not in CB1 knockout mice, indicating that the endocannabinoids contribute to appetite by activating CB1 receptors [41]. Also, AM251 has been shown to decrease food intake in food-restricted rats [15]. In the present study, the potential effect of SR141716A (an analog of AM251) was examined on food intake in 3-h food-deprived birds. Based on the evidence, an interaction exists between melanocortin and cannabinoidergic mechanisms on feeding behavior through MC4R and CB1 receptors [44]. SR141716 and α-MSH weakened food intake, and ICV injection of sub-effective doses of SR 141716 and α-MSH weakened baseline food intake synergistically [44]. Both cannabinoid and melanocortin receptors localized in the hypothalamus and administration of THC, SR141716, and MTII lead to c-fos expression, a marker of neural activation [44]. Despite direct cellular mechanisms underlying the interconnection of these systems, it is assumed that they may interact at the signal transduction by increasing cAMP synthesis through an effect on Gi proteins. GPCRs include cannabinoids and melanocortin, and blockade of CB1 receptors and stimulation of MC4R enhance cAMP production [45]. Additionally, it is assumed that synergistic interaction between the cannabinoidergic and melanocortin mechanisms is mediated by the opioidergic system [44]. Also, leptin synoptically interacts with the melanocortinergic neurons, while cannabinoid and NPY systems are modulated by the melanocortin system. Thus, signaling by melanocortin receptor seems to be downstream of leptin receptors and upstream of the endogenous cannabinoid, NPY, and opioid-producing neurons. Given the approximate 300 million years of evolutionary distance between mammals and birds, it is not surprising that the differences in the central food intake and energy expenditure regulation have been identified [9].

In conclusion, these results indicated that melanocortin-induced hypophagia is mediated through D1, D2, and CB1 receptors in the neonatal layer chickens. In a rat model, many studies have been conducted on the central regulation of food intake. It is well established that the central food intake regulation differs in mammals and birds [14]. As a result, it is reasonable to believe that regulatory systems in birds manage these processes [10]. As shown, there has never been a study on the melanocortin interconnection with dopaminergic and cannabinoidergic mechanisms on food intake in birds. Therefore, the authors could not compare the results. This data can be seen as a starting point for learning about the central regulation of feeding behavior in chickens.

Materials & Methods

Animals

A total of 396 one-day-old layer chickens (Hy-Line) were purchased from a local hatchery (Morghak Co., Iran). Birds were kept in stabilizing electrically heated batteries at a temperature of 32 °C ± 1, with a relative humidity of 40-50% and a 23:1 lighting/dark period [22]. They were held as flocks for two days, and then a single cage was allocated per bird randomly. During the study, the birds were fed with a commercial diet comprising 2850 kcal/kg metabolizable energy and 21% crude protein, with unlimited access to diet and freshwater (Chineh Co., Iran). The 3-h food-deprived was applied before the injections, while the birds had unlimited access to water. ICV injections were performed at five days of age. Animal handling and experimental practices were carried out in accordance with the Guide for the Care and Use of Laboratory Animals, National Institutes of Health, USA (publication No. 85-23, revised 1996) and existing Iranian government animal welfare regulations, which were approved by the Institutional Animal Ethics Committee (IAEC), Faculty of Veterinary Medicine, University of Tehran.

Experimental medications

The used medications, including MTII (MC3 and MC4 receptors), SCH 23390 (D1 receptor antagonist), AMI-193 (D2 receptor antagonist), NGB2904 (D3 receptor antagonist), L-741,742 (D4 receptor antagonist), L-DOPA (precursor of dopamine), 6-OHDA (6-hydroxy dopamine), SR141716A (CB1 receptor antagonist), AM630 (CB2 receptor antagonist), and Evans blue were purchased from Sigma-Aldrich (USA) and Tocris Co (UK). All of the medications were first dissolved in absolute dimethyl sulfoxide (DMSO) and then diluted with 0.85% saline containing Evans blue with a ratio of 1/250 (0.4% DMSO). The resulting mixture containing Evans blue-contained DMSO/saline mixture was utilized as a control group.

ICV injection protocol

Birds were randomly divided into nine study groups, each with four sub-groups (n = 44). The chickens were weighed and divided into study groups concerning their body weight before each experiment, ensuring that the mean body weight between treatment groups was as standardized as possible. The chickens

were ICV injected once in each of the experiments by applying a microsyringe (Hamilton, Switzerland) with no anesthesia, as defined by Davis et al. [23] and Furuse et al. [24]. According to Van Tienhoven and Juhasz [25], the head of the chickens was held with an acrylic device with a 45º bill holder and a calvarium parallel to the table surface. The right lateral ventricle's skull was pierced using an orifice plate. When a microsyringe was inserted into the ventricle through the orifice plate, the injected needle tip was just 4 mm under the skull skin [26]. All injections were performed in a volume of 10 µL [27]. The control group received control solution (10 µL) [27]. In newly hatched chickens, this method causes no physiological stress [28]. The chickens were sacrificed by decapitation at the end of trials to demonstrate injection accuracy confirmed by Evans blue and sliced frozen brain tissues. Although birds in each of the groups were given injections, only the data for those who had dye in their lateral ventricle were analyzed (11 chickens per group). All experiments were conducted from 08:00 a.m. to 1:30 p.m.

Feeding experiments

To examine the potential effect of specific dopaminergic (D1, D2, D3, and D4) and cannabinoidergic (CB1 and CB2) receptors on the melanocortin-induced feeding behavior in the 3-h food-deprived newly hatched chickens, nine experiments were conducted. In experiment No.1, the control solution and MTII (MC3 and MC4 receptors; 2.5, 5, and 10 ng) were injected into chickens. In experiment No.2, control solution, L-DOPA (125 nmol), MTII (10 ng), and a combination of them were injected intracerebroventricularly. In experiment No.3, the 3-h food-deprived birds were intracerebroventricularly injected with a control solution, 6-OHDA (150 nmol), MTII (10 ng), and 6-OHDA + MTII co-injection. In experiment No.4, the 3-h food-deprived layer chickens were intracerebroventricularly injected with control solution, SCH23390 (5 nmol), MTII (10 ng), and received the SCH23390+MTII co-injection. In experiment No.5, the control solution, AMI-193 (5 nmol), MTII (10 ng), and a combination of them were intracerebroventricularly injected into the birds. In experiment No.6, chickens were intracerebroventricularly injected with control solution, NGB2904 (6.4 nmol), MTII (10 ng), and NGB2904 + MTII. In experiment No.7, control solution, L-741,742 (6 nmol), MTII (10 ng), and L-741,742 + MTII were injected. In experiment No.8, the 3-h food-deprived birds were intracerebroventricularly injected with control solution, SR141716A (6.25 µg), MTII (10 ng), and SR141716A+MTII. In experiment No.9, control solution, AM630 (5 µg), MTII (10 ng), and AM630 + MTII were injected. Immediately following the injection, food was provided to the birds, and cumulative food intake (g) was measured at 30, 60, and 120 min following the injection. Food intake (g) was calculated as percent of body weight (g/100g BW) to minimize the effect of body weight on the amount of food intake. The doses of medications were determined according to the previous studies [4, 10, 29, 30].

Statistical analysis

In this study, nine experiments were designed. Each experiment included four groups (I-IV). In all groups, a sole injection was done. Also, the result of each experiment was apart from the other experiments. Cumulative food intake (as a percent of body weight) from each experiment was analyzed by repeated measure two-way analysis of variance (ANOVA). All analyses were conducted using SPSS 16.0 for Windows (SPSS, Inc., Chicago, IL, USA). Means were compared by Tukey Kramer test ($p < 0.05$), and data was presented as mean ± SEM (standard error of the mean).

Research involving human participants and/or animals

This manuscript does not contain any studies with human subjects performed by any of the authors. According to the Guide for the Care and Use of Laboratory Animals, all experiments were executed and were approved by the institutional animal ethics committee.

Authors' Contributions

All authors provided critical feedback and helped shape the research, analysis and manuscript.

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Competing Interests

Authors have no potential conflicts of interest.

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