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Interconnection between adrenergic and dopaminergic systems on feeding behavior in neonatal chicks

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Abstract

Central dopamine and adrenergic systems have prominent role on appetite regulation but their interaction(s) have not been studied in neonatal layer chicken**.** So, the aim of the current study was to determine interaction of the central dopaminergic and noradrenergic systems on food intake regulation in neonatal layer chicken. In experiment 1, chicken intracerebroventricular (ICV) injected with control solution, parazosin (α_1 adrenergic receptor antagonist, 10nmol), dopamine (40nmol) and parazosin+dopamine. Experiments 2-5 were similar to experiment 1, except birds injected with yohimbine (α_2 receptor antagonist, 13nmol), metoprolol (β_1 adrenergic receptor antagonist, 24nmol), ICI 118,551 (β_2 adrenergic receptor antagonist, 5nmol) and SR59230R (β_3 adrenergic receptor antagonist, 20 nmol) instead of the parazosin. In experiment 6, chicken ICV injected with control solution and noradrenaline (NA; 75, 150 and 300 nmol). In experiment 7, birds injected with control solution, SCH23390 (D_1 dopaminergic receptor antagonist, 5 nmol), NA (300nmol) and SCH23390+NE. In experiment 8, control solution, AMI-193 (D_2 dopaminergic receptor antagonist, 5nmol), NA (300nmol) and AMI-193+ NA was injected. Then, cumulative food intake was recorded at 30, 60 and 120 min after injection. According to the results, ICV injection of the dopamine (40nmol) significantly decreased food intake in comparison to control group (P<0.05). Co-injection of the yohimbine plus dopamine significantly amplified dopamine-induced hypophagia in neonatal chicken (P <0.05). Also, co-administration of the ICI 118,551+dopamine significantly inhibited hypophagic effect of dopamine in neonatal chicken (P <0.05). Furthermore, noradrenaline (75, 150 and 300 nmol) significantly decreased food intake in a dose dependent manner (P <0.05). Co-injection of the

SCH23390+NA decreased hypophagic effect of the NA in neonatal chicken compared to control group (P <0.05). Co-injection of the AMI-193+ NA diminished noradrenaline-induced hypophagia compared to control group (P <0.05). These results suggested an interconnection exists between central dopaminergic and noradrenergic systems through α_2/β_2 adrenergic and D_1/D_2 dopaminergic receptors on food intake regulation in neonatal chicks.

Keywords: Dopamine, Adrenergic, Food intake, Layer chicken

INTRODUCTION

Appetite regulation is one of the complex aspects in animals. It modulates in several parts of the brain cooperate with signals from the peripheral organs (Sharkey et al., 2014). In the central nervous system (CNS) the appetite controls by diverse neurotransmitters via complex neurological pathways (Parker et al., 2014). The NA is a catecholamine neurotransmitter in the CNS (Tachibana et al., 2009). The NA has two major receptors α adrenergic (α_1 and α_2) and β adrenergic (β_1, β_2 and β_3) receptors (Lei, 2014). The brain adrenergic system has key role in appetite regulation and energy expenditure in mammals and avian (Bungo et al., 1999). ICV injection of the NE into the paraventricular nucleus (PVN) increase food intake in domestic fowl (Denbow and Sheppard, 1993). ICV injection of the NE or clonidine (α_2 receptor agonist) increase food intake and this effect inhibited by α_2 receptor antagonist (yohimbine) not by α_1 receptor antagonist (prazosin) (Wellman et al., 1993). ICV injection of clonidine increased food intake in broilers (Bungo et al., 1999). ICV administration of the NE had no effect on feeding behavior in layers (Denbow et al., 1981). ICV injection of salbutamol (β_2 adrenergic receptor agonist) decreased cumulative food intake in rats (Kanzler et al., 2011). ICV injection of the isoproterenol (β_1 and β_2 adrenergic receptor agonist) decreased food and water intake in broilers, respectively (Baghbanzadeh et al., 2010).

Dopamine (DA) is a main catecholamine neurotransmitter in the brain and plays a crucial role on appetite regulation. Dopaminergic (DAergic) neurons expressed in different nucleus of the brain include the substantia nigra, ventral tegmental area and hypothalamus. To date, least five distinct subtypes of DA receptors identified (D_1-D_5) (Cadet et al., 2010). Dopamine impresses its mediatory effects through at least five distinct G protein coupled receptor subtypes (GPCRs) (Cadet et al., 2010). The D_1 and D_2 receptors are more abundant than the other DA receptors in the brain DAergic system participates in many physiological functions such as emotion, locomotor activity, cognition and food intake (Madhavan et al., 2013). Food

intake decreased via D_1 and D_2 receptors in rats (Volkow et al., 2011). Also, DA-induced hypophagia mediates by D_1 receptors in chicken while other receptors (D_2-D_4) may have no role in appetite regulation (Zendehdel et al., 2016). It is well documented that central feeding behavior is not regulated via a single neuropeptide and a wide distributed neural network interacts with other neurotransmitters on feeding status (Irwin et al., 2008).

ICV injection of the α_2 receptors antagonist has crucial role in the treatment of Parkinson's disease (Chopin et al., 1999). In addition, systemic injection of the reboxetine (selective NE reuptake inhibitor) increased firing activity of dopamine neurons in the ventral tegmental area (VTA) (Guiard et al., 2008). Also, systemic administration of the prazosin decreased the burst firing of dopamine neurons and supporting excitatory role of the NE in the VTA (Guiard et al., 2008). Additionally, firing rate and bursting activity of dopamine neurons increased by injection of the selective α_2 receptor antagonist (idazoxan) (Guiard et al., 2008). In a comparative physiological study, Cornil and Ball (2008) revealed dopamine binds to α_2 receptors in birds and mammals. Based on the literature, there is no information on interaction of the DAergic and noradrenergic systems on food intake regulation in avian. So, the aim of the current study was to determine interaction of the central dopaminergic and noradrenergic systems on food intake regulation in 3-h food-deprived (FD_3) neonatal layer chicken.

MATERIAL AND METHODS

Animals

A total of 352 one-day-old layer chickens purchased from a local hatchery (Mahan Co., Iran). Birds were maintained in stabilizing electrically heated batteries at a temperature of 32 ºC ± 1, kept at 40-50% relative humidity and 23:1 lighting/dark period (Olanrewaju et al., 2006). They were kept for 2 days as flocks and then birds randomly allocated into transferred into their individual cages. A commercial diet was offered during the study containing 21 percent crude protein and 2850 kcal/kg of metabolizable energy (Chineh Co., Iran) (table 1). During the study all birds had *ad libitum* access to diet and fresh water. 3 h prior to the injections, birds were food deprived (FD_3) but had free access to water. ICV injections were done at 5 days of age. 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 (publication No. 85-23, revised 1996) and the current laws of the Iranian government for animal care, and were approved by the Institutional Animal Ethics Committee of Faculty of Veterinary Medicine, University of Tehran.

Experimental drugs

Drugs used include dopamine, noradrenaline, parazosin (α_1 receptor antagonist), yohimbine (α_2 receptor antagonist), metoprolol (β_1 adrenergic receptor antagonist), ICI 118,551 (β_2 adrenergic receptor antagonist), SR 59230R (β_3 adrenergic receptor antagonist), SCH23390 (D_1 receptor antagonist, 5 nmol), AMI-193 (D_2 receptor antagonist, 5 nmol), noradrenaline(NA) and Evans blue were purchased from Sigma-Aldrich (USA) and tocris (UK) Co. All the drugs at first dissolved in absolute dimethyl sulfoxide (DMSO) then diluted with 0.85 % saline containing Evans blue at a ratio of 1/250 (0.4% DMSO). The DMSO with this ratio does not have a cytotoxic effect (Blevins et al., 2002; Qi et al., 2008). DMSO/Saline mixture containing Evans blue used as control group.

ICV injection protocol

Birds randomly allocated into 8 experimental groups each having 4 sub-groups (n=44). Prior to each experiment, the chicks were weighed and allocated into experimental groups based on their body weight (BW), thus, the average BW between treatment groups was as uniform as possible. The chicken was ICV injected once in each experiment using a microsyringe (Hamilton, Switzerland) without anesthesia using the Davis et al., (1979) and Furuse et al., (1997) method. Briefly, head of the chicken was held with an acrylic device in which the bill holder was 45º and the calvarium was parallel to the surface of table as explained by Van Tienhoven and Juhasz (1962). An orifice was made in a plate over the skull of right lateral ventricle. A microsyringe was inserted into the ventricle through the orifice in the plate and the tip of the needle perforated only 4 mm below the skin of the skull (Jonaidi and Noori, 2012). All injections were done in a volume of 10 µL (Furuse et al., 1999). The control group received control solution (DMSO/Saline mixture containing Evans blue, 10 µL) (Furuse et al., 1999). This technique does not induce any physiological stress in neonatal chicks (Saito et al., 2005). At the end of the experiments, to recognize the accuracy of injection, the chicks were sacrificed by decapitation. Accuracy of placement of the injection in the 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 the data of those individuals where dye was present in their lateral ventricle were used for analysis (9-11 chickens per group). All experimental procedures were done from 08:00 to 13:30.

Feeding experiments

In this study, 8 experiments were designed to determine the possible role of specific noradrenergic receptors (α_1, α_2, β_1, β_2 and β_3) on hypophagic effect of the dopamine in FD_3

neonatal broiler chicken. In experiment 1, chicken ICV injected with control solution, parazosin (10 nmol), dopamine (40 nmol) and parazosin + dopamine. In experiment 2, control solution, yohimbine (13 nmol), dopamine (40 nmol) and their combination were ICV injected. In experiment 3, FD_3 birds ICV injected with control solution, metoprolol (24 nmol), dopamine (40 nmol) and co-injection of the metoprolol + dopamine. In experiment 4, FD_3 chicks received ICV injection of control solution, ICI 118,551 (5 nmol), dopamine (40 nmol) and co-injetion of the ICI 118,551 + dopamine. In experimet 5, the ICV injection to the birds were control solution, SR 59230R (20 nmol), dopamine (40 nmol) and their combination. In experiment 6, chicken ICV injected with control solution and NA (75, 150 and 300 nmol). In experiment 7, birds injected with control solution, SCH23390 (D_1 receptor antagonist, 5 nmol), noradrenaline (300 nmol) and SCH23390 + NA. In experiment 8, control solution, AMI-193 (D_2 receptor antagonist, 5 nmol), NA (300 nmol) and AMI-193 + NA was injected. Illustration of experimental procedures and treatments during the study are shown in table 2. Immediately after the injection food provided to the birds and cumulative food intake (g) was measured at 30, 60 and 120 min after the injection. Food consumption was calculated as a gram of body weight (g/100g BW) to minimize impact of body weight on the amount of food intake. All doses of drugs determined according to the pilot study and previous studies (Zendehdel and Hassanpour, 2014; Zendehdel et al., 2017).

Statistical analysis

Cumulative food intake was analyzed by repeated measure two-way analysis of variance (ANOVA) and is presented as the mean ± SEM. For treatments found to have an effect according to the ANOVA, mean values were compared with Bonferroni test. $P < 0.05$ were considered to indicate significant differences between the treatments.

RESULTS

Effects and interactions of central dopamine and adrenergic system on cumulative food intake in FD_3 neonatal layers are shown in figures 1-5. In the experiment 1, ICV injection of the parazosin (10 nmol) had no effect on food intake ($P > 0.05$) while dopamine (40 nmol) significantly decreased food intake compared to control group ($P < 0.05$). Co-injection of the parazosin + dopamine had no effect on dopamine-induced hypophagia in neonatal chicken at 30, 60 and 120 min post injection compared to control group ($P > 0.05$) (figure 1).

In experiment 2, ICV administration of the yohimbine (13 nmol), had no effect on food intake (P >0.05) while dopamine (40 nmol) had hypophagic effect compared to control group (p<0.05). Co-injection of the yohimbine + dopamine amplified dopamine-induced hypophagia in neonatal chicken compared to control group (P <0.05) (figure 2).

In experiment 3, no signifcnat defference was detected on food intake by ICV injection of the metoprolol (24 nmol). ICV injection of the dopamine (40 nmol) significantly decreased food intake in comparison to control group (P <0.05). Co-injection of the metoprolol + dopamine had no effect on hypophagic effect of the dopamine (40 nmol) compared to control group (P >0.05) (figure 3).

In experiment 4, ICV inejction of the ICI 118,551 (5 nmol) had no effect on food intake (P >0.05). ICV injection of the dopamine (40 nmol) significantly decreased food intake compared to control group (P <0.05). Co-administration of the ICI 118,551 + dopamine significantly inhibited dopamine-induced hypophagia in neonatal chicken (P <0.05) (figure 4).

In experiment 5, ICV injection of SR 59230R (20 nmol), had no effect on food intake (P >0.05); while dopamine (40 nmol) significantly decreased food intake compared to control group (P <0.05). Also, co-injection of the SR 59230R + dopamine had no effect on dopamine-induced hypophagia compared to control group (P >0.05) (figure 5).

In the experiment 6, ICV injection of the NA (75, 150 and 300 nmol) in a dose dependent manner decreased food intake compared to control group (P <0.05) (figure 6).

In experiment 7, ICV administration of the SCH23390 (5 nmol), had no effect on food intake (P >0.05) while NA (300 nmol) had hypophagic effect compared to control group (P <0.05). Co-injection of the SCH23390 + NA decreased hypophagic effect of the NA in neonatal chicken compared to control group (P <0.05) (figure 7).

In experiment 8, no signifcnat defference was detected on food intake by ICV injection of the AMI-193 (5 nmol). ICV injection of the NA (300 nmol) significantly decreased food intake in comparison to control group (P <0.05). Co-injection of the AMI-193 + NA diminished NA -induced hypophagia compared to control group (P <0.05) (figure 8).

DISCUSSION

To the best of our knowledge, this is the first report on interaction of central dopamine and noradrenergic system on food intake regulation in layer chicken. On the obtained results, ICV

injection of the dopamine (40 nmol) decreased food intake in FD_3 neonatal chicken. Recently, Ghand Foroushan et al., (2017) reported ICV injection of the 40 nmol dopamine decreased food intake in FD_3 neonatal chicken. A daily decrease on cumulative food intake was reported using SKF 38393 (D_1) and apomorphine (D_2) receptors agonists in rats (Kuo et al., 2002). A dose dependent response on food intake decrease was detected using SKF 38393 in both food deprived and non-deprived rats (Terry et al., 1992). The result of current study was similar to our previous study which the ICV injection of the dopamine decreased food intake in broiler chickens (Zendehdel et al., 2014). Dopamine acts through its projections from the VTA into the nucleus accumbens (NAcc) and arcuate nucleus (ARC) (Volkow et al., 2011). DAergic neurons of the Substantia Nigra, Pars Compacta, VTA and hypothalamus give origin to three main pathways, Nigrostriatal, Mesolimbocortical and Tuberoinfundibular in CNS (Cadet et al., 2010).

Controversial reports exist on role of α-adrenergic receptors on feeding behavior in avian. ICV injection of the clonidine stimulated food intake in broiler (Bungo et al., 1999). Also, Denbow et al., (1981) reported ICV injection of the NE had no effect on food consumption in chicken. In broilers, ICV injection of the NA into the paraventricular and ventromedial increased feed intake while inhibited after ICV injection into the reticularis superiorand pars dorsalis and Tractus occipitomesencephalicus (Denbow, 1999). ICV injection of β adrenergic receptor antagonists decreased food and water intake in broilers (Baghbanzadeh and Hajinezhad, 2010). Zendehdel and Hasasnpour, 2014) reported ICV injection of ICI 118,551 (β_2 adrenergic receptor antagonists, 5 nMol) or SR 59230R (β_3 adrenergic receptor antagonists, 20 nMol) increased cumulative food intake in broilers. It seems, adrenergic receptors have both stimulatory and inhibitory roles on appetite regulation (Ferrari et al., 1991). ICV injection of isoproterenol (nonselective β adrenergic receptor agonist) decreased food intake in rats (Wellman, 1992) where injection of β_3 adrenergic receptor agonist showed an anorexigenic effect (Tsujii and Bray, 1998).

As observed, co-injection of the α_2 receptor antagonist (yohimbine, 13nmol) plus dopamine amplified dopamine-induced hypophagia in FD_3 neonatal chicken. Co-administration of the β_2 adrenergic receptor antagonist (ICI 118,551, 5nmol) plus dopamine significantly inhibited dopamine-induced hypophagia in FD_3 neonatal chicken. It is reported ICV injection of the noradrenalin diminished feed intake in mammalians (Bungo et al., 1999). There is a long literature of promiscuous interaction between dopamine and adrenergic systems (Lin et al., 2008). Interaction between noradrenergic and DAergic neurons mediates via α receptors (Nalepa et al., 2013). ICV injection of the prazosin (α_1 receptors antagonist) decreases the

locomotor effect of acute amphetamine and cocaine (Drouin et al., 2002). Thus, dopamine-induced behavioral effects primarily mediate via α receptors (Nalepa et al., 2013). Additionally, dopamine and adrenergic system modulate theta and gamma oscillatory activity in primary motor cortex via D_1, D_2 and α receptors (Ozkan et al., 2017). Also, injection of the dopamine increases intracellular Ca^{2+} release in pineal cells (Lei et al., 2014). However, intracellular Ca^{2+} is unaltered in response to D_1 receptor agonist (SKF-38393), D_2 receptor agonist (quinpirole) and a D_1/D_2 receptors agonist (apomorphine) (Lei et al., 2014). The lack of dopamine receptor agonists on intracellular Ca^{2+} revealed that there is alternative mechanism for observed results. For instance, prazosin (α_1 receptor antagonist) blocked dopamine-induced intracellular Ca^{2+} release which revealed intracellular Ca^{2+} release is mediated via α_1 adrenergic (Lei et al., 2014). The effects of dopamine blocked by α_1 receptor antagonist (prazosin) and α_2 receptor antagonist are suggesting the involvement of adrenergic on DAergic receptors (Lei et al., 2014). In Parkinson's disease because of the degeneration of the nigrostriatal dopamine pathway, α_2 receptors antagonists can increase effect of the direct dopamine agonist apomorphine on circling behavior in rats indicates a facilitatory influence as site postsynaptic to the dopamine neurons (Chopin et al., 1999).

Despite direct mechanism(s) for interaction between DAergic and Adrenergic receptors is not fully determined, it is reported D_1 receptors couple to adenylyl cyclase, increase cAMP and activating protein kinase A (Ozkan et al., 2017). This phenomenon modulates voltage-dependent Na^+ channels, activation of L-type Ca^{2+} channels and attenuation of a slowly inactivating outward rectifying K^+ current (Ozkan et al., 2017). Dopamine-induced membrane hyper-polarisation mediates through adrenergic receptors (Yang et al., 2014). Also, interconnection of the dopamine on adrenergic receptors in the entorhinal cortex produces membrane depolarisation via the inhibition of inward rectifier K^+ channels and enhances the frequency of miniature inhibitory post synaptic potential and spontaneous inhibitory post synaptic potential (Yang et al., 2014). Interaction between adrenergic and dopamine receptors act as G-protein or second messenger systems (Ozkan et al., 2017). Also, interconnection revealed between DAergic and β-adrenergic receptors. In patients with heart failure, dopamine-induced inotropic effect mediates via β adrenergic receptors (Lei et al., 2014). Dopamine binds to α_2 receptors in quail and rat (Cornil and Ball, 2008). In rodent brain, α_2 receptors receive DAergic inputs in conjunction or not with noradrenergic inputs nucleus accumbens (NAcc), amygdala, hypothalamic nuclei and locus coeruleus (Cornil and Ball, 2008). Dopamine releases in these regions in response to stimuli such as stress. Also, because dopamine is a part of the synthesis pathway of NE, one would expect that

noradrenergic terminals would always express dopamine (Cornil and Ball, 2008). The α_2 receptors expressed in the cell bodies and axons of mesoprefrontal DAergic neurons provides a morphological basis to the vast functional evidence that nerve-terminal α_2 receptors control DAergic activity and dopamine release in the prefrontal cortex (Castelli et al., 2016). Although an axo-axonic relationship between dopamine and noradrenergic terminals remains to be recognized, extracellular noradrenaline may diffuse trans-synaptically to access, through volume transmission, α_2 receptors on dopamine terminals (Fuxe et al., 2015). The local application of the selective α_2 receptor antagonist (idazoxan) reduced the suppressant effect of on VTA dopamine neurons (Guiard et al., 2008). Idazoxan has 1000-fold lower affinity for D_2 receptors than for α_2 receptor addition to the stimulation of D_2 receptors in the rat cortex. Dopamine inhibits the dopamine neurons activity by α_2 receptors (Castelli et al., 2016). The role of α_2 receptors in a direct regulation of dopamine neurons themselves remained debatable, especially in rat brain which affinity of dopamine for α_2 receptors is lower than NE (Castelli et al., 2016).

In conclusion, DAergic and adrenergic systems are widely expressed in the CNS, with their distribution and expression levels largely mirroring the density of innervating fibers. Both systems are required for proper operation and cannot act independently without affecting the other system (Xing et al., 2016). High NE and dopamine levels cause recruitment of α, β, and excessive D_1 receptor activation during abnormal conditions such as stress, weakening neuronal firing and prefrontal functioning (Xing et al., 2016). Based on the literature, there is no report on interaction of these systems on food intake regulation in mammalian and rodents. So, this is the first report and these results suggested an interaction exists between central dopaminergic and noradrenergic systems through α_2 and β_2 adrenergic and D_1 and D_2 dopaminergic receptors on food intake regulation in neonatal chicks. Beside the previous research on central food intake regulation in the poultry, obtained results revealed that DAergic and adrenergic systems interaction regulates appetite in chicks. Scarce information is present on interaction of the neurotransmitters on feeding behavior in avian. We think obtained results can use as base information for further researches. Also, merit studies needed to determine cellular and molecular mechanism(s) involved in interaction of dopamine with adrenergic system.

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Compliance with Ethical Standards

Authors have no potential conflicts of interest There is no informed consent in this study. This manuscript does not contain any studies with human subjects performed by any of the authors. All experiments were executed according to the Guide for the Care and Use of Laboratory Animals and were approved by the institutional animal ethics committee.

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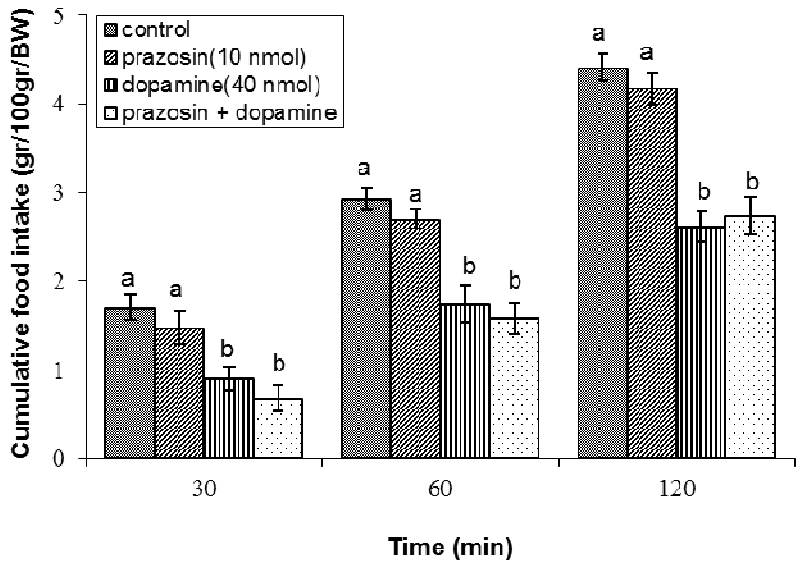

Fig 1. Effect of ICV injection of parazosin (10 nmol), dopamine (40 nmol) and their combination on percent of body weight cumulative food intake in neonatal layer type chicken (n=44). parazosin: α_1 receptor antagonist. Data are expressed as mean ± SEM. Different letters (a and b) indicate significant differences between treatments ($P < 0.001$).

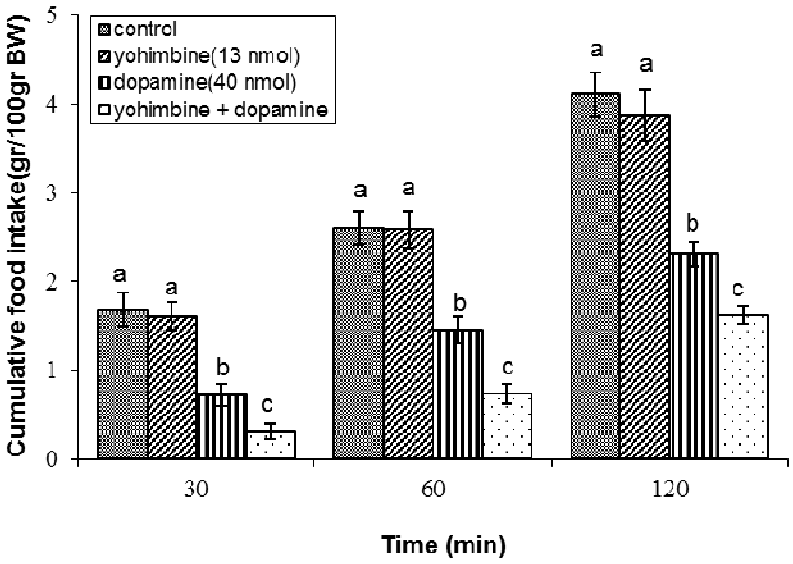

Fig 2. Effect of ICV injection of yohimbine (13 nmol), dopamine (40 nmol) and their combination on percent of body weight cumulative food intake in neonatal layer type chicken (n=44). yohimbine: α_2 receptor antagonist. Data are expressed as mean ± SEM. Different letters (a, b and c) indicate significant differences between treatments ($P < 0.001$).

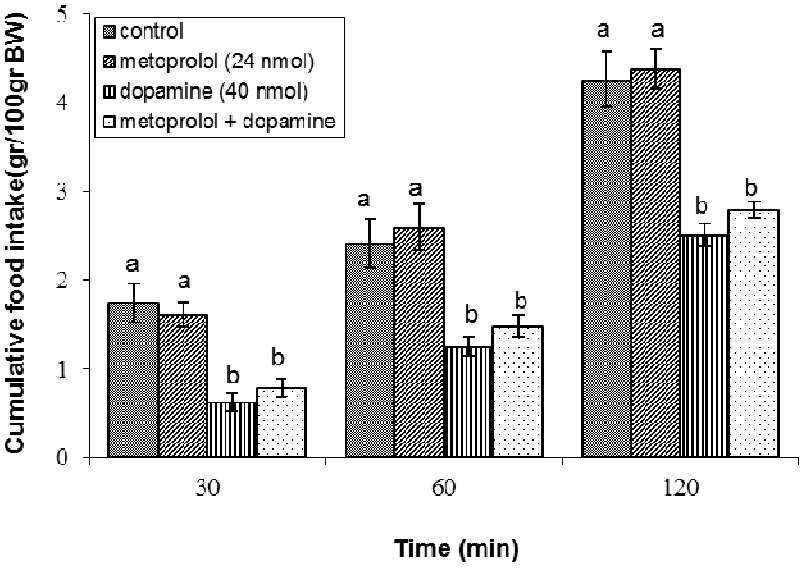

Fig 3. Effect of ICV injection of metoprolol (24 nmol), dopamine (40 nmol) and their combination on percent of body weight cumulative food intake in neonatal layer type chicken (n=44). metoprolol: β_1 adrenergic receptor antagonist. Data are expressed as mean ± SEM. Different letters (a and b) indicate significant differences between treatments ($P < 0.001$).

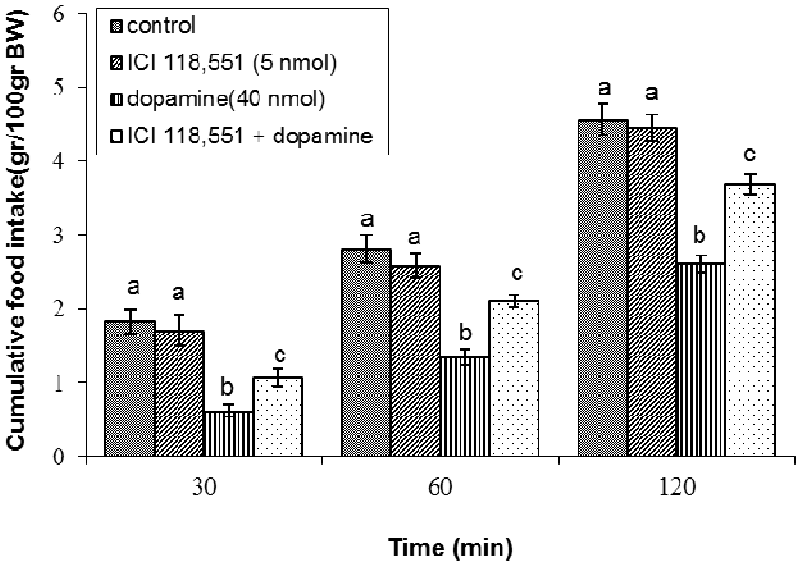

Fig 4. Effect of ICV injection of ICI 118,551 (5 nmol), dopamine (40 nmol) and their combination on percent of body weight cumulative food intake in neonatal layer type chicken (n=44). ICI 118,551: β_2 adrenergic receptor antagonist. Data are expressed as mean ± SEM. Different letters (a, b and c) indicate significant differences between treatments ($P < 0.001$).

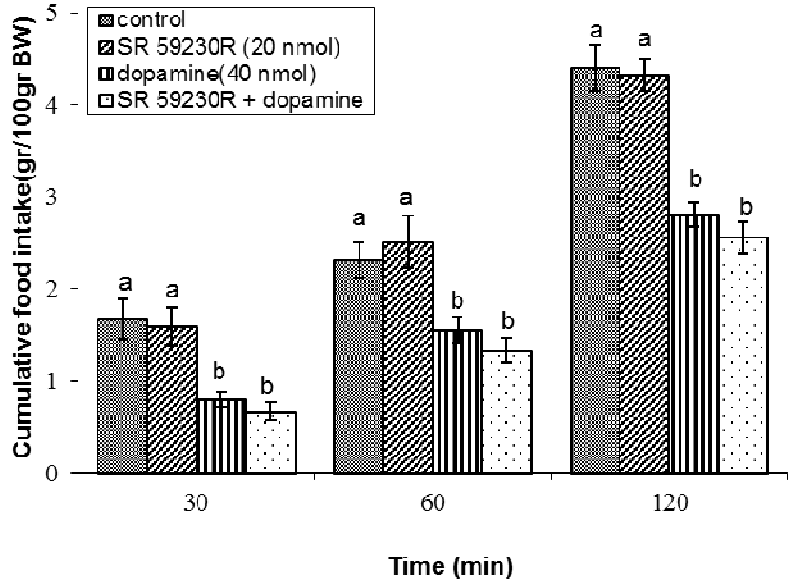

Fig 5. Effect of ICV injection of SR 59230R (20 nmol), dopamine (40 nmol) and their combination on percent of body weight cumulative food intake in neonatal layer type chicken (n=44). SR 59230R: β_3 adrenergic receptor antagonist, Data are expressed as mean ± SEM. Different letters (a and b) indicate significant differences between treatments ($P < 0.001$).

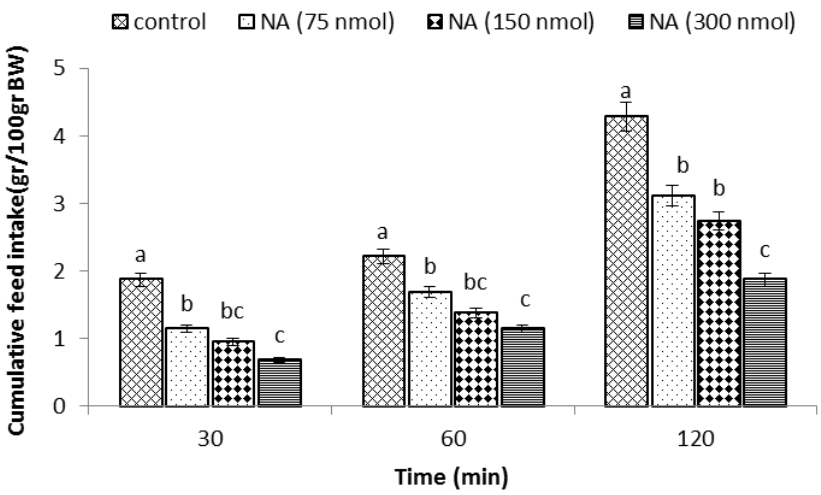

Fig 6. Effect of ICV injection of NA (75, 150 and 300 nmol) on cumulative food intake in neonatal chicken (n=44). NA: noradrenaline. Data are expressed as mean ± SEM. Different letters (a, b and c) indicate significant differences between treatments ($P < 0.001$).

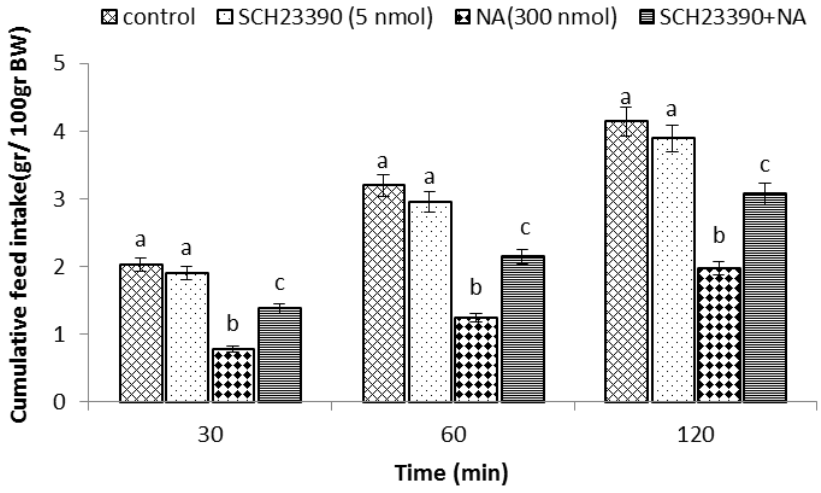

Fig 7. Effect of ICV injection of SCH23390 (5 nmol), NA (300 nmol) and their combination on cumulative food intake in neonatal chicken (n=44). SCH23390: D_1 receptor antagonist, NA: noradrenaline. Data are expressed as mean ± SEM. Different letters (a, b and c) indicate significant differences between treatments ($P < 0.001$).

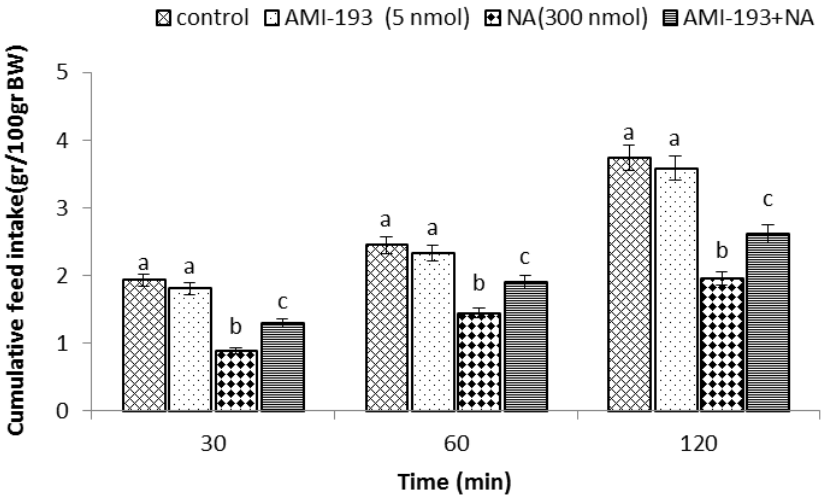

Fig 8. Effect of ICV injection of AMI-193 (5 nmol), NA (300 nmol) and their combination on cumulative food intake in neonatal chicken (n=44). AMI-193: D_2 receptor antagonist, NA: noradrenaline. Data are expressed as mean ± SEM. Different letters (a, b and c) indicate significant differences between treatments ($P < 0.001$).

Table 1. Ingredient and nutrient analysis of experimental diet

Ingredient	**(%)**	**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 D_3	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 MnSO4·H2O; 22 g iron from FeSO4·H2O; 35.2 g zinc from ZnO; 4.4 g copper from CuSO4·5H2O; 0.68 g iodine from ethylene diamine dihydroiodide; 0.12 g seleniumfrom Na2SeO3. 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. Treatments procedure in experiments 1-8

Exp. 1	**ICV Injection**
Treatment groups	
I	CS*
II	parazosin (10 nmol)
III	dopamine (40 nmol)
IV	parazosin (10 nmol) + dopamine (40 nmol)

Exp. 2	**ICV Injection**
Treatment groups	
I	CS *
II	yohimbine (13 nmol)
III	dopamine (40 nmol)
IV	yohimbine (13 nmol) + dopamine (40 nmol)

Exp. 3	**ICV Injection**
Treatment groups	
I	CS *
II	metoprolol (24 nmol)
III	dopamine (40 nmol)
IV	metoprolol (24 nmol) + dopamine (40 nmol)

Exp. 4	**ICV Injection**
Treatment groups	

I	CS *
II	ICI 118,551 (5 nmol)
III	dopamine (40 nmol)
IV	ICI 118,551 (5 nmol) + dopamine (40 nmol)
Exp. 5	**ICV Injection**
Treatment groups	
I	CS *
II	SR 59230R (20 nmol)
III	dopamine (40 nmol)
IV	SR 59230R (20 nmol) + dopamine (40 nmol)
Exp. 6	**ICV Injection**
Treatment groups	
I	CS *
II	NA (75 nmol)
III	NA (150 nmol)
IV	NA (300 nmol)
Exp. 7	**ICV Injection**
Treatment groups	
I	CS *
II	SCH23390 (5 nmol)
III	NA (300 nmol)
IV	SCH23390 (5 nmol) + NA (300 nmol)
Exp. 8	**ICV Injection**
Treatment groups	
I	CS *
II	AMI-193 (5 nmol)
III	NA (300 nmol)
IV	AMI-193 (5 nmol) + NA (300 nmol)

CS: control solution, parazosin: α_1 receptor antagonist, yohimbine: α_2 receptor antagonist, metoprolol: β_1 adrenergic receptor antagonist, ICI 118,551: β_2 adrenergic receptor antagonist, SR 59230R: β_3 adrenergic receptor antagonist), SCH23390: D_1 receptor antagonist, AMI-193: D_2 receptor antagonist, NA: noradrenaline.