

Role of cannabinoidergic system on food intake in neonatal layer-type chicken

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Abstract Central regulatory mechanisms for neurotransmitters of food intake vary among animals. Endocannabinoids have crucial role on central food intake regulation in mammals but its role has not been studied in layer-type chicken. Thus, in this study 6 experiments designed to evaluate effects of intracerebroventricular (ICV) administration of 2-AG (2-Arachidonoylglycerol, selective CB₁ receptors agonist), SR141716A (selective CB₁ receptors antagonist), JWH015 (selective CB₂ receptors agonist), AM630 (selective CB₂ receptors antagonist) on feeding behavior in 3 h food deprived neonatal layer-type chickens. In experiment 1, birds ICV injected with control solution and 2-AG (0.25, 0.5 and 1 µg). In experiment 2: control solution, SR141716A (6.25, 12.5 and 25 µg) were ICV injected to birds. In experiment 3 animals received: control solution, SR141716A (6.25 µg), 2-AG (1 µg) and co-injection of SR141716A+2-AG. In experiment 4, chickens received control solution and JWH015 (6.25, 12.5 and 25 µg). In experiment 5, control solution and AM630 (1.25, 2.5 and 5 µg) were injected. In experiment 6, the birds received control solution, AM630 (1.25 µg), JWH015 (25 µg) and co-administration of AM630+JWH015. Then, cumulative food intake was recorded until 120 min after injection. According to the results, 2-AG dose dependently increased cumulative food intake while SR141716A reduced appetite compared to control group ($P<0.05$). Injection of 2-AG (1 µg) amplified food intake

and its effect minimized by SR141716A (6.25 µg) ($P<0.05$). Also, ICV injection of JWH015 (25 µg) dose dependently increased food intake and co-injection of JWH015+AM630 decreased JWH015-induced food intake ($P<0.05$). These results suggest CB₁ and CB₂ receptors have an important role on ingestive behavior in FD₃ neonatal layer-type chicken.

Keywords Endocannabinoids · Food intake · Layer-type Chicken

Introduction

Several factors with complicated neurological mechanisms are responsible for food intake regulation in animals (Levine 2006). Feeding behavior is modulated by neurochemical mediators known as neurotransmitters in several parts of the brain such as striatum, hypothalamus, amygdala, nucleus tractus solitaries (NTS) and arcuate nucleus (ARC) (Parker et al. 2014).

Cannabinoids are originally known as psychoactive ingredients of marijuana (Δ_9 -tetrahydrocannabinol, THC) (Novoseletsky et al. 2011). It has been used as medication and recreational purposes for thousands of years (Di Marzo et al. 2001). The endocannabinoids (ECBs) are derivatives of arachidonic acid, resembling other lipid transmitters such as prostaglandins or leukotrienes. ECBs are conjugated with ethanolamine to form fatty acid amides or with glycerol to generate monoacylglycerols, *N*-arachidonylethanolamine (anandamide, AEA), 2-arachidonoylglycerol (2-AG) (D'Addario et al. 2014). In the central nervous system (CNS) and peripheral tissues, 2-AG and AEA, the ECBs ligands were identified (López 2010). To date, two cannabinoid (CB) receptors have been cloned: CB₁ and CB₂ both belong to G-protein coupled

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receptors (GPCRs) (Sharkey et al. 2014). CB₁ receptors are expressed abundantly in the CNS. CB₂ receptors are plentiful in peripheral nervous system (PNS), immune cells and tissues (Pertwee 2005) but also identified in the brain (Onaivi et al. 2012). It is reported EBCs regulate several physiological functions such as pain relief, thermoregulation and hypotension, motor control, learning and memory formation (Sanudo-Pena et al. 2000; Di Marzo et al. 2001).

So far, several researches done to determine effect of neurotransmitters on feeding behavior in mammals, but aspects of food intake regulation in avian still unclear (Zendehdel and Hassanpour 2014). Given the estimated 300 million years of evolutionary distance between mammals and avians, it is not surprising that significant differences have been found in the activities of a number of components involved in the regulation of energy homeostasis (Novoseletsky et al. 2011). For example, ICV injection of μ -opioid receptors agonist decreased food intake in chicks (Bungo et al. 2005; Alimohammadi et al. 2015) but increased in rat (Le Merrer et al. 2009; Kaneko et al. 2012). For instance, ghrelin, is an orexigenic peptide in rat (Wren et al. 2000; Kaiya et al. 2011) while known as an anorexigenic neurotransmitter in birds (Saito et al. 2005; Zendehdel and Hassanpour 2014; Zendehdel et al. 2013). Furthermore, interestingly comparative physiological studies suggested there are differences on appetite regulation pathways between the meat-type (broiler) and layer-type (hens) chickens (Denbow 1994; Shiraiishi et al. 2011).

In the ARC nucleus of hypothalamus, neuropeptide Y (NPY)/agouti related protein (AgRP) and pro-opiomelanocortin (POMC) and cocaine/amphetamine regulated transcript (CART) are the main sites which regulate appetite. NPY and AgRP neurons have orexigenic effect of in mammalian. Interestingly, AgRP increased cumulative food intake by layer but not by broiler chicken (Saneyasu et al. 2011).

Following the detection of ECBs and CB receptors in the prefrontal cortex (PFC), amygdala, septohippocampal system, nucleus accumbens (NAcc), hypothalamus and ARC associated with ingestive behavior (Di Marzo et al. 2001) researchers proved the involvement of CBs in central food intake regulation (Wiley et al. 2012). ICV administration of CB agonists stimulated food intake in rodents while SR141716A (selective CB₁ receptors antagonist) or AM251 (CB₁ cannabinoid receptors inverse agonist) decreased food consumption in rat (Chen et al. 2006). Little is known about the role of ECBs on feeding behavior in domestic fowl. Scarce reports exist on effects of CB₁ receptors in chicken. It is reported CB₁ receptors involved in memory recall in chicks (Adam et al. 2008) and might have no role on food intake in neonatal broilers (Emadi et al. 2011). In a sole study, Novoseletsky et al. (2011) reported intravenous injection of AM251 (inverse

CB₁ receptors agonist) leads to transient attenuation on food intake in meat-type chicken.

Most of the present knowledge regarding on behavioral effects of CBs on food intake has been derived from studies in mammalian species. On the basis of comparative physiology it is important to determine the role of ECBs in other species. No report exists on involvement of the CBergic system on food intake regulation and energy balance in neonatal layer-type chicken. Therefore, the possible contribution of CB₁ and CB₂ receptors on reward and consumption behavior will employ in the layer industry to enhance hen's productivity by manipulating appetite and lessen malnutrition concerns. So, the objective of this study was to assess role of the CBergic system on feeding behavior in 3 h food deprived (FD₃) neonatal layer-type chicken.

Materials and methods

Animals

In this study to determine role of central the CBergic system on food intake, 288 day-old layer-type (Hy-Line) chickens were used (Morghak Co. Iran). Animal handling and experimental procedures were performed according to the Guide for the Care and Use of Laboratory animals by the National Institutes of Health (USA) and the current laws of the Iranian government for animal care. Birds at first were kept for 2 days as flocks. Then, randomly distributed into individual cages at a temperature of 30±1 °C with 50±2 % humidity until 5 days of age (Olanrewaju et al. 2006). A mesh diet contains 21 % crude protein and 2850 kcal/kg of metabolizable energy (Chineh Co. Iran) were provided for animals. During the study birds had ad libitum access to food and fresh water. A 3-h prior the intracerebroventricular (ICV) injections, animals were food deprived (FD₃) but given free access to water. ICV injections were done on day 5 of age.

Experimental drugs

2-AG (2-Arachidonoylglycerol, a selective CB₁ receptors agonist), SR141716A (a selective CB₁ receptors antagonist), JWH015 (a selective CB₂ receptors agonist), AM630 (a selective CB₂ receptors antagonist) and Evans blue were purchased from Sigma Co. (Sigma, USA). Drugs except 2-AG at first dissolved in absolute dimethyl sulfoxide (DMSO) then diluted with 0.85 % saline containing Evans blue at a ratio of 1/250. 2-AG dissolved in 0.1 % Evans blue solution which was prepared in either 0.85 % saline.

ICV injection procedures

Before the initiation of the study, chickens were weighed and allocated into treatment groups based on their body weight. So, the mean body weight between treatment groups was as uniform as possible. In this study, 6 experiments (each includes 4 treatment groups within 11 replicates in each group; $n=44$ birds per experiment) designed to assume the role of central the CBergic system on food intake in layer-type chicken. ICV injections were done using a Microsyringe (Hamilton, Switzerland) without anesthesia in accordance to Davis et al. (1979) and Furuse et al. (1997). Briefly in this technique, head of the bird was held with an acrylic device which the bill holder was 45° and calvarium parallel to the surface of the table (Van Tienhoven and Juhasz 1962). A hole was drilled in a plate where the skull over the right lateral ventricle directly overlaid through this plate. For injection, the Microsyringe inserts into the right ventricle using this hole where the tip of the needle penetrated 4 mm beneath the skin of the skull. It is well documented there is no ICV injection induced physiological stress using this method in neonatal chicks (Saito et al. 2005). Each chick received an ICV injection (with vehicle or drug solution) in a volume of 10 μl . Right away after injection, FD_3 birds returned to their individual cages and supplied fresh water and food (pre-weighed). Cumulative food intake (gr) was measured at 30, 60 and 120 min post the injection. Food consumption was calculated as a percentage of body weight to minimize impact of body weight on the amount of food intake. Each bird just used once in each experimental group. At the end of the experiments, to recognize the accuracy of injection, chicks were sacrificed by decapitation and accuracy of placement of the injection in the lateral ventricle was verified by the presence of Evans blue followed by slicing the frozen brain tissue. In each group, 11 birds received injection, but just data of those individuals were used for analysis where dye was present in their lateral ventricle (8–11 chickens per group). All experimental procedures were done from 8:00 A.M. until 3:30 P.M.

Feeding experiments

Experiment 1 designed to investigate effect of CB_1 receptors agonist on food intake in FD_3 chickens where control group intracerebroventricularly injected with saline whereas other groups received an ICV injection of 2-AG at doses of 0.25, 0.5 and 1 μg , respectively. In experiment 2, effect of the CB_1 receptors antagonist was studied on appetite. FD_3 chickens received ICV injections as follows: control solution, SR141716A at doses of 6.25, 12.5 and 25 μg , respectively. In experiment 3, fasted chickens were ICV injected with control solution, SR141716A (6.25 μg), 2-AG (1 μg) and co-injection of SR141716A+2-AG. In experiment 4, effect of CB_2 receptors agonist on food intake was investigated where

injection groups received vehicle and JWH015 at levels of 6.25, 12.5 and 25 μg , respectively. In experiment 5, the birds received vehicle, AM630, a selective CB_2 receptors antagonist at doses of 1.25, 2.5 and 5 μg , respectively. In experiment 6, birds received ICV injection of control solution, AM630 (1.25 μg), JWH015 (25 μg) and co-injection of AM630+JWH015. These doses of drugs were determined according to the previous and our pilot studies (Chen et al. 2006; Irwin et al. 2008; Onaivi et al. 2008; Emadi et al. 2011; Novoseletsky et al. 2011).

Statistical analysis

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

Results

Effects of central the CBergic system on cumulative food intake in FD_3 neonatal layer-type chicks is shown in Figs. 1, 2, 3, 4, 5 and 6.

In experiment 1, ICV injection of 2-AG (a selective CB_1 receptors agonist, 0.25 μg) had no significant effect on cumulative food intake (% BW) in comparison with control group [$F(1,87)=3.12$, $P>0.05$]; but 0.5 and 1 μg of 2-AG in a dose-dependent manner increased cumulative food intake [$F(1,87)=98.42$, $P<0.01$] (Fig. 1).

In experiment 2, ICV injection of SR141716A (a selective CB_1 receptors antagonist) at levels of 12.5 and 25 μg but not 6.25 μg significantly increased food consumption compared to control group in chicken [$F(1,87)=124.07$, $P<0.01$] (Fig. 2).

In experiment 3, ICV injection of 2-AG (1 μg) significantly amplified food intake [$F(1,87)=179.65$, $P<0.01$]. Also, CB_1 receptors-induced hyperphagia diminished by co-injection of 2-AG and SR141716A (6.25 μg) [$F(1,87)=109.31$, $P<0.01$] (Fig. 3). Thus, it seems that CB_1 receptors have an important role on food intake control in layer-type chick.

According to the results of experiment 4, ICV injection of JWH015 (a selective CB_2 receptors agonist, 6.25 μg) had no significant effect on cumulative food intake (% BW) in comparison with control group [$F(1,87)=1.73$, $P>0.05$]; but levels of 12.5 and 25 μg doses dependently increased food intake [$F(1,87)=117.01$, $P<0.01$] (Fig. 4).

As seen in experiment 5, ICV injection of AM630 (at doses of 2.5 and 5 μg a selective CB_2 receptors antagonist) significantly induced hypophagia in FD_3 neonatal layer-type chicks

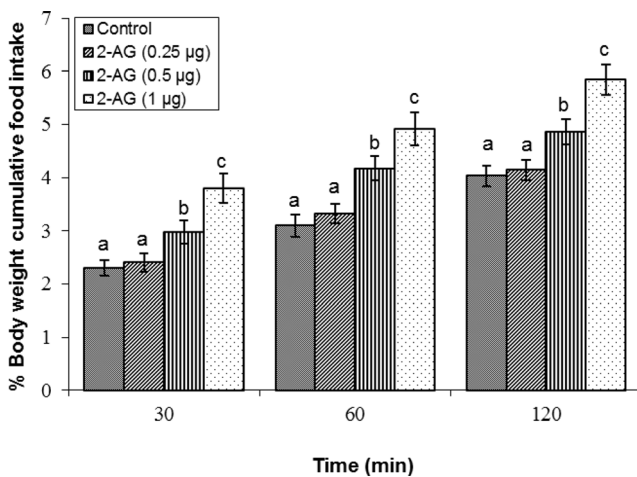


Fig 1 Effect of ICV injection of 2-AG on cumulative food intake (% BW) in neonatal layer type chicken. 2-AG: a selective CB₁ receptors agonist. There are significant differences between groups with different superscripts in a column (a, b and c; $P < 0.05$)

compared to control group at 30, 60 and 120 min after injection [$F(1,87) = 79.58, P < 0.01$] (Fig. 5). However, 1.25 µg of AM630 had no effect on food intake [$F(1,87) = 5.06, P > 0.05$] (Fig. 5).

In experiment 6, ICV injection of JWH015 (25 µg) significantly increased food intake compared to control group [$F(1,87) = 136.14, P < 0.01$]. However, Co-injection of AM630 (1.25 µg)+JWH015 significantly attenuated JWH015-induced hyperphagia in FD₃ layer-type chicken [$F(1,87) = 94.18, P < 0.01$] (Fig. 6).

Discussion

To our knowledge this paper is the first report on the specific role of CB₁ and CB₂ receptors on feeding behavior in neonatal

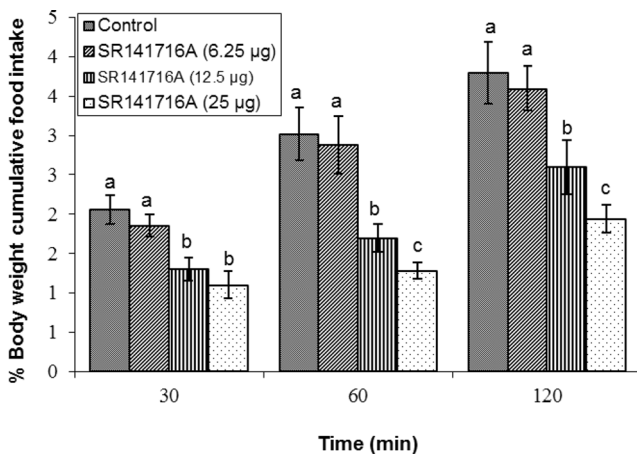


Fig 2 Effect of ICV injection of SR141716A on cumulative food intake (% BW) in neonatal layer type chicken. SR141716A: a selective CB₁ receptors antagonist. There are significant differences between groups with different superscripts in a column (a, b and c; $P < 0.05$)

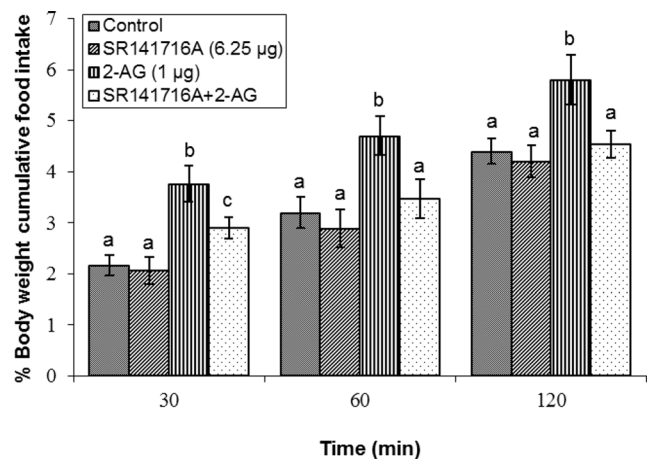


Fig 3 Effect of ICV injection of SR141716A (6.25 µg), 2-AG (1 µg) and their combination on cumulative food intake (% BW) in neonatal layer type chicken. 2-AG: a selective CB₁ receptors agonist; SR141716A: a selective CB₁ receptors antagonist. There are significant differences between groups with different superscripts in a column (a, b and c; $P < 0.05$)

layer-type chicken. Also, this study provides the first demonstration of hyperphagia induced by ICV injection of a selective CB₁ receptor agonist in layer-type chicks. More than 40 years passed from the isolation of specific CB receptors and several researches have done on the role of the CBergic system in the CNS but several physiologic roles of the CBergic system remains unclear. Evidences imply ECBS regulate several behavior and emotional states, such as food intake, pain, anxiety and go forth (López 2010).

Earlier studies had shown that pharmacological stimulation of CB receptors by systemic administration of plant-derived or ECBS stimulate eating and produce anabolic effects (D’Addario et al. 2014).

As observed in this study food intake increased via both CB₁ and CB₂ receptors layer-type chicks which was similar to

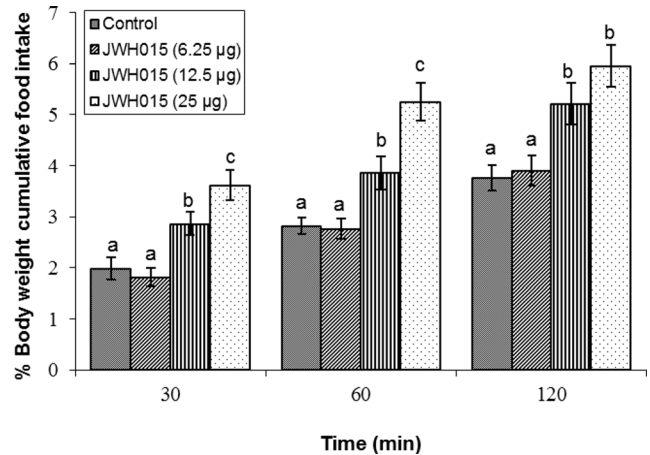


Fig 4 Effect of ICV injection of JWH015 on cumulative food intake (% BW) in neonatal layer type chicken. JWH015: a selective CB₂ receptors agonist. There are significant differences between groups with different superscripts in a column (a, b and c; $P < 0.05$)

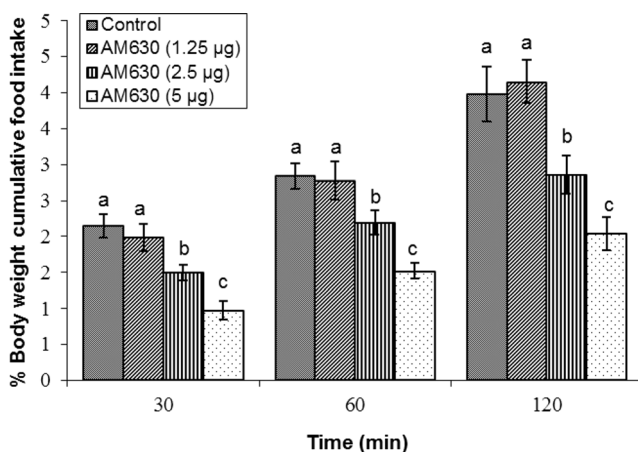


Fig. 5 Effect of ICV injection of AM630 on cumulative food intake (% BW) in neonatal layer type chicken. AM630: a selective CB₂ receptors antagonist. There are significant differences between groups with different superscripts in a column (*a*, *b* and *c*; $P < 0.05$)

mammals (Di Marzo et al. 2001; Chen et al. 2006; Wiley et al. 2012) but dissimilar to broilers which only CB₂ receptors interact on feeding (Emadi et al. 2011; Novoseletsky et al. 2011). ICV injection of SR141716SA or AM251 reduced food intake in normal mice, but not in CB₁ knockout mice where contributing to the role of the ECBs system on appetite by activating CB₁ receptors (Di Marzo et al. 2001). Also, AM251 has been shown to decrease food intake in food-restricted rats (Irwin et al. 2008). In the present study, we have evaluated the potential effect of SR141716A (an analogue of AM251) on food intake in FD₃ birds.

There are different between ECBs and other neurotransmitters. Almost all neurotransmitters are water-soluble and stored in high concentrations in vesicles. In depolarization, neurotransmitter release from the presynaptic terminal into the synaptic cleft and binds to its specific receptors on postsynaptic

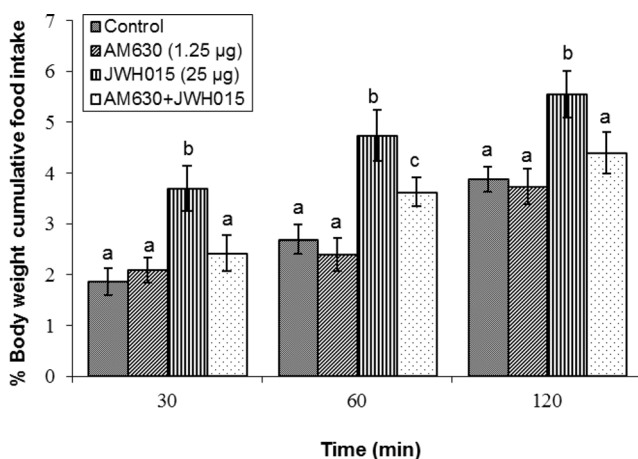


Fig. 6 Effect of ICV injection of AM630 (1.25 µg), JWH015 (25 µg) and their combination on cumulative food intake (% BW) in neonatal layer type chicken. AM630: a selective CB₂ receptors antagonist; JWH015: a selective CB₂ receptors agonist. There are significant differences between groups with different superscripts in a column (*a*, *b* and *c*; $P < 0.05$)

neuron (Nicoll and Alger 2004). In mammals and birds, CB₁ receptors are expressed in presynaptic terminals of both inhibitory and excitatory nerves (Sharkey et al. 2014). ECBs are synthesized in postsynaptic neurons and binds to CB receptors on the presynaptic membrane. These receptors belong to G protein, inhibits Ca²⁺ influx which decreases the release of other neurotransmitters (Williams and Kirkham 2002). Additionally, CB₁ receptors may interact at the signal transduction mechanism with cyclic adenosine monophosphate (cAMP) where SR141716A increase cAMP synthesis via an effect on G_i proteins (Verty et al. 2004). In the brain, the ECB system tonically reinforces food consumption by interacting with the mesolimbic pathways engaged in reward mechanisms (D'Addario et al. 2014). Interconnections reported between ECBs with orexigenic and anorexigenic neurotransmitters (Chen et al. 2006; Tedesco et al. 2008; Alimohammadi et al. 2015; Zendehdel et al. 2015). Ventromedial, dorsomedial and lateral hypothalamus, together with paraventricular and ARC nuclei are the hypothalamic areas involved in food intake control. In such a framework, these regions are interconnected by the neuronal pathways with other neurotransmitters. Recent studies have found ECBs reinforces release of orexigenic neurotransmitters on these areas (D'Addario et al. 2014). Numerous hypotheses have been postulated to explain the mechanisms underlying the direct action for how ECBs regulates food intake, despite accuracy of these theories remain unclear. One of the suggested pathways is that ECBs via CB₁ receptors modulate signaling in POMC neurons, anorexigenic neurotransmitter in the ARC (Hentges et al. 2005). However, in this study, POMC level was not measured after ICV injection of CBs receptors agonists or antagonists. Presumably, CB₁ receptors impress their hyperphagic role by blocking POMC neurons in the ARC nucleus (D'Addario et al. 2014). In our opinion, additional studies will uncover possible interconnection(s) in layer-type chicken. Also, CB₁ receptors are expressed in presynaptic terminals of excitatory nerves (Sharkey et al. 2014). ICV injection of the AEA or CB₁ receptors increases NPY levels (Verty et al. 2004; Gamber et al. 2005; Lim et al. 2010). C-Fos expression increases by ICV injection of CB₁ receptors in the lateral hypothalamus, suggesting the existence of a connection on hypothalamus feeding centers (Soria-Gomez et al. 2007). Therefore, the CBergic system not only modulates neurotransmitter release, but it may also influence the expression and/or release of other feeding related neurotransmitters (Emadi et al. 2011). Of particular new findings of the current study is that CB₁ receptors play important role on food intake regulation in layers compared to cockerels. Layer has indirectly been selected for slow growth and low body weight while broilers have been genetically selected for rapid muscle and body weight gain. Genetic selection altered chicken's brain neurological pathways associated with food intake (Richards 2003). Broilers have higher feed consumption, basal metabolic rate and energy

expenditure, possibly because of a genetically altered mechanism of food intake control (Denbow 1994). For example, brain AMP-activated protein kinase (AMPK) systems response to food intake regulation altered because of genetic selection among domestic fowl (Pingwen et al. 2011). This inconsistency may be due to the differences in localization, affinity or expression of CB₁ receptors in layer- and meat-type chicks (Emadi et al. 2011; Novoseletsky et al. 2011). In this study, we were not able to find information about alteration on CB receptors in meat- and layer-type chickens. The mechanisms by which CB₁ receptors influence the food intake in layer chicks have still to be explored in much greater detail.

There are no reports on effect of CB₂ agonist, JWH015, on food intake in neonatal layer-type chicken. Despite researches showed CB₂ receptor is expressed mainly in the immune system, but they are cloned from brain derived immune cells (Van Sickle et al. 2005). It is now believed CB₂ receptors carry out important functions in the brain. In this study hyperphagia observed after ICV injection of CB₂ receptors agonist in FD₃ neonatal layer-type birds. Previously, Emadi et al. (2011) reported food intake increases following ICV injection of CB₆₅ (a CB₂ receptors agonist) in FD₃ neonatal broiler chicken. Following 12-h food deprivation, peripheral injection of AM630 (selective CB₂ receptors antagonist) stimulated appetite in rat (Onaivi et al. 2008). There is only one research describing the presence of a CB₂-like protein in the CNS of chicken embryos, which disappears in adult chicken (Fowler et al. 2001). Perhaps observed effect of CB₂ receptors might relate to indirect effects of these receptors on the digestive system (Emadi et al. 2011). Stimulation of CB₂ receptors reduces inflammatory response by suppressing brain microglial activation (Ehrhart et al. 2005). In the current study, we focused on the role of central the CB₂ system on feeding behavior in chicken. Evidence indicated ECBs promote food intake through peripheral sites (Galiegue et al. 1995). Although the mechanisms whereby the cannabinoids influence food intake remains unclear, results suggest that the CB system will be an important target in future studies in obesity. The authors recommend further research needed to clarify any direct cellular and molecular signaling pathway on appetite regulation in layer-type chicken.

Conflict of interest Abbas Alizadeh, Morteza Zendehtdel, Vahab Babapour, Saeed Charkhkar and Shahin Hassanpour declare that they have no conflict of interest.

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

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

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